https://www.fda.gov/food/generally-recognized-safe-gras/gras-notice-inventory



ENVIRONMENT & HEALTH

Via Express Courier

GRAS Notification Program
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

SUBJECT: GRAS NOTIFICATION FOR

L-ARABINOSE (BETAWELL® ARABINOSE)

Dear GRN Coordinator:

In accordance with the Food and Drug Administration's Final Rule for Substances Generally Recognized as Safe (GRAS) (Fed. Reg. 81(159):54960-55055, August 17, 2016), and on behalf of Sensus America, Inc. (Sensus) ("the Notifier"), Ramboll US Corporation is pleased to submit this Notification of the GRAS Determination for the ingredient, L-arabinose derived from sugar beet pulp for use in foods for the general population.

May 4, 2018

Ramboll

2111 Highland Ave Suite 402 Phoenix, AZ 85016 USA

T: +1 602 734 7704 F: +1 602 734 7701 gthompson@ramboll.com

Sincerely,

(b) (6)

Gavin P. Thompson, Ph.D. | Principal Consultant +1 602 734 7704 | <a href="mailto:gthompson@ramboll.com">gthompson@ramboll.com</a>

cc: Carl Volz, Sensus America, Inc. Alex Benschop, Sensus B.V.

**Enclosures** 

|   |  |  | Form  | Approved: OMB No.     |  |  |
|---|--|--|---|-----------------------|--|--|
|   |  |  |   | FDA US                | (See last page for OMB Statement)  FONI Y  |  |
|   |  |  | GRN NUMBER                                    |                       | DATE OF RECEIPT  |  |
| DEPART                                      | MENT OF HEALTH AN<br>Food and Drug Adm           |  | ESTIMATED DAI                                 | LY INTAKE             | INTENDED USE FOR INTERNET  |  |
| GENER                                       | _  | NIZED AS SAFE  |   |                       |  |  |
| (GRAS) NOTICE                               |  | NAME FOR INTERNET  |   |                       |  |  |
|   |  |  | KEYWORDS                                      |                       |  |  |
| completed form                              | and attachments in pa                            |  | media to: Office                              | of Food Additive S    | ee Instructions); OR Transmit<br>Safety (HFS-200), Center for<br>ge Park, MD 20740-3835. |  |
|   | PART I – II                                      | NTRODUCTORY INFORM   | MATION ABOU                                   | T THE SUBMISS         | SION   |  |
| 1. Type of Subm                             | ission (Check one)                               |  |   |                       |  |  |
| New   | Amendment t                                      | o GRN No   | Supple  | ement to GRN No.      |  |  |
| 2. X All electi                             | ronic files included in th                       | is submission have been che                                | ecked and found                               | to be virus free. (Cl | neck box to verify)  |  |
| 3a. For New Sub                             | missions Only: Most                              | recent presubmission meeti<br>on the subject substance (y) | ng (if any) with                              |                       |  |  |
|   | or supplement submitte<br>a communication from F |  |   | /mm/dd):              |  |  |
|   | Name of Contact Pers                             | con  |   | Position              |  |  |
|   | Carl Volz  | SOIT   |   | General Manager       |  |  |
|   |  | (-)  |   | 131                   |  |  |
| 1a. Notifier                                | Company (if applicable) Sensus America Inc.      |  |   |                       |  |  |
|   |  |  |   |                       |  |  |
|   | Mailing Address (num                             | ·  | and street) Center 100 Lenox Drive, Suite 104 |                       |  |  |
|   | Timeeton ike corpe                               |  |   |                       |  |  |
| City<br>Lawrenceville                       |  | State or Province  | ¬   |                       | Country  |  |
|   | T  | New Jersey   | 08648   |                       | United States of America   |  |
| Telephone Numb                              | er Fax Number                                    |  | E-Mail Address                                |                       |  |  |
| 646-452-6142                                |  |  | carl.volz@s                                   | ensus.us              |  |  |
|   | Name of Contact Per                              | son  |   | Position              |  |  |
|   | Gavin P. Thompson                                |  | Principal Consultant                          |                       |  |  |
| 1b. Agent<br>or Attorney<br>(if applicable) | Company (if applicable) Ramboll U.S. Corporation |  |   |                       |  |  |
|   | Mailing Address (num<br>2111 East Highland       | •  |   |                       |  |  |
| City  | -  | State or Province  | Zip Code/Po                                   | ostal Code            | Country  |  |
| Phoenix                                     |  | Arizona  | 85016   |                       | United States of America   |  |
| Telephone Numb<br>602-734-7704              | er   | Fax Number   | E-Mail Addr                                   | ress<br>n@ramboll.com |  |  |

| PART III – GENERAL ADMINISTRATIVE INFOR   | MATION  |  |  |  |
|---|---|--|--|--|
| Name of Substance   |   |  |  |  |
| Betawell® Arabinose   |   |  |  |  |
| Submission Format: (Check appropriate box(es))  | 3. For paper submissions only:                  |  |  |  |
| ☐ Electronic Submission Gateway ☐ Electronic files on physical media  |   |  |  |  |
| Paper With paper signature page   | Number of volumes                               |  |  |  |
| If applicable give number and type of physical media  | Total number of pages 493                       |  |  |  |
| 1-CD  |   |  |  |  |
| <ol> <li>Does this submission incorporate any information in FDA's files by reference? (Check one</li></ol>   | <del>)</del> )                                  |  |  |  |
|   | as indicated holow (Charle all that apply)      |  |  |  |
| 5. The submission incorporates by reference information from a previous submission to FDA   | . as indicated below (Crieck all trial apply)   |  |  |  |
| a) GRAS Notice No. GRN b) GRAS Affirmation Petition No. GRP   |   |  |  |  |
| c) Food Additive Petition No. FAP   |   |  |  |  |
| d) Food Master File No. FMF   |   |  |  |  |
| e) Other or Additional (describe or enter information as above)   |   |  |  |  |
| 6. Statutory basis for determination of GRAS status (Check one)   |   |  |  |  |
| Scientific Procedures (21 CFR 170.30(b)) Experience based on common use in  | n food (21 CFR 170.30(c))                       |  |  |  |
| 7. Does the submission (including information that you are incorporating by reference) conta  |   |  |  |  |
| or as confidential commercial or financial information?   |   |  |  |  |
| Yes (Proceed to Item 8)   |   |  |  |  |
| No (Proceed to Part IV)  8. Have you designated information in your submission that you view as trade secret or as co   | onfidential commercial or financial information |  |  |  |
| (Check all that apply)  | Sindernal Commercial of Infancial Information   |  |  |  |
| Yes, see attached Designation of Confidential Information   |   |  |  |  |
| Yes, information is designated at the place where it occurs in the submission   |   |  |  |  |
| No No   |   |  |  |  |
| <ol> <li>Have you attached a redacted copy of some or all of the submission? (Check one)</li> <li>Yes, a redacted copy of the complete submission</li> </ol>  |   |  |  |  |
| Yes, a redacted copy of the complete submission  Yes, a redacted copy of part(s) of the submission  |   |  |  |  |
| □ No  |   |  |  |  |
| PART IV – INTENDED USE  |   |  |  |  |
| FART IV - INTENDED USE  |   |  |  |  |
| <ol> <li>Describe the intended use of the notified substance including the foods in which the substances, the purpose for which the substance will be used, and any special population that will</li> </ol> |   |  |  |  |
| stance would be an ingredient in infant formula, identify infants as a special population).   | consume the substance (e.g., when a sub-        |  |  |  |
| The proposed use of Betawell® Arabinose is as an additive in foods and  |   |  |  |  |
| partial replacement of sucrose by 2 to 30%, or as a complete replacement  |   |  |  |  |
| arabinose/sucrose mixture with an arabinose composition of 2-30%. Bet<br>the general population in the foods and beverages.   | tawell® Arabinose is proposed for use in        |  |  |  |
| the general population in the roods and beverages.  |   |  |  |  |
|   |   |  |  |  |
|   |   |  |  |  |
|   |   |  |  |  |
|   |   |  |  |  |
|   |   |  |  |  |
| 2. Does the intended use of the notified substance include any use in meat, meat food produ   | uct, poultry product, or egg product?           |  |  |  |
| (Check one)   |   |  |  |  |
| ☐ Yes   |   |  |  |  |
|   |   |  |  |  |

| PART \ | / _ I | DEN | YTITL |
|--------|-------|-----|-------|
|        |       |     | 4111  |

|   | Name of Substance <sup>1</sup> | Registry<br>Used<br>(CAS, EC) | Registry No. <sup>2</sup> | Biological Source<br>(if applicable) | Substance Category<br>(FOR FDA USE ONLY) |
|---|--------------------------------|-------------------------------|---------------------------|--------------------------------------|--|
| 1 | L-Arabinose                    | CAS                           | 5328-37-0                 | Sugar beets                          |  |
| 2 |                                |                               |                           |                                      |  |
| 3 |                                |                               |                           |                                      |  |

<sup>&</sup>lt;sup>1</sup> Include chemical name or common name. Put synonyms (whether chemical name, other scientific name, or common name) for each respective item (1 - 3) in Item 3 of Part V (synonyms)

# 2. Description

Provide additional information to identify the notified substance(s), which may include chemical formula(s), empirical formula(s), structural formula(s), quantitative composition, characteristic properties (such as molecular weight(s)), and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source (e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source), and include any known toxicants that could be in the source.

L-Arabinose is a ubiquitous sugar that occurs in common foods both as a monosaccharide and as a component of polysaccharides. Sensus' Betawell® Arabinose is composed of L-arabinose manufactured from sugar beet fiber, a GRAS substance. Betawell® Arabinose is produced from sugar beets grown in the Netherlands and Germany. Betawell® Arabinose is a water-soluble, white, crystalline, sweet tasting powder. The empirical formula for Betawell® Arabinose is  $C_5H_{10}O_5$ . The simplified molecular-input line-entry system (SMILES) notation for arabinose is O=CC(O)C(O)C(O)CO. The molecular weight of Betawell® Arabinose is 150.1 g/mol.

| 3. | Sy | no | ny | ms |
|----|----|----|----|----|
|----|----|----|----|----|

Provide as available or relevant:

| 1 | (2R,3S,4S)-2,3,4,5-tetrahydroxypentanal |
|---|---|
| 2 | Betawell® Arabinose                     |
| 3 | Betawell® beet root extract             |

<sup>&</sup>lt;sup>2</sup> Registry used e.g., CAS (Chemical Abstracts Service) and EC (Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))

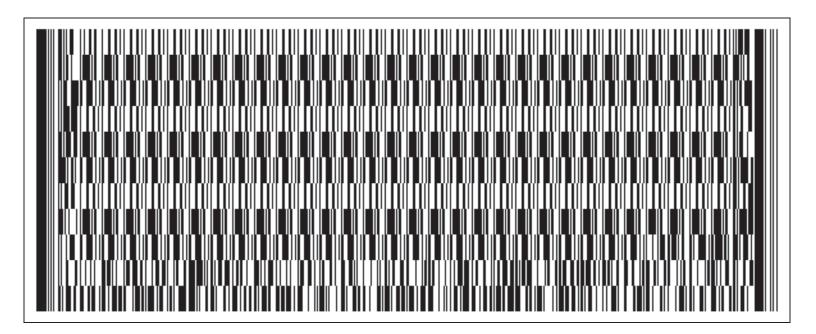
| (check list to help ensure your submission is complete – check all that apply)   |  |  |  |  |  |
|--|--|--|--|--|--|
|  |  |  |  |  |  |
| Method of Manufacture  |  |  |  |  |  |
| Specifications for food-grade material   |  |  |  |  |  |
| Information about dietary exposure   |  |  |  |  |  |
| Information about any self-limiting levels of use (which may include a statement that the intended use of the notified substance is  |  |  |  |  |  |
| <sup>△</sup> not-self-limiting)<br>☑ Use in food before 1958 <i>(which may include a statement that there is no information about use of the notified substan</i>  | ance in food   |  |  |  |  |
| prior to 1958)   | ando m rood  |  |  |  |  |
| Comprehensive discussion of the basis for the determination of GRAS status   |  |  |  |  |  |
| ∑ Bibliography   |  |  |  |  |  |
| Other Information  |  |  |  |  |  |
| Did you include any other information that you want FDA to consider in evaluating your GRAS notice?  |  |  |  |  |  |
| ∑ Yes  |  |  |  |  |  |
| Did you include this other information in the list of attachments?   |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| PART VII – SIGNATURE   |  |  |  |  |  |
|  |  |  |  |  |  |
| 1. The undersigned is informing FDA that Gavin Thompson  |  |  |  |  |  |
| (name of notifier)   |  |  |  |  |  |
| has concluded that the intended use(s) of Betawell® Arabinose  |  |  |  |  |  |
| has concluded that the intended use(s) of (name of notified substance)   |  |  |  |  |  |
|  |  |  |  |  |  |
| described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of   | of section 409 of the  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.  |  |  |  |  |  |
| Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.  |  |  |  |  |  |
| <ol> <li>Gavin Thompson</li> <li>agrees to make the data and information that are the bate</li> </ol>  | basis for the  |  |  |  |  |
|  | basis for the<br>A asks to see them.   |  |  |  |  |
| 2.   Gavin Thompson  (name of notifier)  agrees to make the data and information that are the bad determination of GRAS status available to FDA if FDA and the status available to FDA and the st | A asks to see them.  |  |  |  |  |
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| 2. Gavin Thompson  Gavin Thomp | A asks to see them.  Information during a asks to do so.  Information during a asks to do so.  Information during a asks to do so.   |  |  |  |  |
| 2.   | A asks to see them.  Information during a asks to do so.  |  |  |  |  |

#### PART VIII – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

| Attachment<br>Number | Attachment Name   | Folder Location (select from menu) (Page Number(s) for paper Copy Only) |
|----------------------|---|---|
|                      | BETAWELL® ARABINOSE<br>GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR THE<br>USE OF BETAWELL® ARABINOSE IN FOOD | 8-82  |
|                      | Appendix A  | 83-89   |
|                      | Appendix B  | 90-128  |
|                      | Appendix C  | 129-473   |
|                      | Appendix D  | 474-495   |
|                      | Appendix E  | 496-1079  |
|                      | Appendix F  | 1080-1091   |
|                      |   |   |
|                      |   |   |

**OMB Statement:** Public reporting burden for this collection of information is estimated to average XX hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, Room 400, Rockville, MD 20850. (Please do NOT return the form to this address.). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



Prepared for Sensus America, Inc.

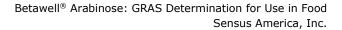
Prepared by
Ramboll US Corporation
2111 East Highland Avenue, Suite 402
Phoenix, Arizona 85016

Project Number **1690007396** 

Date **May 3**, **2018** 

# BETAWELL® ARABINOSE GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR THE USE OF BETAWELL® ARABINOSE IN FOOD





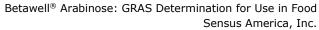


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# **Contents**

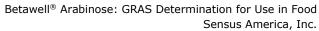
|       |  | Page |
|-------|--|------|
| 1     | Signed Statements and Certification of Conformity (in accordance with 21 CFR         |      |
|       | §170.220-§170.255)   | 1    |
| 1.1   | Submission of GRAS Notice  | 1    |
| 1.2   | Name and Address of the Sponsor  | 1    |
| 1.3   | Name of the Notified Substance   | 1    |
| 1.4   | Intended Conditions of Use   | 1    |
| 1.5   | Basis for GRAS Determination   | 1    |
| 1.6   | Premarket Approval Requirements  | 2    |
| 1.7   | Availability of Information  | 2    |
| 1.8   | Freedom of Information Act (FOIA)  | 2    |
| 1.9   | Information Included in the GRAS Notification  | 2    |
| 2     | Identity, Method of Manufacture, Specifications, and Physical or Technical Effective | :t   |
|       | (in accordance with 21 CRF§170.230)  | 5    |
| 2.1   | Identity   | 5    |
| 2.2   | Description of Betawell® Arabinose   | 6    |
| 2.3   | Manufacturing Process  | 6    |
| 2.4   | Specifications for Food-Grade Material   | 7    |
| 2.4.1 | Batch Analysis Results   | 7    |
| 2.4.2 | Residual Impurities  | 7    |
| 2.4.3 | Stability  | 7    |
| 2.4.4 | Section 2 Summary  | 11   |
| 3     | Dietary Exposure (in accordance with 21 CFR §170.235)                                | 13   |
| 3.1   | Intended Effect  | 13   |
| 3.2   | Uses of Arabinose  | 13   |
| 3.3   | Exposure to Arabinose from the Diet  | 14   |
| 3.4   | Approved Food Additive Uses  | 15   |
| 3.4.1 | United States Regulations  | 15   |
| 3.4.2 | Related Substances   | 15   |
| 3.5   | Intended Uses of Betawell® Arabinose   | 17   |
| 3.6   | EDI from the Proposed Uses of Betawell® Arabinose                                    | 18   |
| 3.7   | Cumulative EDIs  | 29   |
| 3.8   | Section 3 Summary  | 29   |
| 4     | Self-Limiting Levels of Use (in accordance with 21 CFR §170.240)                     | 31   |
| 5     | Experience Based on Common Use in Food Before 1958 (in accordance with 21            | 22   |
|       | CFR §170.245)  | 33   |
| 5.1   | History of Use   | 33   |





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| 6     | Safety Narrative (in accordance with 21 CFR §170.250)   | 35 |
|-------|---|----|
| 6.1   | Introduction  | 35 |
| 6.2   | Mode of Action  | 35 |
| 6.2.1 | Acute Toxicity of Arabinose   | 35 |
| 6.2.2 | Subchronic Toxicity of Arabinose  | 35 |
| 6.2.3 | Reproductive and Developmental Toxicity   | 36 |
| 6.2.4 | Carcinogenicity   | 36 |
| 6.2.5 | Genotoxicity  | 36 |
| 6.2.6 | Mutagenicity  | 37 |
| 6.2.7 | Dermal Irritation and Sensitization   | 38 |
| 6.2.8 | Other Toxicological Considerations  | 38 |
| 6.3   | Studies Evaluating Arabinose in Humans  | 38 |
| 6.3.1 | Biodisposition: Absorption, Distribution, Metabolism, Kinetics and Excretion                  | 38 |
| 6.3.2 | Other Studies of Arabinose in Humans  | 38 |
| 6.3.3 | Case Reports  | 42 |
| 6.4   | Other Studies Evaluating Arabinose in Animals and In Vitro                                    | 42 |
| 6.5   | International Regulations and Guidelines  | 47 |
| 6.6   | Section 6 Summary   | 47 |
| 7     | List of Supporting Data and Information (in accordance with 21 CFR §170.255)                  | 65 |
| 7.1   | Reference Literature (generally available)  | 65 |
| 7.2   | List of Exhibits (Appendices)   | 67 |
| LIST  | OF TABLES   |    |
| Table | 2-1. Physical and Chemical Properties   | 6  |
|       | 2-2. Betawell® Arabinose Product Specifications and Batch Data                                | 8  |
|       | 2-3. Betawell® Arabinose Storage Stability Analysis   | 10 |
|       | 3-1. Uses of Arabinose Reported by FEMA   | 13 |
|       | 3-2. Estimated Daily Intake of Arabinose in United States                                     | 14 |
| Table | 3-3. Estimated Daily Intake of Fiber in United States and Resulting Arabinose Intakes (g/day) | 15 |
|       | 3-4. EDIs for Substances Related to Arabinose   | 16 |
|       | 3-5. Proposed Uses of Betawell® Arabinose   | 17 |
|       | 3-6. Betawell® Arabinose Estimated Daily Intakes by Use Level (mg/kg-bw/day)                  | 19 |
|       | 3-7. Betawell® Arabinose Estimated Daily Intakes Comparison                                   | 24 |
|       | (90th percentile; mg/kg-bw/day)   | 24 |
| Table | 3-8. Betawell® Arabinose Estimated Daily Intakes Comparison                                   | 29 |
|       | 6-1. Summary of Studies Regarding L-Arabinose in Humans                                       | 49 |
|       | 6-2. Summary of Studies Regarding Arabinose in Animal and In Vitro Models                     | 56 |







# **LIST OF FIGURES**

| Figure 2-1. Structural Formulas of Betawell® Arabinose and Related Sugars | 5 |
|---|---|
| Figure 2-2. Betawell® Arabinose Manufacturing Process                     | 7 |

# **APPENDICES**

| Appendix A | Specifications and Batch Data       |
|------------|-------------------------------------|
| Appendix B | Residuals and Contaminants Analyses |
| Appendix C | Toxicological Studies               |
| Appendix D | Selected Food Codes and Categories  |
| Appendix E | Reference Literature                |
| Appendix F | GRAS Expert Panel Report            |



# **Acronyms and Abbreviations**

ADME Absorption, distribution, metabolism, and excretion

ATP adenosine triphosphate

bw body weight C celcius

CASRN Chemical Abstracts Service Registry Number

CDC Center for Disease Control

cEDI cumulative estimated daily intake

CFR Code of Federal Regulations

cGMP Current Good Manufacturing Practice

cm centimeter(s)

EAFUS Everything Added to Food in the United States

EC European Commission
EDI estimated daily intake

f female

FDA Food and Drug Administration

FEMA Flavor & Extract Manufacturers Association
FFDCA Federal Food, Drug, and Cosmetic Act

FNU Formazin Nephelometric Units
FOIA Freedom of Information Act
FOSHU Food for Specified Health Uses

FSANZ Food Standards Australia New Zealand

g gram(s)

g/p/d gram(s) per person per day

GI gastrointestinal

GLP Good Laboratory Practice
GRAS Generally Recognized as Safe

GRN GRAS Notification

HDL high-density lipoprotein HFHS high-fat high-sucrose

ICP-MS inductively coupled plasma mass spectrometry

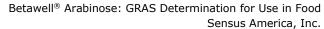
IOM Institute of Medicine

ISO International Organization for Standardization

IUCLID International Uniform Chemical Information Database
IUPAC International Union of Pure and Applied Chemistry
JECFA Joint FAO/WHO Expert Committee on Food Additives

kg kilogram(s)

LDL low-density lipoprotein



V



μg microgram(s)

m male

mg milligram(s)

mg/kg-bw/d milligram(s) per kilogram of body weight per day

mL milliliter(s)
mol mole(s)

mRNA messenger ribonucleic acid

n sample sizeN/A not applicableNA not available

NHANES National Health and Nutrition Examination Survey

NOAEL no-observed-adverse-effect-levels

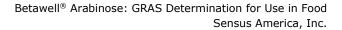
OECD Organization for Economic Co-operation and Development

PAD pulsed amperometric detection
PADI possible average daily intake

ppm parts per million

SMILES simplified molecular-input line-entry system

y year(s)





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# 1 Signed Statements and Certification of Conformity

(in accordance with 21 CFR §170.220-§170.255)

#### 1.1 Submission of GRAS Notice

Sensus America Inc. (Sensus), a part of the Royal Cosun group, in cooperation with Cosun Biobased Products B.V. (Cosun), also a part of the Royal Cosun group, is hereby submitting a Generally Recognized as Safe (GRAS) notice in accordance with subpart E of 21 CFR §170.220 - §170.255. Note that the original development and safety assessment for the ingredient was prepared under the direction of Cosun and references to Cosun are present throughout this document and the supporting documents (appendices). Throughout this document, "Sensus" refers to one or all of these business entities.

# 1.2 Name and Address of the Sponsor

Carl Volz General Manager

Sensus America Inc.

Princeton Pike Corporate Center 100 Lenox Drive, Suite 104 Lawrenceville, NJ 08648, USA

Tel: +16464526142 Email: <u>carl.volz@sensus.us</u>

#### 1.3 Name of the Notified Substance

The manufacturer's trade name for this substance is "Betawell® Arabinose." Synonyms include Betawell® beet root extract, Betawell® beet pulp extract, Betawell® beet pectin extract, L-arabinose, and pectinose.

#### 1.4 Intended Conditions of Use

Betawell® Arabinose will be added in the following foods and beverages for consumption by the general population at levels of 0.1% to 10% by weight: baked goods and baking mixes, beverages and bars (energy, snack, and sports nutrition), cereal-based products, confectionary and frostings, chewing gum, condiments, dairy products (frozen desserts, ice creams and yogurts), desserts (gelatins, puddings, etc.), fruit and water ices, spreads, snack foods, sweet sauces and syrups. The intended technical effects of the L-arabinose are as a nonnutritive sweetener and to reduce the bioavailability of sucrose.

#### 1.5 Basis for GRAS Determination

This GRAS determination is based upon scientific procedures as described under 21 CFR §170.30(b). The use of L-arabinose as an ingredient in foods at the levels described above has been shown to be safe and GRAS, using scientific procedures, under the Federal Food, Drug, and Cosmetic Act (FFDCA), Section 201(s). To demonstrate that the L-arabinose product is safe, and GRAS, under the intended conditions of use, the safety of the proposed intake of L-arabinose has been reviewed by experts qualified by both scientific training and experience to evaluate the safety of substances directly added to food, and is based on generally available and accepted information.



Determination of the GRAS status of Betawell® Arabinose (L-arabinose), under the intended conditions of use, has been made through the deliberations of Joseph F. Borzelleca, Ph.D. (Professor Emeritus, Virginia Commonwealth University School of Medicine); Judith K. Jones, M.D., Ph.D. (President and CEO, The Degge Group, Ltd. and President, Pharmaceutical Education & Research Institute), and John A. Thomas, Ph.D., ATS (Adjunct Professor, Department of Pharmacology & Toxicology, Indiana University School of Medicine). These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. These experts, independently and collectively, carefully and critically reviewed and evaluated the information contained in and referenced in this document prepared by Ramboll Environ US Corporation (since January 1, 2018, now named Ramboll US Corporation (Ramboll)). This document incorporates publicly available information regarding the safety of Betawell® Arabinose (L-arabinose) including toxicological studies, supporting data from Sensus, and estimates of the potential human exposure to L-arabinose resulting from its intended use as a food ingredient.

The experts concluded that the proposed uses of Betawell® Arabinose (L-arabinose) in term infant and toddler formulas and in food for general population are GRAS based on scientific procedures. Therefore, Betawell® Arabinose (L-arabinose) is GRAS at the proposed levels of inclusion in term infant food, toddler food, and food for general population, and thus, is excluded from the definition of a food additive, and may be used in the U.S. without the promulgation of a food additive regulation by the FDA under 21 CFR.

# 1.6 Premarket Approval Requirements

Betawell® Arabinose is not subject to the premarket approval requirements of the FFDCA based on Ramboll's conclusion that the substance is GRAS under the intended use conditions.

# 1.7 Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the U.S. FDA upon request, or will be made available to FDA for reviewing and copying at reasonable times at the office of Gavin P. Thompson, Ph.D., Principal Consultant, Ramboll U.S. Corporation, 2111 East Highland Avenue, Suite 402, Phoenix, Arizona, 85016 or 4350 North Fairfax Drive, Suite 300, Arlington, Virginia 22203; telephone: +1 602-734-7704; facsimile: +1 602-734-7701; e-mail: gthompson@ramboll.com.

# 1.8 Freedom of Information Act (FOIA)

Parts 2 through 7 of this GRAS notification do not contain data or information that is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552 (FOIA).

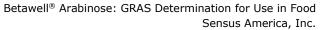
#### 1.9 Information Included in the GRAS Notification

To the best of our knowledge, the information and data contained in this GRAS notification is complete, representative, and balanced. It contains both favorable and unfavorable information, known to Sensus and pertinent to the evaluation of the safety and GRAS status of the intended use of this substance.



| Sensus America, Inc. hereby makes this notice of a GRAS Exemption Claim for the food   |
|--|
| ingredient, Betawell® Arabinose (L-arabinose), under the intended conditions of use as |
| described herein.  |

| (b) (6)             | 4/26/18 |
|---------------------|---------|
| Carl Volz           | Date    |
| General Manager     |         |
| Sensus America Inc. |         |







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# 2 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect (in accordance with 21 CRF§170.230)

# 2.1 Identity

The subject of this GRAS notification is L-arabinose, a pentose (five carbon or C5) sugar commonly found in the pectin and hemicellulose of plants and fruits.

The International Uniform Chemical Information Database (IUCLID) name for arabinose is L-arabinose. The International Union of Pure and Applied Chemistry (IUPAC) name is (2R,3S,4S)-2,3,4,5-tetrahydroxypentanal. The manufacturer's trade name for this substance is "Betawell® Arabinose." Synonyms include Betawell® beet root extract, Betawell® beet pulp extract, Betawell® beet pectin extract, L-arabinose, and pectinose.

The Chemical Abstracts Service Registry Number (CASRN) for arabinose is 5328-37-0. The European Community (EC) Number is 226-214-6. The PubChem compound identification number is 5460291.

The empirical formula for Betawell® Arabinose is  $C_5H_{10}O_5$  and the structure is provided in Figure 2-1. The simplified molecular-input line-entry system (SMILES) notation for arabinose is O=CC(O)C(O)C(O)CO.

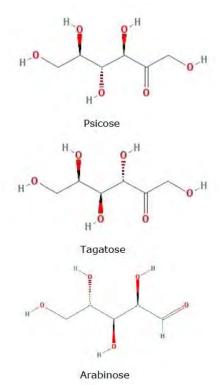


Figure 2-1. Structural Formulas of Betawell® Arabinose and Related Sugars



# 2.2 Description of Betawell® Arabinose

L-Arabinose is a ubiquitous sugar that occurs in common foods both as a monosaccharide and as a component of polysaccharides. Sensus' Betawell® Arabinose is composed of L-arabinose manufactured from sugar beet fiber, a GRAS substance. Betawell® Arabinose is produced from sugar beets grown in the Netherlands and Germany. Betawell® Arabinose is a water-soluble, white, crystalline, sweet tasting powder. Specific physical and chemical properties are described in Table 2-1.

| Table 2-1. Physical and Chemical Properties   |                           |  |  |  |  |  |
|---|---------------------------|--|--|--|--|--|
| Parameter   | Betawell® Arabinose       |  |  |  |  |  |
| Molecular Weight<br>(g/mol)   | 150.1ª                    |  |  |  |  |  |
| Color   | White <sup>a</sup>        |  |  |  |  |  |
| Sugar content (%)   | NA                        |  |  |  |  |  |
| Degree of polymerization  | NA                        |  |  |  |  |  |
| Taste   | Sweet <sup>a</sup>        |  |  |  |  |  |
| Odor  | NA                        |  |  |  |  |  |
| Density (g/cm³)   | NA                        |  |  |  |  |  |
| Melting Point (°C)  | 159.5 °C⁵                 |  |  |  |  |  |
| Solubility in water   | Very soluble <sup>b</sup> |  |  |  |  |  |
| Notes and Abbreviations:  C = celcius; cm = centimeter(s); g = gram(s);  mol = mole(s); NA = Not available.  Sources:  a Sensus America, Inc. b Burdock, 2009 |                           |  |  |  |  |  |

# 2.3 Manufacturing Process

Betawell® Arabinose is manufactured by Sensus B.V. in the Netherlands.

The L-arabinose feed material is sugar beet pulp sourced directly from the sugar mill. The process starts with hydrolysis of the pulp. The remaining solid material is removed by a decanter centrifuge resulting in a hydrolysate.

The hydrolysate is filtered several times to separate the arabinose from the other carbohydrates. The product is a diluted syrup with a high relative L-arabinose content. The syrup is further purified by first removing organic acids and salts, followed by the remaining oligosaccharides.

The syrup now contains a mixture of C5 and C6 sugars. The C6 sugars are removed by a digestion step using baker's yeast (*Saccharomyces cerevisiae*). The yeast is removed by a microfiltration step. The syrup is then heated to evaporate the liquid and subsequently cooled to form the L-arabinose crystals. This step can be repeated two or three times to optimize the production of L-arabinose. The L-arabinose crystals are centrifuged and dried. After a grinding step to remove solid particles and lumps, the L-arabinose is packaged in food approved bags and/or bag in boxes. This manufacturing process is depicted in Figure 2-2.



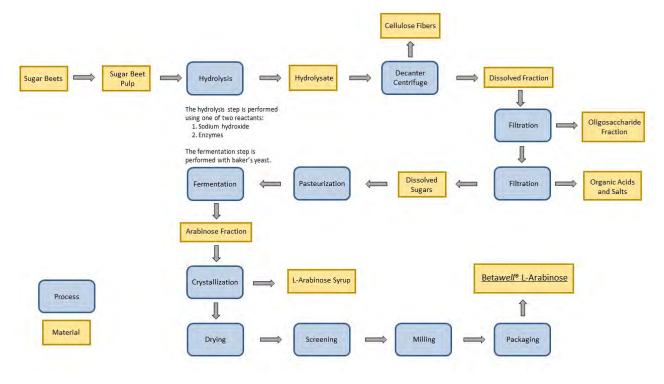


Figure 2-2. Betawell® Arabinose Manufacturing Process

# 2.4 Specifications for Food-Grade Material

# 2.4.1 Batch Analysis Results

Sensus analyzed three typical batches to ensure a consistent product compliant with their specifications is generated (Table 2-2 and Appendix A).

# 2.4.2 Residual Impurities

Sensus analyzed for the following types of impurities: Metals, microbial contaminants, residual pesticides (Table 2-2 and Appendix B).

# 2.4.3 Stability

Sensus states that Betawell $^{\otimes}$  Arabinose has a shelf life of 24 months when stored in dry conditions out of sunlight. The data in Table 2-3 support this claim.



|                                  |               | Alkaline Process |        |        | Enzymatic Process |        |        | Analytical |                  |
|----------------------------------|---------------|------------------|--------|--------|-------------------|--------|--------|------------|------------------|
| Parameter                        | Specification | Units            | C61-1  | C62-1  | C65-1             | C7-1   | C12-1  | C15-1      | Method           |
| Arabinose                        | ≥99.0         | wt%              | >99.5  | >99.9  | >99.9             | 99.8   | 99.5   | >99.0      | Dionex-PAD       |
| Fucose                           |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.01   | < 0.01     | Dionex-PAD       |
| Rhamnose                         |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.12   | 0.07       | Dionex-PAD       |
| Galactose                        |               | wt%              | 0.13   | < 0.01 | 0.03              | < 0.1  | 0.03   | 0.01       | Dionex-PAD       |
| Glucose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Mannose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Xylose                           |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.06   | 0.03       | Dionex-PAD       |
| Fructose                         |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Sucrose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Other saccharides, total         | 1.0           | wt%              | < 1.0  | < 1.0  | < 1.0             | 0.1    | 0.22   | 0.11       | Dionex-PAD       |
| Galacturonic acid                |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Glucuronic acid                  |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01 | < 0.01     | Dionex-PAD       |
| Dry matter                       | ≥99.0         | wt%              | 99.9   | 99.95  | 99.98             |        |        | 99.8       | 3 hours 105 °C   |
| APHA color                       |               | hazen            | 0      | <1     | 0                 | -      |        |            | 10% Solution     |
| Moisture                         | 0.3           | wt%              |        |        |                   | 0.1    | 0.22   | 0.11       |                  |
| Turbidity                        |               | FNU              | 2.7    | 1.50   | 1.2               | -      |        |            | 10% Solution     |
| Microbiological                  |               |                  |        |        |                   |        |        |            |                  |
| Aerobic plate count 30°C         | ≤1000         | cfu/g            | 32     | 7      | 6                 | 0      | 25     | 2.5        | ISO 4833:2003    |
| Molds                            | ≤20           | cfu/g            | 0      | 0      | 0                 | 0      | 2.5    | 0          | ISO 7954:1987    |
| Yeasts                           | ≤20           | cfu/g            | 0      | 0      | 0                 | 0      | 0      | 0          | ISO 7954:1987    |
| Clostridium perfringens / 10 g   | Absent        | cfu/g            | 0      | 0      | 0                 | 0      | 0      | 0          | ISO 7937:2004    |
| Listeria / 10 g                  | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 11290-1:1997 |
| Bacillus cereus                  | ≤100          | cfu/g            | 0      | 0      | 0                 | 0      | 0      | 0          | ISO 7932:2004    |
| Staph. aureus / g                | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 6888-3:2003  |
| Enterobacteriaceae (kwal) / 10 g | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 21528-1:2004 |
| Salmonella / 10 g                | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 6579:2002    |
| E. coli / 10 g                   | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 16649-2:200  |
| Coliforms / 10 g                 | Absent        | cfu/g            | Absent | Absent | Absent            | Absent | Absent | Absent     | ISO 4832:2006    |
| Fecal Streptococci               | Absent        | cfu/g            | <10    | <10    | <10               | Absent | Absent | Absent     | KF Agar Method   |



| Table 2-2. Betawell <sup>®</sup> Arabinose Product Specifications and Batch Data |               |        |         |           |         |                   |         |         |                 |
|--|---------------|--------|---------|-----------|---------|-------------------|---------|---------|-----------------|
|  |               |        | Alkalin | e Process |         | Enzymatic Process |         |         | Analytical      |
| Parameter  | Specification | Units  | C61-1   | C62-1     | C65-1   | C7-1              | C12-1   | C15-1   | Method          |
| Cronobacter sakazakii / 10 g   | Absent        | cfu/g  | Absent  | Absent    | Absent  | Absent            | Absent  | Absent  | ISO 22964:2006  |
| Metals   |               |        |         |           |         |                   |         |         |                 |
| Antimony   |               | cfu/g  | < 0.005 | < 0.005   | < 0.005 | < 0.005           | < 0.005 | < 0.005 | ICP-MS          |
| Arsenic  |               | mg/kg  | < 0.01  | < 0.01    | < 0.01  | < 0.01            | < 0.01  | < 0.01  | ICP-MS          |
| Cadmium  |               | mg/kg  | < 0.005 | < 0.005   | < 0.005 | <0.005            | < 0.005 | < 0.005 | ICP-MS          |
| Copper   |               | mg/kg  | 0.066   | 0.02      | 0.027   | 0.011             | 0.11    | 0.03    | ICP-MS          |
| Lead   |               | mg/kg  | < 0.01  | < 0.01    | < 0.01  | < 0.01            | < 0.01  | < 0.01  | ICP-MS          |
| Mercury  |               | μg/kg  | < 0.5   | < 0.5     | < 0.5   | <0.5              | < 0.5   | < 0.5   | ICP-MS          |
| Molybdenum   |               | μg/kg  | < 0.01  | < 0.01    | 0.03    | 0.01              | < 0.01  | 0.03    | ICP-MS          |
| Tin  |               | mg/kg  | < 0.01  | < 0.01    | < 0.01  | < 0.01            | < 0.01  | < 0.01  | ICP-MS          |
| Bismuth  |               | mg/kg  | < 0.2   | <0.2      | <0.2    | <0.2              | <0.2    | <0.2    | Analog §64 LFGB |
| Silver   |               | mg/kg  | < 0.05  | < 0.05    | < 0.05  | < 0.05            | < 0.05  | < 0.05  | Analog §64 LFGB |
| Total metals   | < 0.3         | mg/kg  | < 0.3   | < 0.3     | < 0.3   | 0.21              | 0.11    | 0.06    | NA              |
| Other Toxins   |               |        |         |           |         |                   |         |         |                 |
| Aflatoxin B1   | < 0.05        | μg/kg  | < 0.05  | < 0.05    | < 0.05  | <0.05             | <0.05   | <0.05   | IM W8333        |
| Aflatoxin B2   | < 0.02        | μg/kg  | < 0.02  | < 0.02    | < 0.02  | < 0.02            | < 0.02  | < 0.02  | IM W8333        |
| Aflatoxin G1   | <0.05         | μg/kg  | < 0.05  | <0.05     | < 0.05  | <0.05             | <0.05   | <0.05   | IM W8333        |
| Aflatoxin G2   | < 0.03        | μg/kg  | < 0.03  | < 0.03    | < 0.03  | <0.03             | < 0.03  | <0.03   | IM W8333        |
| Aflatoxins Total   | < 0.15        | μg/kg  | < 0.15  | <0.15     | < 0.15  | <0.15             | <0.15   | <0.15   | IM W8333        |
| Pesticides (see Appendix B)  | Various       | Variou | Meets   | Meets     | Meets   | Meets             | Meets   | Meets   | Various         |

Notes and Abbreviations:

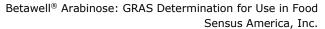
<sup>-- =</sup> not provided or not available; cfu = colony forming units; g = gram(s); ICP-MS = inductively coupled plasma mass spectrometry; IM = Internal Method; kg = kilogram(s); μg = microgram(s); mg = milligram(s); NA = Not Applicable; ND = not detected.



| Table 2-3. Betawell® Arabinose Storage Stability Analysis |                |              |              |                        |  |  |  |
|---|----------------|--------------|--------------|------------------------|--|--|--|
|   | Batch Results  |              |              |                        |  |  |  |
|   |                | C7-1         | C7-1         |                        |  |  |  |
| Parameter   | Units          | 7-11-2012    | 4-11-2016    | Analytical Method      |  |  |  |
| Physical/Chemical Properties                              |                |              |              |                        |  |  |  |
| Arabinose   | %              | 99.9         | 99.8         | Dionex-PAD             |  |  |  |
| Fucose  | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Rhamnose  | %              | 0.01         | 0.01         | Dionex-PAD             |  |  |  |
| Galactose   | %              | 0.04         | 0.04         | Dionex-PAD             |  |  |  |
| Glucose   | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Mannose   | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Xylose  | %              | 0.03         | 0.03         | Dionex-PAD             |  |  |  |
| Fructose  | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Sucrose   | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Galacturonic acid   | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Glucuronic acid   | %              | < 0.01       | < 0.01       | Dionex-PAD             |  |  |  |
| Dry matter  | %<br>          | 99.9         | 99.9         | 3 hours 105 °C         |  |  |  |
| Apha color (Hazen)  | Hazen          | 0            | 0            | 10% solution           |  |  |  |
| Turbidity (FNU)   | FNU            | <1<br><0.005 | <1<br><0.005 | 10% solution<br>ICP-MS |  |  |  |
| Antimony<br>Arsenic                                       | mg/kg          | <0.003       | < 0.005      | ICP-MS                 |  |  |  |
| Cadmium   | mg/kg<br>mg/kg | <0.01        | <0.005       | ICP-MS                 |  |  |  |
| Copper  | mg/kg          | 0.011        | 0.011        | ICP-MS                 |  |  |  |
| Lead  | mg/kg          | < 0.011      | < 0.011      | ICP-MS                 |  |  |  |
| Mercury   | μg/kg          | <0.5         | <0.5         | ICP-MS                 |  |  |  |
| Molybdenum  | mg/kg          | <0.01        | < 0.01       | ICP-MS                 |  |  |  |
| Tin   | mg/kg          | <0.01        | < 0.01       | ICP-MS                 |  |  |  |
| Bismuth   | mg/kg          | <0.2         | <0.2         | Analog §64 LFGB        |  |  |  |
| Silver  |                | < 0.05       | < 0.05       | = -                    |  |  |  |
|   | mg/kg          | <0.03        | <0.03        | Analog §64 LFGB        |  |  |  |
| Microbiological Components                                |                |              |              |                        |  |  |  |
| Aerobic plate count 30 °C / 10 g                          | cfu/g          | <1000        | <1000        | ISO 4833:2003          |  |  |  |
| Molds / 10 g  | cfu/g          | 0            | 0            | ISO 7954:1987          |  |  |  |
| Yeasts / 10 g   | cfu/g          | <20 CFU/g    | <20 CFU/g    | ISO 7954:1987          |  |  |  |
| Clostridium perfringens / 10 g                            | cfu/g          | <20 CFU/g    | <20 CFU/g    | ISO 7937:2004          |  |  |  |
| Listeria / 10 g   | cfu/g          | Absent       | Absent       | ISO 11290-1:1997       |  |  |  |
| Bacillus cereus / g                                       | cfu/g          | <100 CFU/g   | <100 CFU/g   | ISO 7932:2004          |  |  |  |
| Staph. aureus / g   | cfu/g          | Absent       | Absent       | ISO 6888-3 :2003       |  |  |  |
| Enterobacteriaceae (kwal) / 10 g                          | cfu/g          | Absent       | Absent       | ISO 21528-1:2004       |  |  |  |
| Salmonella / 10 g   | cfu/g<br>cfu/g | Absent       | Absent       | ISO 6579:2002          |  |  |  |
| E. coli / 10 g  | cfu/g<br>cfu/g | Absent       | Absent       | ISO 16649-2:2001       |  |  |  |
| Coliforms / 10 g  | cfu/g<br>cfu/g | Absent       | Absent       | ISO 4832:2006          |  |  |  |
| Cronobacter sakazakii                                     | cfu/g<br>cfu/g | Absent       | Absent       | ISO 22964:2006         |  |  |  |
| Fecal Streptococci  | cfu/g          | Absent       | Absent       | KG agar method         |  |  |  |
| Aflatoxin B1  | μg/kg          | < 0.05       | < 0.05       | IM W8333               |  |  |  |
| Aflatoxin B2  | μg/kg          | < 0.02       | <0.02        | IM W8333               |  |  |  |
| Aflatoxin G1  | μg/kg          | < 0.05       | < 0.05       | IM W8333               |  |  |  |
| Aflatoxin G2  | μg/kg          | < 0.03       | < 0.03       | IM W8333               |  |  |  |
| Aflatoxins Total  | μg/kg          | < 0.15       | <0.15        | IM W8333               |  |  |  |
| Notes and Abbreviations:                                  | , ,, ,         | -            |              |                        |  |  |  |

Notes and Abbreviations:

cfu = colony forming units; FNU = Formazin Nephelometric Units; g = gram(s); ICP-MS = inductively coupled plasma mass spectrometry; ISO = International Organization for Standardization; kg = kilogram(s);  $\mu = microgram(s)$ ;  $\mu = microgram(s)$ 



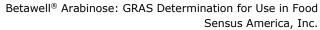
11



# 2.4.4 Section 2 Summary

Sensus provided a detailed description of their Betawell® Arabinose product and also provided a detailed illustration of the manufacturing process. The manufacturing process does not use organic solvents or highly toxic chemicals. Sensus demonstrated and confirmed the purity of the product and its manufacturing consistency by meeting specifications with six unique production batches as demonstrated in the certificates of analysis.

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# 3 Dietary Exposure (in accordance with 21 CFR §170.235)

# 3.1 Intended Effect

The intended technical effects of the L-arabinose are as a nonnutritive sweetener and to reduce the bioavailability of sucrose.

The intended technical effect of Betawell® Arabinose may be in accordance with the following regulatory terms:

21 CFR 170.3(o)(19) - as a nonnutritive sweetening substance having less than two percent of the caloric value of sucrose per equivalent unit of sweetening capacity, or

21 CFR 170.3(o)(31) – as a synergist used to act or react with another food ingredient to produce a total effect different or greater than the sum of the effects produced by the individual ingredients. That is, the arabinose would act with sucrose to produce the effect of reduced or delayed sucrose uptake.

### 3.2 Uses of Arabinose

Uses of arabinose reported by the Flavor & Extract Manufacturers Association (FEMA) are listed in Table 3-1. FEMA reported individual intake of arabinose to be 0.03 mg/kg/day and a possible average daily intake (PADI) to be 38.6 mg based on the known uses.

| Table 3-1. Uses of Arabinose Reported by FEMA |                     |                      |  |  |  |  |  |
|---|---------------------|----------------------|--|--|--|--|--|
|   | Usual concentration | Maximum              |  |  |  |  |  |
| Food Category                                 | (wt %)              | concentration (wt %) |  |  |  |  |  |
| Baked goods                                   | 0.015               | 0.045                |  |  |  |  |  |
| Condiments, relishes                          | 0.0075              | 0.045                |  |  |  |  |  |
| Jams, jellies                                 | 0.015               | 0.045                |  |  |  |  |  |
| Nonalcoholic beverages                        | 0.015               | 0.045                |  |  |  |  |  |
| Soft candy                                    | 0.015               | 0.045                |  |  |  |  |  |
| Source: Burdock, 2009.                        |                     |                      |  |  |  |  |  |

Arabinose is also used as an ingredient in dietary supplements. Pharmachem Laboratories, Inc. (Pharmachem) produces a supplement called Prenulin that contains L-arabinose and is intended to function as a "Sugar Blocker." The Pharmachem L-arabinose is derived from corn and, according to the website, the substance is GRAS. The basis for this determination is not publicly available. The scientific studies cited in the Prenulin Science Dossier (Pharmachem 2013) are Preuss et al. (2007a), Osaki et al. (2001), and Seri et al. (1996). These studies are reviewed in Section 6. The supplement label for Prenulin recommends two 950 mg of L-arabinose daily for an EDI of 1900 mg L-arabinose from Prenulin. Ramboll did not identify any reports of adverse events for "Prenulin" or "arabinose" in the FDA CFSAN Adverse Event Reporting System data from 2004-2016, inclusive.<sup>2</sup>

<sup>&</sup>lt;sup>1</sup> http://www.pharmachemlabs.com/about/our-brands; http://www.prenulininfo.com/

<sup>&</sup>lt;sup>2</sup> http://www.fda.gov/Food/ComplianceEnforcement/ucm494015.htm; accessed 2-13-2017.



# 3.3 Exposure to Arabinose from the Diet

Arabinose is found as sugar residues in wheat bran, rye bran, potatoes, carrots, peas, white cabbage, lettuce, and apples as residues of the pectin (Spiller, 2001). Arabinose is a component of gum arabic with molar ratios of 0.73-16.2 mol arabinose/mol acacia gum, varying by species of *Acacia* (Whistler, 1973). Due to the natural occurrence of arabinose in plants and fruits and as a component of pectins, exposure to arabinose from the diet is expected but an estimated daily intake (EDI) has not been established in the scientific literature.

Ramboll prepared an estimate of the average dietary intake of arabinose based on the National Health and Nutrition Examination Survey (NHANES) and the existing body of scientific knowledge of the natural occurrence of arabinose. Table 3-2 provides a summary of this EDI of arabinose in the United States for various age groups.

| Age Group                   | Free Arabinose<br>(mg/kg-bw/day) | Arabinose in<br>Dietary Fiber<br>(mg/kg-bw/day) | Total Arabinose<br>(mg/kg-bw/day) |
|-----------------------------|----------------------------------|---|-----------------------------------|
| Infants, < 12 mo            | 29                               | 77  | 106                               |
| Infants, 12-23 mo           | 41                               | 108   | 149                               |
| Toddlers, 2-5 y             | 38                               | 100   | 138                               |
| Males, 6-11 y               | 24                               | 64  | 88                                |
| Females, 6-11 y             | 23                               | 59  | 82                                |
| Males, 12-18 y              | 13                               | 35  | 48                                |
| Females, 12-18 y            | 12                               | 30  | 42                                |
| Males, 19-49 y              | 12                               | 32  | 44                                |
| Females, 19-49 y            | 11                               | 30  | 41                                |
| Males, 50+ y                | 12                               | 30  | 42                                |
| Females, 50+ y              | 12                               | 31  | 44                                |
| Pregnant or lactating women | 14                               | 36  | 50                                |

mg/kg-bw/day = milligrams per kilogram of body weight per day; mo = month(s); y = year(s).

The estimates for free arabinose intakes were calculated based on the average daily consumption of foods containing free arabinose: beer, tea, instant coffee, red wine, rice wine, fruit wine, and soy sauce.<sup>3</sup> For arabinose intake sourced from dietary fiber, the foods considered were barley, oats, rice, rye, wheat, peas, potatoes, carrots, apples, bananas, cabbage, and lettuce. The intakes were calculated by first averaging the percent concentrations of naturally occurring arabinose in the fibers of these foods, and then applying this percent to the average total daily dietary fiber intake for each age group.

Most Americans, however, consume well below the amount of fiber considered adequate by the Institute of Medicine (IOM), even at the 90<sup>th</sup> percentile of fiber intake (Table 3-3). If fiber were consumed at the level the IOM deems adequate, then arabinose intake, as a portion of

<sup>&</sup>lt;sup>3</sup> Flavored teas account for the free arabinose intake of infants.



that fiber, would be up to 5.1 grams of arabinose per person per day. This is based on an average arabinose content of approximately 13.5% arabinose in fibers (Stephen, 2009).

Table 3-3. Estimated Daily Intake of Fiber in United States and Resulting Arabinose Intakes (q/day)

| 711 de moss man             |      | Tota | Arabinose                 |                    |                     |
|-----------------------------|------|------|---------------------------|--------------------|---------------------|
| Age Group                   | n    | Mean | 90 <sup>th</sup><br>%Tile | Adequate<br>Intake | Intake <sup>2</sup> |
| Infants, 12-23 mo           | 464  | 9    | 22                        | 19                 | 2.6                 |
| Toddlers, 2-5 y             | 1685 | 12   | 22                        | 25                 | 3.4                 |
| Males, 6-11 y               | 1174 | 15   | 25                        | 31                 | 4.2                 |
| Females, 6-11 y             | 1120 | 14   | 20                        | 26                 | 3.5                 |
| Males, 12-18 y              | 1083 | 16   | 33                        | 38                 | 5.1                 |
| Females, 12-18 y            | 1008 | 13   | 26                        | 26                 | 3.5                 |
| Males, 19-49 y              | 2793 | 19   | 31                        | 38                 | 5.1                 |
| Females, 19-49 y            | 2929 | 15   | 26                        | 25                 | 3.4                 |
| Males, 50+ y                | 2510 | 19   | 31                        | 21                 | 2.8                 |
| Females, 50+ y              | 2535 | 16   | 26                        | 21                 | 2.8                 |
| Pregnant or lactating women | 137  | 19   | 30                        | 28                 | 3.8                 |

Notes and Abbreviations:

g = gram(s); mo = month(s); n = sample size; NA = not available; y = year(s).

Consumption data from NHANES 2009-2012, two day averages where both days were recorded, and one day value where only one day was recorded.

<sup>1</sup>Total Fiber; IOM. 2005. Dietary reference intakes for energy, carbohydrate, fiber, fact, fatty acids, cholesterol, protein, and amino acids. Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. National Academies Press, Washington DC.

<sup>2</sup>Based on the daily intakes and average arabinose content of the fiber (13.5%) in barley, oats, rice, rye, wheat, dried peas, potatoes, carrots, apples, bananas, cabbage, and lettuce. Source: Food Polysaccharides and Their Applications. Second Edition. Alistair M. Stephen. 2009.

# 3.4 Approved Food Additive Uses

### 3.4.1 United States Regulations

Betawell® Arabinose is derived from sugar beet fiber. Sugar beet fiber is a GRAS substance for use in "various non-standardized meat and poultry products as a binder and texturizing agent, in bakery products as a binder and source of fiber, in cereals and muesli as a texturizing agent and source of fiber, in sauces as a thickening agent, and in cheese as an anti-caking and/or dispersing agent" according to GRAS notification (GRN) 430.

#### 3.4.2 Related Substances

There are several closely related substances for which GRNs have been submitted. These include D-ribose, a C5 sugar very similar to arabinose, D-tagatose, an epimer of D-fructose isomerized at C-4, and D-psicose, an epimer of D-fructose isomerized at C-3. D-Ribose is the subject of GRN 243, D-tagatose is the subject of GRNs 78 and 352 and D-psicose is the



subject of GRNs 400 and 498. The EDIs for these substances range from approximately 4.5 to 30 grams per person per day (g/p/d) (Table 3-4). These substances are very similar to L-arabinose in both structure and proposed uses and are recognized for their safety as food ingredients.

| GRN | Substance           | Formula                                       | Uses  | EDI<br>(90 <sup>th</sup> percentile) |
|-----|---------------------|---|---|--------------------------------------|
| 498 | Psicose             | C <sub>6</sub> H <sub>12</sub> O <sub>6</sub> | Cereals, chewing gum, confections & frostings, salad dressings, jams & jellies, sugar, sugar substitutes (carrier), and various low-calorie or dietetic foods including low-calorie, reduced-calorie, sugar-free beverages (non-alcoholic), cereals, frozen dairy desserts, yogurt (inc. frozen) gelatins, pudding & fillings, hard & soft candies, and sweet sauces & syrups.  | 30.4 g/p/d                           |
| 430 | Sugar Beet<br>Fiber | N/A   | 1-5% for bread products, $1-10%$ for cereals and muesli and $1-5%$ for non-standardized meat and poultry products.  | 5.5  g/p/d (0.67 g/p/d as arabinose) |
| 400 | D-Psicose           | C <sub>6</sub> H <sub>12</sub> O <sub>6</sub> | As a sugar substitute in the following food categories: rolls, cakes, pies, pastries, and cookies, dietetic or low calories, chewing gum, fat-based cream used in modified fat/calorie cookies, cakes, and pastries, hard candies-low calorie, frozen dairy desserts-low calorie, carbonated beverages-low calorie, non-carbonated beverages-reduced and low calorie, soft candies-low-calorie, sugar substitutes (carrier), yogurt (regular and frozen), low calorie, medical foods, ready-to-eat cereals (< 5 percent sugar), coffee mix. | 28.5 g/p/d                           |
| 352 | D-Tagatose          | C <sub>6</sub> H <sub>12</sub> O <sub>6</sub> | Ready-to eat breakfast cereals, soft drinks, confectionery, formula diets for meal replacement, meal replacement drink mix (powder), cake, pie, cake mix, frostings, ice cream and frozen yogurt, yogurt, frostings, chewing gum (sugar free), jelly and pudding, coffee mix powder, biscuits, cookies, and cereal bars.  | 3.9 g/p/d                            |
| 243 | D-Ribose            | C <sub>5</sub> H <sub>10</sub> O <sub>5</sub> | Non-cola carbonated beverages; meal replacements beverages and bars, ice cream and frozen milk desserts and yogurt (excluding frozen novelties), milk drinks (excluding malts, shakes), Reduced-calorie non-cola carbonated beverages, reduced-calorie fruit drinks and ades, teas, fruit nectars and juices, vegetable juice, hard & soft candies, sports and energy drinks/bars, yogurt.  | 7.2 g/p/d                            |

Arabinogalactan is permitted for direct addition to food for human consumption in the U.S. under 21 CFR §172.610. The regulation recognizes arabinogalactan as "a polysaccharide extracted by water from Western larch wood, having galactose units and arabinose units in the

approximate ratio of six to one." Arabinogalactan is permitted as a non-nutritive sweetener.

applicable.



# 3.5 Intended Uses of Betawell® Arabinose

According to information provided by Sensus, the proposed use of Betawell® Arabinose is as an additive in foods and beverages as a carbohydrate source, a partial replacement of sucrose by 2 to 30%, or as a complete replacement of other sweetening systems as an arabinose/sucrose mixture with an arabinose composition of 2-30%. Betawell® Arabinose is proposed for use in the general population in the foods and use levels shown in Table 3-5.

| Table 3-5. Proposed Uses of Betawell® Arabinose |   |                       |  |  |  |  |
|---|---|-----------------------|--|--|--|--|
|   |   | Proposed<br>Use Level |  |  |  |  |
| Food Category Baked goods, baking mixes         | Example foods Cakes, brownies, pastries, cookies  | (wt %)                |  |  |  |  |
|   |   | 0.1-10                |  |  |  |  |
| Beverages                                       | Soft drinks, energy drinks, sports and isotonic drinks, instant drink preparations and meal replacers, teas                             | 0.1-10                |  |  |  |  |
| Cereal-based products                           | Breakfast cereals, cereal bars  | 0.1-10                |  |  |  |  |
| Bars  | Breakfast bars, granola bars, energy bars, diet/meal replacement bars   | 0.1-10                |  |  |  |  |
| Chewing gum                                     |   | 0.1-10                |  |  |  |  |
| Condiments                                      | Ketchup   | 0.1-10                |  |  |  |  |
| Confectionary and frostings                     | Hard candies, soft candies, cough drops, toffees, chocolates, compressed goods, fondants, frostings, fillings, crèmes, toppings, nougat | 0.1-15                |  |  |  |  |
| Dairy products                                  | Yogurt  | 0.1-10                |  |  |  |  |
| Frozen dairy desserts                           | Ice cream and other frozen dairy dessert mixes  | 0.1-15                |  |  |  |  |
| Fruit and water ices                            |   | 0.1-15                |  |  |  |  |
| Gelatins, puddings, desserts                    |   | 0.1-10                |  |  |  |  |
| Snack foods                                     |   | 0.1-15                |  |  |  |  |
| Spreads   | Jams, jellies, nut and peanuts spreads  | 0.1-10                |  |  |  |  |
| Toppings  | Sweet sauces, syrups  | 0.1-10                |  |  |  |  |
| Others  | Sports nutrition, energy-reduced foods, meal replacement/slimming foods   | 0.1-10                |  |  |  |  |
| Source: Sensus America, Inc.                    |   |                       |  |  |  |  |



# 3.6 EDI from the Proposed Uses of Betawell® Arabinose

Estimates of potential intakes of the ingredient resulting from these intended uses (Section 3.5 and Table 3-5) were calculated using food consumption data reported in the U.S. Department of Health and Human Service's 2009-2010 and 2011-2012 National Health and Nutrition Examination Survey (NHANES). This NHANES data set provides nationally representative nutrition and health data and prevalence estimates for nutrition and health status measures in the U.S. (Center for Disease Control; CDC 2012).

During the NHANES, trained dietary interviewers collect detailed information on all foods and beverages consumed by respondents in the previous 24 hour time period (midnight to midnight). A second dietary recall is administered by telephone 3 to 10 days after the first dietary interview, but not on the same day of the week as the first interview. A total of 9,043 respondents provided complete dietary intakes for the Day 1 recall, and 8,354 of the individuals provided a complete Day 2 recall. Using the list of food codes (Appendix D) and the NHANES dietary recall data files from individuals with two complete days of dietary recall, Ramboll estimated mean and 90<sup>th</sup> percentile 2-day average intakes of the ingredient.

We assumed all the food in the specified categories contained Betawell® Arabinose at the intended use levels (as consumed). The 2-day average intakes represent the total estimated intakes of ingredient during the two days of recall divided by two (i.e., (Intake Day 1 + Intake Day 2)/2). Because this is a daily average, some participants who had Day 1 but not Day 2 data are included using a single day of consumption. Intakes were calculated for fourteen subpopulations (separated by male and female for ages 2+): infants < 12 months, infants and toddlers 12-23 months, children 2-5 years, children 6-11 years, teens 12-18 years, adults 19-49 years, and adults 50+ years, as well as pregnant and lactating women. The estimates were generated using survey sample weights to adjust for differences in representation of subpopulations; results are therefore representative of the U.S. population.

Notably, the EDIs can be skewed high when applying the incorporation by weight to the beverages category (Table 3-5). To address this, we also evaluated the NHANES data based on the sucrose content of the foods and assumed the maximum use level of 30% replacement of sucrose by Betawell® Arabinose (Table 3-7). This approach addresses the beverages category more accurately while remaining relatively consistent with the use level by weight approach used with the other food categories. The results of both analyses are provided herein for comparison.

The EDIs for Betawell® Arabinose range from a mean of 290 mg/kg-bw/day to 1500 mg/kg-bw/day at the 90<sup>th</sup> percentile in the infant population when evaluated by the maximum use levels across all food categories and assuming all users are consuming foods in all categories (Table 3-6). These intakes are largely the result of the beverages category and the evaluation by weight noted above. Betawell® Arabinose is intended for adults limiting their sucrose intake by the use of "low sugar," "energy," and "sports nutrition" foods and beverages. Such foods are unlikely to be purchased for or consumed by infants. When the EDIs are calculated by replacement of sucrose rather than use level by weight percent, they range from 202 – 684 mg Betawell® Arabinose/kg-bw/day at the 90<sup>th</sup> percentile across all populations evaluated and again assuming the maximum sucrose replacement level of 30% (Table 3-7).



| Age Group                  | n    | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile |
|----------------------------|------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|
| Baked Goods                |      | 0.1                     |      |                           | 5                       |      |                           | 10                      |      |                           |
| Infants, < 12 mo           | 48   |                         | 2    | 4                         |                         | 100  | 203                       |                         | 200  | 406                       |
| Infants, 12-23 mo          | 178  |                         | 3    | 6                         |                         | 147  | 297                       |                         | 293  | 594                       |
| Toddlers, 2-5 y            | 723  |                         | 2    | 4                         |                         | 108  | 206                       |                         | 216  | 412                       |
| Males, 6-11 y              | 515  |                         | 2    | 3                         |                         | 80   | 146                       |                         | 160  | 293                       |
| Females, 6-11 y            | 491  |                         | 1    | 3                         |                         | 69   | 136                       |                         | 138  | 272                       |
| Males, 12-18 y             | 420  |                         | 1    | 2                         |                         | 47   | 92                        |                         | 94   | 185                       |
| Females, 12-18 y           | 393  |                         | 1    | 2                         |                         | 45   | 104                       |                         | 91   | 208                       |
| Males, 19-49 y             | 841  |                         | 1    | 1                         |                         | 35   | 69                        |                         | 71   | 138                       |
| Females, 19-49 y           | 999  |                         | 1    | 1                         |                         | 33   | 65                        |                         | 67   | 129                       |
| Males, 50+ y               | 1001 |                         | 1    | 1                         |                         | 32   | 64                        |                         | 64   | 127                       |
| Females, 50+ y             | 981  |                         | 1    | 1                         |                         | 30   | 55                        |                         | 59   | 111                       |
| regnant or lactating women | 54   |                         | 1    | 1                         |                         | 37   | 66                        |                         | 75   | 132                       |
| Beverages <sup>2</sup>     |      | 0.1                     |      |                           | 5                       |      |                           | 10                      |      |                           |
| Infants, < 12 mo           | 18   |                         | 14   | 22                        |                         | 713  | 1118                      |                         | 1426 | 223                       |
| Infants, 12-23 mo          | 53   |                         | 11   | 21                        |                         | 541  | 1032                      |                         | 1082 | 206                       |
| Toddlers, 2-5 y            | 205  |                         | 12   | 24                        |                         | 609  | 1190                      |                         | 1217 | 237                       |
| Males, 6-11 y              | 192  |                         | 10   | 17                        |                         | 498  | 853                       |                         | 996  | 170                       |
| Females, 6-11 y            | 185  |                         | 8    | 15                        |                         | 425  | 750                       |                         | 849  | 1499                      |
| Males, 12-18 y             | 261  |                         | 8    | 14                        |                         | 409  | 715                       |                         | 818  | 143                       |
| Females, 12-18 y           | 254  |                         | 8    | 15                        |                         | 394  | 748                       |                         | 789  | 149                       |
| Males, 19-49 y             | 779  |                         | 7    | 12                        |                         | 353  | 613                       |                         | 705  | 122                       |
| Females, 19-49 y           | 809  |                         | 6    | 11                        |                         | 323  | 550                       |                         | 647  | 1099                      |
| Males, 50+ y               | 560  |                         | 6    | 10                        |                         | 293  | 518                       |                         | 586  | 103                       |
| Females, 50+ y             | 641  |                         | 6    | 12                        |                         | 293  | 587                       |                         | 586  | 1173                      |
| regnant or lactating women | 31   |                         | 7    | 13                        |                         | 332  | 633                       |                         | 663  | 1266                      |



| Age Group                 | n   | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile |
|---------------------------|-----|-------------------------|------|---------------------------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|
| Cereals                   |     | 0.1                     |      |                           | 5                       |      |                           | 10                      |      | _                         |
| Infants, < 12 mo          | 20  |                         | 2    | 2                         |                         | 78   | 122                       |                         | 156  | 244                       |
| Infants, 12-23 mo         | 150 |                         | 2    | 3                         |                         | 100  | 158                       |                         | 200  | 316                       |
| Toddlers, 2-5 y           | 728 |                         | 2    | 3                         |                         | 87   | 141                       |                         | 174  | 281                       |
| Males, 6-11 y             | 521 |                         | 1    | 2                         |                         | 70   | 123                       |                         | 140  | 246                       |
| Females, 6-11 y           | 470 |                         | 1    | 2                         |                         | 62   | 99                        |                         | 124  | 199                       |
| Males, 12-18 y            | 355 |                         | 1    | 1                         |                         | 42   | 71                        |                         | 84   | 142                       |
| Females, 12-18 y          | 319 |                         | 1    | 2                         |                         | 43   | 77                        |                         | 86   | 154                       |
| Males, 19-49 y            | 506 |                         | 1    | 1                         |                         | 38   | 68                        |                         | 77   | 137                       |
| Females, 19-49 y          | 554 |                         | 1    | 1                         |                         | 34   | 61                        |                         | 69   | 121                       |
| Males, 50+ y              | 414 |                         | 1    | 1                         |                         | 35   | 54                        |                         | 70   | 108                       |
| Females, 50+ y            | 438 |                         | 1    | 1                         |                         | 31   | 53                        |                         | 62   | 107                       |
| egnant or lactating women | 47  |                         | 1    | 1                         |                         | 38   | 71                        |                         | 76   | 141                       |
| Chewing Gum               |     | 0.1                     |      |                           | 5                       |      |                           | 10                      |      |                           |
| Toddlers, 2-5 y           | 43  |                         | 0.2  | 0.4                       |                         | 11   | 19                        |                         | 21   | 38                        |
| Males, 6-11 y             | 49  |                         | 0.2  | 0.3                       |                         | 9    | 15                        |                         | 19   | 31                        |
| Females, 6-11 y           | 72  |                         | 0.1  | 0.2                       |                         | 7    | 11                        |                         | 14   | 22                        |
| Males, 12-18 y            | 53  |                         | 0.1  | 0.1                       |                         | 3    | 4                         |                         | 6    | 9                         |
| Females, 12-18 y          | 65  |                         | 0.1  | 0.1                       |                         | 4    | 4                         |                         | 7    | 9                         |
| Males, 19-49 y            | 96  |                         | 0.1  | 0.1                       |                         | 3    | 6                         |                         | 7    | 13                        |
| Females, 19-49 y          | 126 |                         | 0.1  | 0.1                       |                         | 3    | 6                         |                         | 7    | 13                        |
| Males, 50+ y              | 24  |                         | 0.1  | 0.3                       |                         | 6    | 14                        |                         | 12   | 29                        |
| Females, 50+ y            | 53  |                         | 0.1  | 0.1                       |                         | 3    | 6                         |                         | 6    | 13                        |
| egnant or lactating women | 3   |                         | 0.0  | 0.1                       |                         | 2    | 3                         |                         | 4    | 5                         |



| Age Group                  | n    | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile |
|----------------------------|------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|
| Condiments                 |      | 0.1                     |      |                           | 5                       |      |                           | 10                      |      |                           |
| Infants, < 12 mo           | 12   |                         | 1    | 1                         |                         | 27   | 40                        |                         | 53   | 81                        |
| Infants, 12-23 mo          | 82   |                         | 1    | 1                         |                         | 32   | 64                        |                         | 64   | 129                       |
| Toddlers, 2-5 y            | 620  |                         | 1    | 1                         |                         | 31   | 57                        |                         | 61   | 114                       |
| Males, 6-11 y              | 507  |                         | 0.5  | 1                         |                         | 23   | 51                        |                         | 45   | 102                       |
| Females, 6-11 y            | 454  |                         | 0.4  | 1                         |                         | 18   | 39                        |                         | 37   | 78                        |
| Males, 12-18 y             | 455  |                         | 0.3  | 1                         |                         | 13   | 27                        |                         | 25   | 54                        |
| Females, 12-18 y           | 364  |                         | 0.2  | 1                         |                         | 12   | 25                        |                         | 25   | 50                        |
| Males, 19-49 y             | 1059 |                         | 0.2  | 0.4                       |                         | 10   | 19                        |                         | 19   | 37                        |
| Females, 19-49 y           | 933  |                         | 0.2  | 0.3                       |                         | 8    | 16                        |                         | 16   | 32                        |
| Males, 50+ y               | 775  |                         | 0.2  | 0.4                       |                         | 8    | 18                        |                         | 17   | 36                        |
| Females, 50+ y             | 578  |                         | 0.2  | 0.4                       |                         | 8    | 18                        |                         | 16   | 35                        |
| regnant or lactating women | 56   |                         | 0.1  | 0.2                       |                         | 6    | 10                        |                         | 12   | 20                        |
| Confections                |      | 0.1                     |      |                           | 7.5                     |      |                           | 15                      |      |                           |
| Infants, < 12 mo           | 15   |                         | 2    | 4                         |                         | 136  | 291                       |                         | 273  | 582                       |
| Infants, 12-23 mo          | 136  |                         | 2    | 4                         |                         | 125  | 285                       |                         | 250  | 569                       |
| Toddlers, 2-5 y            | 745  |                         | 1    | 2                         |                         | 96   | 172                       |                         | 192  | 344                       |
| Males, 6-11 y              | 481  |                         | 1    | 2                         |                         | 62   | 133                       |                         | 125  | 265                       |
| Females, 6-11 y            | 511  |                         | 1    | 2                         |                         | 59   | 127                       |                         | 117  | 254                       |
| Males, 12-18 y             | 353  |                         | 1    | 1                         |                         | 45   | 88                        |                         | 91   | 175                       |
| Females, 12-18 y           | 410  |                         | 1    | 1                         |                         | 42   | 83                        |                         | 84   | 167                       |
| Males, 19-49 y             | 734  |                         | 0.5  | 1                         |                         | 36   | 66                        |                         | 73   | 132                       |
| Females, 19-49 y           | 925  |                         | 0.4  | 1                         |                         | 32   | 66                        |                         | 63   | 133                       |
| Males, 50+ y               | 665  |                         | 0.4  | 1                         |                         | 28   | 57                        |                         | 55   | 115                       |
| Females, 50+ y             | 787  |                         | 0.4  | 1                         |                         | 29   | 58                        |                         | 59   | 116                       |
| regnant or lactating women | 42   |                         | 0.4  | 1                         |                         | 33   | 61                        |                         | 66   | 121                       |



| Age Group                  | n   | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile |
|----------------------------|-----|-------------------------|------|---------------------------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|
| Desserts                   |     | 0.1                     |      |                           | 5                       |      |                           | 10                      |      |                           |
| Infants, < 12 mo           | 15  |                         | 7    | 12                        |                         | 341  | 576                       |                         | 682  | 1151                      |
| Infants, 12-23 mo          | 51  |                         | 7    | 12                        |                         | 361  | 588                       |                         | 722  | 117                       |
| Toddlers, 2-5 y            | 239 |                         | 4    | 9                         |                         | 218  | 430                       |                         | 436  | 861                       |
| Males, 6-11 y              | 175 |                         | 3    | 6                         |                         | 158  | 294                       |                         | 317  | 588                       |
| Females, 6-11 y            | 181 |                         | 2    | 4                         |                         | 114  | 225                       |                         | 227  | 450                       |
| Males, 12-18 y             | 98  |                         | 2    | 4                         |                         | 81   | 193                       |                         | 162  | 386                       |
| Females, 12-18 y           | 110 |                         | 2    | 6                         |                         | 89   | 276                       |                         | 179  | 553                       |
| Males, 19-49 y             | 271 |                         | 1    | 2                         |                         | 61   | 111                       |                         | 121  | 222                       |
| Females, 19-49 y           | 300 |                         | 1    | 3                         |                         | 68   | 130                       |                         | 135  | 260                       |
| Males, 50+ y               | 314 |                         | 1    | 3                         |                         | 68   | 137                       |                         | 136  | 275                       |
| Females, 50+ y             | 355 |                         | 1    | 3                         |                         | 72   | 146                       |                         | 145  | 292                       |
| regnant or lactating women | 14  |                         | 1    | 1                         |                         | 39   | 71                        |                         | 77   | 142                       |
| Frozen Deserts             |     | 0.1                     |      |                           | 7.5                     |      |                           | 15                      |      |                           |
| Infants, < 12 mo           | 20  |                         | 4    | 9                         |                         | 282  | 642                       |                         | 564  | 128                       |
| Infants, 12-23 mo          | 69  |                         | 5    | 9                         |                         | 385  | 708                       |                         | 769  | 141                       |
| Toddlers, 2-5 y            | 392 |                         | 4    | 7                         |                         | 317  | 520                       |                         | 635  | 104                       |
| Males, 6-11 y              | 351 |                         | 4    | 7                         |                         | 292  | 521                       |                         | 584  | 104                       |
| Females, 6-11 y            | 323 |                         | 3    | 6                         |                         | 246  | 481                       |                         | 492  | 962                       |
| Males, 12-18 y             | 247 |                         | 2    | 4                         |                         | 180  | 324                       |                         | 361  | 648                       |
| Females, 12-18 y           | 255 |                         | 3    | 6                         |                         | 189  | 428                       |                         | 378  | 856                       |
| Males, 19-49 y             | 486 |                         | 2    | 4                         |                         | 129  | 268                       |                         | 257  | 535                       |
| Females, 19-49 y           | 566 |                         | 2    | 3                         |                         | 125  | 226                       |                         | 251  | 452                       |
| Males, 50+ y               | 622 |                         | 2    | 3                         |                         | 124  | 248                       |                         | 249  | 495                       |
| Females, 50+ y             | 658 |                         | 2    | 3                         |                         | 115  | 216                       |                         | 229  | 432                       |
| regnant or lactating women | 22  |                         | 1    | 2                         |                         | 95   | 170                       |                         | 191  | 340                       |



| Table 3-6. Betawell® Arabinose | Table 3-6. Betawell® Arabinose Estimated Daily Intakes by Use Level (mg/kg-bw/day) <sup>1,2</sup> |                         |      |                           |                         |      |                           |                         |      |                           |
|--------------------------------|---|-------------------------|------|---------------------------|-------------------------|------|---------------------------|-------------------------|------|---------------------------|
| Age Group                      | n   | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile | Use<br>Levels<br>(wt %) | Mean | 90 <sup>th</sup><br>%Tile |
| All Categories                 |   |                         |      |                           |                         |      |                           |                         |      |                           |
| Infants, < 12 mo               | 110   |                         | 5    | 14                        |                         | 289  | 748                       |                         | 578  | 1495                      |
| Infants, 12-23 mo              | 369   |                         | 5    | 12                        |                         | 279  | 611                       |                         | 558  | 1221                      |
| Toddlers, 2-5 y                | 1527  |                         | 5    | 9                         |                         | 262  | 545                       |                         | 524  | 1091                      |
| Males, 6-11 y                  | 1092  |                         | 4    | 10                        |                         | 243  | 575                       |                         | 487  | 1149                      |
| Females, 6-11 y                | 1048  |                         | 4    | 8                         |                         | 205  | 482                       |                         | 411  | 963                       |
| Males, 12-18 y                 | 978   |                         | 3    | 8                         |                         | 180  | 405                       |                         | 359  | 810                       |
| Females, 12-18 y               | 919   |                         | 3    | 8                         |                         | 170  | 425                       |                         | 340  | 850                       |
| Males, 19-49 y                 | 2299  |                         | 3    | 7                         |                         | 152  | 388                       |                         | 304  | 777                       |
| Females, 19-49 y               | 2488  |                         | 3    | 7                         |                         | 138  | 344                       |                         | 276  | 688                       |
| Males, 50+ y                   | 2091  |                         | 2    | 6                         |                         | 129  | 301                       |                         | 258  | 602                       |
| Females, 50+ y                 | 2123  |                         | 2    | 5                         |                         | 135  | 310                       |                         | 269  | 619                       |
| Pregnant or lactating women    | 115   |                         | 2    | 5                         |                         | 126  | 263                       |                         | 252  | 526                       |

Notes and Abbreviations:

mg/kg-bw/d = milligrams per kilogram of body weight per day; mo = month; n = sample size; y = year(s).

<sup>&</sup>lt;sup>1</sup>Data from NHANES 2009-2012, two day averages where both days were recorded, and one day value where only one day was recorded.

<sup>&</sup>lt;sup>2</sup>Addition of L-arabinose as a weight percent of the total food weight.

<sup>&</sup>lt;sup>3</sup>Beverages category does not include fruit juices.



| Table 3-7. Betawell® Arabinose Estimated Daily Intakes Comparison (90th percentile; mg/kg-bw/day) <sup>1</sup> |     |                            |  |  |  |  |  |
|--|-----|----------------------------|--|--|--|--|--|
| Age Group and Food Category  | n   | 30% Sucrose<br>Replacement | 10% Arabinose Use<br>Level by Wt% <sup>2</sup> |  |  |  |  |
| Baked Goods  |     |                            |  |  |  |  |  |
| Infants, < 12 mo   | 48  | 280                        | 406  |  |  |  |  |
| Infants, 12-23 mo  | 178 | 529                        | 594  |  |  |  |  |
| Toddlers, 2-5 y  | 723 | 387                        | 412  |  |  |  |  |
| Males, 6-11 y  | 515 | 275                        | 293  |  |  |  |  |
| Females, 6-11 y  | 491 | 255                        | 272  |  |  |  |  |
| Males, 12-18 y   | 420 | 165                        | 185  |  |  |  |  |
| Females, 12-18 y   | 393 | 207                        | 208  |  |  |  |  |
| Males, 19-49 y   | 841 | 131                        | 138  |  |  |  |  |
| Females, 19-49 y   | 999 | 119                        | 129  |  |  |  |  |
| Males, 50+ y   | 999 | 119                        | 127  |  |  |  |  |
| Females, 50+ y   | 981 | 109                        | 111  |  |  |  |  |
| Pregnant or lactating women  | 54  | 124                        | 132  |  |  |  |  |
| Beverages <sup>3</sup>   |     |                            |  |  |  |  |  |
| Infants, < 12 mo   | 14  | 407                        | 2236   |  |  |  |  |
| Infants, 12-23 mo  | 50  | 354                        | 2064   |  |  |  |  |
| Toddlers, 2-5 y  | 198 | 405                        | 2379   |  |  |  |  |
| Males, 6-11 y  | 187 | 350                        | 1705   |  |  |  |  |
| Females, 6-11 y  | 176 | 290                        | 1499   |  |  |  |  |
| Males, 12-18 y   | 251 | 282                        | 1431   |  |  |  |  |
| Females, 12-18 y   | 241 | 319                        | 1496   |  |  |  |  |
| Males, 19-49 y   | 706 | 278                        | 1226   |  |  |  |  |
| Females, 19-49 y   | 681 | 255                        | 1099   |  |  |  |  |
| Males, 50+ y   | 474 | 222                        | 1036   |  |  |  |  |
| Females, 50+ y   | 495 | 176                        | 1173   |  |  |  |  |
| Pregnant or lactating women  | 24  | 302                        | 1266   |  |  |  |  |



| Age Group and               |     | 30% Sucrose | 10% Arabinose Use         |
|-----------------------------|-----|-------------|---------------------------|
| Food Category               | n   | Replacement | Level by Wt% <sup>2</sup> |
| Cereals                     |     |             |                           |
| Infants, < 12 mo            | 19  | 235         | 244                       |
| Infants, 12-23 mo           | 150 | 336         | 316                       |
| Toddlers, 2-5 y             | 728 | 276         | 281                       |
| Males, 6-11 y               | 521 | 251         | 246                       |
| Females, 6-11 y             | 468 | 200         | 199                       |
| Males, 12-18 y              | 354 | 133         | 142                       |
| Females, 12-18 y            | 319 | 145         | 154                       |
| Males, 19-49 y              | 504 | 135         | 137                       |
| Females, 19-49 y            | 547 | 102         | 121                       |
| Males, 50+ y                | 403 | 85          | 108                       |
| Females, 50+ y              | 428 | 69          | 107                       |
| Pregnant or lactating women | 47  | 107         | 141                       |
| Chewing gum                 |     |             |                           |
| Toddlers, 2-5 y             | 42  | 35          | 38                        |
| Males, 6-11 y               | 49  | 33          | 31                        |
| Females, 6-11 y             | 71  | 25          | 22                        |
| Males, 12-18 y              | 53  | 6           | 9                         |
| Females, 12-18 y            | 65  | 11          | 9                         |
| Males, 19-49 y              | 96  | 8           | 13                        |
| Females, 19-49 y            | 124 | 9           | 13                        |
| Males, 50+ y                | 24  | 17          | 29                        |
| Females, 50+ y              | 53  | 8           | 13                        |
| Pregnant or lactating women | 2   | 2           | 5                         |



| Table 3-7. Betawell® Arabinose Estimated Daily Intakes Comparison (90th percentile; mg/kg-bw/day) <sup>1</sup> |      |                            |  |  |  |  |  |
|--|------|----------------------------|--|--|--|--|--|
| Age Group and Food Category  | n    | 30% Sucrose<br>Replacement | 10% Arabinose Use<br>Level by Wt% <sup>2</sup> |  |  |  |  |
| Condiments   |      |                            |  |  |  |  |  |
| Infants, < 12 mo   | 12   | 55                         | 81   |  |  |  |  |
| Infants, 12-23 mo  | 82   | 85                         | 129  |  |  |  |  |
| Toddlers, 2-5 y  | 618  | 77                         | 114  |  |  |  |  |
| Males, 6-11 y  | 507  | 64                         | 102  |  |  |  |  |
| Females, 6-11 y  | 452  | 50                         | 78   |  |  |  |  |
| Males, 12-18 y   | 455  | 35                         | 54   |  |  |  |  |
| Females, 12-18 y   | 364  | 27                         | 50   |  |  |  |  |
| Males, 19-49 y   | 1059 | 20                         | 37   |  |  |  |  |
| Females, 19-49 y   | 933  | 20                         | 32   |  |  |  |  |
| Males, 50+ y   | 775  | 22                         | 36   |  |  |  |  |
| Females, 50+ y   | 577  | 20                         | 35   |  |  |  |  |
| Pregnant or lactating women  | 56   | 13                         | 20   |  |  |  |  |
| Confections  |      |                            |  |  |  |  |  |
| Infants, < 12 mo   | 15   | 674                        | 582  |  |  |  |  |
| Infants, 12-23 mo  | 136  | 586                        | 569  |  |  |  |  |
| Toddlers, 2-5 y  | 745  | 410                        | 344  |  |  |  |  |
| Males, 6-11 y  | 481  | 291                        | 265  |  |  |  |  |
| Females, 6-11 y  | 511  | 289                        | 254  |  |  |  |  |
| Males, 12-18 y   | 353  | 213                        | 175  |  |  |  |  |
| Females, 12-18 y   | 410  | 173                        | 167  |  |  |  |  |
| Males, 19-49 y   | 734  | 146                        | 132  |  |  |  |  |
| Females, 19-49 y   | 925  | 154                        | 133  |  |  |  |  |
| Males, 50+ y   | 665  | 130                        | 115  |  |  |  |  |
| Females, 50+ y   | 787  | 135                        | 116  |  |  |  |  |
| Pregnant or lactating women  | 42   | 122                        | 121  |  |  |  |  |



| Table 3-7. Betawell® Arabinose Estimated Daily Intakes Comparison (90th percentile; mg/kg-bw/day)¹ |     |                            |  |  |  |  |  |
|--|-----|----------------------------|--|--|--|--|--|
| Age Group and<br>Food Category   | n   | 30% Sucrose<br>Replacement | 10% Arabinose Use<br>Level by Wt% <sup>2</sup> |  |  |  |  |
| Desserts   |     |                            |  |  |  |  |  |
| Infants, < 12 mo   | 14  | 552                        | 1151   |  |  |  |  |
| Infants, 12-23 mo  | 47  | 598                        | 1175   |  |  |  |  |
| Toddlers, 2-5 y  | 233 | 432                        | 861  |  |  |  |  |
| Males, 6-11 y  | 171 | 347                        | 588  |  |  |  |  |
| Females, 6-11 y  | 177 | 237                        | 450  |  |  |  |  |
| Males, 12-18 y   | 97  | 203                        | 386  |  |  |  |  |
| Females, 12-18 y   | 109 | 259                        | 553  |  |  |  |  |
| Males, 19-49 y   | 267 | 155                        | 222  |  |  |  |  |
| Females, 19-49 y   | 293 | 161                        | 260  |  |  |  |  |
| Males, 50+ y   | 306 | 147                        | 275  |  |  |  |  |
| Females, 50+ y   | 332 | 129                        | 292  |  |  |  |  |
| Pregnant or lactating women  | 14  | 109                        | 142  |  |  |  |  |
| Frozen Desserts  |     |                            |  |  |  |  |  |
| Infants, < 12 mo   | 20  | 408                        | 1285   |  |  |  |  |
| Infants, 12-23 mo  | 69  | 570                        | 1416   |  |  |  |  |
| Toddlers, 2-5 y  | 392 | 442                        | 1041   |  |  |  |  |
| Males, 6-11 y  | 351 | 457                        | 1041   |  |  |  |  |
| Females, 6-11 y  | 323 | 389                        | 962  |  |  |  |  |
| Males, 12-18 y   | 247 | 310                        | 648  |  |  |  |  |
| Females, 12-18 y   | 255 | 359                        | 856  |  |  |  |  |
| Males, 19-49 y   | 486 | 224                        | 535  |  |  |  |  |
| Females, 19-49 y   | 566 | 196                        | 452  |  |  |  |  |
| Males, 50+ y   | 622 | 214                        | 495  |  |  |  |  |
| Females, 50+ y   | 658 | 177                        | 432  |  |  |  |  |
| Pregnant or lactating women  | 22  | 158                        | 340  |  |  |  |  |



| Table 3-7. Betawell <sup>®</sup> Arabinose Estimated Daily Intakes Comparison (90 <sup>th</sup> percentile; mg/kg-bw/day) <sup>1</sup> |      |                            |  |  |  |  |  |  |
|--|------|----------------------------|--|--|--|--|--|--|
| Age Group and<br>Food Category   | n    | 30% Sucrose<br>Replacement | 10% Arabinose Use<br>Level by Wt% <sup>2</sup> |  |  |  |  |  |
| All Categories   |      |                            |  |  |  |  |  |  |
| Infants, < 12 mo   | 104  | 543                        | 1495   |  |  |  |  |  |
| Infants, 12-23 mo  | 368  | 684                        | 1221   |  |  |  |  |  |
| Toddlers, 2-5 y  | 1524 | 616                        | 1091   |  |  |  |  |  |
| Males, 6-11 y  | 1092 | 546                        | 1149   |  |  |  |  |  |
| Females, 6-11 y  | 1047 | 440                        | 963  |  |  |  |  |  |
| Males, 12-18 y   | 977  | 341                        | 810  |  |  |  |  |  |
| Females, 12-18 y   | 916  | 325                        | 850  |  |  |  |  |  |
| Males, 19-49 y   | 2290 | 244                        | 777  |  |  |  |  |  |
| Females, 19-49 y   | 2458 | 228                        | 688  |  |  |  |  |  |
| Males, 50+ y   | 2070 | 202                        | 602  |  |  |  |  |  |
| Females, 50+ y   | 2088 | 202                        | 619  |  |  |  |  |  |
| Pregnant or lactating women  | 115  | 213                        | 526  |  |  |  |  |  |

Notes and Abbreviations:

mg/kg-bw/d = milligrams per kilogram of body weight per day; mo = month; n = sample size; y = year(s).

 $<sup>^{1}</sup>$  Data from NHANES 2009-2012, two day averages where both days were recorded, and one day value where only one day was recorded.

<sup>&</sup>lt;sup>2</sup> Beverages category does not include fruit juices.

<sup>&</sup>lt;sup>3</sup> Addition of L-arabinose as a weight percent of the total food weight.



#### 3.7 Cumulative EDIs

The cumulative EDI (cEDI) of the naturally occurring L-arabinose with the uses described in Section 3 amount to 5.1 g/p/d (from "adequate fiber intake") + 660 mg/p/d (from arabinose in sugar beet fiber) + 38.6 mg/p/d (from FEMA PADI) for a total daily consumption of approximately 5.8 g L-arabinose/p/d. The use of the L-arabinose dietary supplement currently on the market would be an additional 1.9 g L-arabinose/p/d. Based on these background intakes and the proposed uses, the EDI of L-arabinose ranges from 5.8 to 22 grams L-arabinose per person per day.

| Table 3-8. Betawell® Arabinose Estimated Daily Intakes Comparison <sup>1</sup> |      |  |                         |                |  |  |  |  |
|--|------|--|-------------------------|----------------|--|--|--|--|
| Age Group  | n    | 30% Sucrose<br>Replacement<br>(mg/kg-bw/d) | Body<br>weight²<br>(kg) | EDI<br>(g/p/d) |  |  |  |  |
| Infants, < 12 mo   | 104  | 543  | 7.5                     | 4.1            |  |  |  |  |
| Infants, 12-23 mo  | 368  | 684  | 11                      | 7.8            |  |  |  |  |
| Toddlers, 2-5 y  | 1524 | 616  | 16                      | 10             |  |  |  |  |
| 6-11 y   | 1092 | 546  | 32                      | 17             |  |  |  |  |
| 12-18 y  | 977  | 341  | 64                      | 22             |  |  |  |  |
| 19-49 y  | 2290 | 244  | 80                      | 19             |  |  |  |  |
| 50+ y  | 2070 | 202  | 80                      | 16             |  |  |  |  |
| Background intakes   |      |  |                         | 5.8            |  |  |  |  |

Notes and Abbreviations:

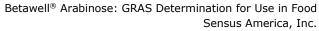
bw = body weight; EDI = estimated daily intake; d = day; g = gram(s); kg = kilogram(s); mg = milligram(s); mo = month(s); p = person; y = year(s).

# 3.8 Section 3 Summary

Ramboll evaluated two sets of data to estimate consumer intakes of Betawell® Arabinose. The first is a list of foods to which Betawell® Arabinose could be added and the proposed maximum use level of Betawell® Arabinose in those foods as provided by Sensus. The second set of data was generated internally by Ramboll and consists of EDIs of the foods proposed to which Betawell® Arabinose may be added. Using these data, Ramboll calculated estimates for the levels of Betawell® Arabinose that would be consumed if all of the proposed food categories received with the maximum proposed use level of Betawell® Arabinose and if the Betawell® Arabinose were used as a replacement for up to 30% of the sucrose content of these foods. This analysis demonstrates that even an exaggerated EDI of Betawell® Arabinose is consistent with the EDIs of similar sugar substitutes (up to 22 g Betawell® Arabinose/d versus up to 30 g/d tagatose or psicose).

<sup>&</sup>lt;sup>1</sup> Data from NHANES 2009-2012, two day averages where both days were recorded, and one day value where only one day was recorded; 90<sup>th</sup> percentile shown.

<sup>&</sup>lt;sup>2</sup> U.S. Environmental Protection Agency (EPA). (2011) Exposure Factors Handbook: 2011 Edition. National Center for Environmental Assessment, Washington, DC; EPA/600/R-09/052F; where age ranges span multiple weights the weights were averaged.







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# 4 Self-Limiting Levels of Use (in accordance with 21 CFR §170.240)

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# 5 Experience Based on Common Use in Food Before 1958

# (in accordance with 21 CFR §170.245)

# 5.1 History of Use

Arabinose is a naturally occurring monosaccharide most commonly found in *Acacia* and *Larix* species of plants as a complex polysaccharide (Burdock, 2009). Arabinose is a pentose or C5 sugar; a family that includes D-xylose, D-lyxose, and D-ribose. Arabinose occurs in both the D and L configuration, however, unlike most other pentoses and hexoses where the D configuration predominates, the L configuration is the most common. Arabinose is consumed as a component of gum arabic which is a food additive and dietary fiber derived from Acacia trees (Whistler, 1973). Arabinose is also a component of many foods including fruits, grains, and vegetables (Spiller, 2001). It often occurs as a constituent monomer of the various polysaccharides that comprise the fibrous portions of these foods such as pectin and hemicellulose. Arabinose can also be found as a free monosaccharide in many beverages, including tea, wine, beer and coffee, with the highest concentration being found in instant coffee. Arabinose is added to processed foods as a flavoring extract and is available as a dietary supplement.

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# 6 Safety Narrative (in accordance with 21 CFR §170.250)

#### 6.1 Introduction

Ramboll identified numerous studies evaluating arabinose in the scientific literature. These included clinical and animal studies evaluating the efficacy of achieving the intended effects of arabinose, such as decreased blood glucose and body weight, as well as gastrointestinal effects associated with arabinose ingestion. Ramboll also reviewed animal and in vitro toxicological studies evaluating Betawell® Arabinose and assisted with the preparation of manuscripts of these studies that are currently under review (Beerens et al. 2017). Studies contributing to the safety assessment of Betawell® Arabinose are summarized herein.

#### 6.2 Mode of Action

Ramboll identified numerous studies that investigated the biological effects of arabinose in humans (Table 6-1) and animals including rats and pigs (Table 6-2). The scientific consensus based on these studies is that L-arabinose binds to sucrase (a brush border enzyme), even when the enzyme is already bound to sucrose, and thus prevents or delays the sucrose from being broken into glucose and fructose. L-arabinose activity is non-competitive, dosedependent, and does not alter or destroy the enzyme or the sucrose (Krog-Mikkelson et al., 2011; Osaki et al., 2001). The result is reduced or delayed uptake of glucose and fructose into the blood stream thereby limiting blood sugar concentration spikes and associated metabolic responses (e.g., insulin response)(Krog-Mikkelson et al., 2011).

# 6.2.1 Acute Toxicity of Arabinose

Ramboll did not identify studies regarding the acute toxicity of arabinose. Arabinose is expected to have an acute toxicity comparable to similar GRAS saccharides such as psicose, ribose, and tagatose.

# 6.2.2 Subchronic Toxicity of Arabinose

#### General Information

Sensus commissioned Charles River Laboratories Den Bosch B.V. (Charles River), a contract research organization, to evaluate the subchronic (90-day) oral toxicity of Betawell® Arabinose in rats, based on Organization for Economic Co-operation and Development (OECD) test guideline 408. Charles River, Sensus, and Ramboll prepared a manuscript that included this study for submission to a peer reviewed scientific journal (Beerens et al. 2017). The manuscript is currently under review by the journal.

#### Materials and Methods

Betawell® Arabinose was administered as a dietary mixture at concentrations of 0, 3,000, 10,000, and 30,000 parts per million (ppm) for 90 consecutive days followed by a recovery period of 28 days. There were 10 male and 10 female Wistar rats (Crl:WI(Han)(outbred, SPF-Quality)) per group. These dietary concentrations corresponded to mean intakes of 0, 216, 760, and 2218 mg/kg-bw/day for males and 0, 251, 872, and 2614 mg/kg-bw/day for females.

#### Results

Charles River reported that there were no toxicologically significant changes from the administration of the L-arabinose. The study parameters included clinical appearance,



functional observations, ophthalmoscopy, food consumption, clinical laboratory investigations (hematology, clinical chemistry, urinalysis), macroscopic examination, organ weights, and microscopic examination.

Charles River reported that a slight, but statistically significant at some observations, lower body weight gain in females in the 10,000 ppm and 30,000 ppm treatment groups; these were not accompanied by a decrease in food consumption. This effect was not reported for males. The lab reported that because these changes were not dose-dependent, were "slight in nature" (reported as statistically significant for week 9 for the 10,000 ppm group and weeks 5, 6, and 13 for the 30,000 ppm group) and because no corroborative findings in clinical signs and food consumption were noted, these were considered not toxicologically relevant. Body weights and body weight gain of males did not differ significantly from controls.

Slightly but statistically significant increased bile acids in both sexes and changes in glucose (slightly lower in males in the 30,000 ppm treatment group and slightly higher in females of the 30,000 ppm treatment group) were reported. Since these changes in glucose were not dose-dependent, and because responses differed between the sexes, and because the values for the bile acids were within the normal range for this strain and age of rats, they were considered not toxicologically relevant.

Macroscopic examination at necropsy and microscopic examination of organs and tissues did not reveal any treatment-related findings.

#### Conclusion

The no-observed-adverse-effect level (NOAEL) was reported to be the highest concentration fed, namely 30,000 ppm of the diet (2218 mg/kg body weight/day for males and 2614 g/kg body weight/day for females).

#### 6.2.3 Reproductive and Developmental Toxicity

Ramboll did not identify any reproductive or developmental toxicity studies regarding L-arabinose.

In GRN 243, the notifiers reported a embryotoxicity/teratogenicity study of D-ribose, a C5 saccharide like L-arabinose, using dietary concentrations of 0, 5, 10, or 20% of the diet, which equates to approximately 0.0, 4.25, 7.94, and 9.91 g/kg-bw/day, respectively. In the study, D-Ribose had a NOAEL for teratogenicity of 20% ribose in the diet (9.91 g/kg-bw/day), the highest concentration fed, and a NOAEL for developmental toxicity of 5% ribose in the diet (between 3.64 and 4.61 g/kg-bw/day). The authors noted that the D-ribose groups had increased cecal weights as "a nutritional effect due to the high carbohydrate levels in the D-ribose-containing diets" and that this is not uncommon in rats with high carbohydrate diets.

# 6.2.4 Carcinogenicity

Ramboll did not identify any carcinogenicity studies regarding L-arabinose.

# 6.2.5 Genotoxicity

Sensus sponsored a genotoxicity study through WIL Research Europe B.V. (now Charles River) that was conducted in accordance with OECD Test Guideline 487 and Good Laboratory Practice (GLP) guidance. Charles River, Sensus, and Ramboll prepared a manuscript that included this study for submission to a peer reviewed scientific journal (Beerens et al. 2017). The manuscript is currently under review by the journal.



The study consisted of an *in vitro* micronucleus assay that evaluated the effect of Betawell<sup>®</sup> Arabinose on the number of micronuclei formed in cultured peripheral human lymphocytes in the presence and absence of a metabolic activation system (phenobarbital and B-naphthoflavone induced rat liver S9-mix).

The possible clastogenicity and aneugenicity of Betawell® Arabinose was tested in two independent experiments. In the first cytogenetic assay, Betawell® Arabinose was tested up to  $1501~\mu g/mL$  for an exposure time of three (3) hours with a harvest time of 27 hours (with and without metabolic activation). In the second cytogenetic assay, Betawell® Arabinose was also tested up to  $1501~\mu g/mL$  for an exposure time of 24 hours with a harvest time of 24 hours (with and without metabolic activation).

Betawell® Arabinose did not induce a statistically significant or biologically relevant increase in the number of mono- and binucleated cells with micronuclei with or without metabolic activation, in either of the two experiments.

The solvent control produced mono- and binucleated cells with micronuclei within the 95% control limits of the distribution of the historical negative control database. The positive controls (mitomycin C and cyclophosphamide) produced statistically significant increases in the number of binucleated cells with micronuclei. The positive control colchicine produced a statistically significant increase in the number of mononucleated cells with micronuclei. The number of mono- and binucleated cells with micronuclei found in the positive control cultures was within the 95% control limits of the distribution of the historical positive control database. These positive controls confirmed the validity of the test conditions and the sensitivity of the test system.

#### Conclusion

Betawell® Arabinose is not clastogenic or aneugenic in human lymphocytes under the conditions of this study.

# 6.2.6 Mutagenicity

Sensus sponsored a mutagenicity study through WIL Research Europe B.V. (now Charles River) that was conducted in accordance with OECD Test Guideline 471 and Good Laboratory Practice (GLP) guidance. Charles River, Sensus, and Ramboll prepared a manuscript that included this study for submission to a peer reviewed scientific journal (Beerens et al. 2017). The manuscript is currently under review by the journal.

In a bacterial reverse mutation study (Appendix C), Betawell® Arabinose was examined for mutagenic activity using the histidine-requiring  $Salmonella\ typhimurium$  strains TA98, TA100, TA1535, and TA1537 and in the  $Escherichia\ coli$  tryptophan-requiring strain (WP2uvrA) in the absence and presence of metabolic activation (rat liver S9-mix induced Arochlor 1254). Concentrations up to 5000 µg/plate of Betawell® Arabinose were used. No signs of cytotoxicity were reported. No increase in revertant colony numbers was reported in plate incorporation and pre-incubation tests compared with control counts for Betawell® Arabinose at concentrations up to 5000 µg/plate, in any of the four test strains of  $S.\ typhimurium$  and the  $E.\ coli$  in two independent experiments with Betawell® Arabinose (cytotoxicity and mutagenicity), with and without metabolic activation. The positive control tests showed a significant increase in the number of revertant colonies for each of the corresponding test strains and confirmed the validity of the test conditions and the sensitivity of the test system.



#### Conclusion

Betawell® Arabinose is not mutagenic under the conditions of this study.

#### 6.2.7 Dermal Irritation and Sensitization

Ramboll did not identify any dermal irritation or sensitization studies.

### 6.2.8 Other Toxicological Considerations

Ramboll did not identify other toxicological considerations.

# **6.3 Studies Evaluating Arabinose in Humans**

Table 6-1 presents summaries of human arabinose studies identified in the publicly available scientific literature. There are a significant number of publicly available studies evaluating arabinose ingestion in humans. While many studies were of short duration (two plus hours) Liu et al. (2013b) (Study 2) and Yang et al. (2013) performed the studies with the longest exposure durations (six months). The highest dose administered was 45 g L-arabinose per day for 180 days in the studies performed by Liu et al. (2013b) (Study 1) and Yang et al. (2013). Several studies indicate decreased blood glucose levels and reduced postprandial serum insulin peaks in diets containing arabinose (Inoue et al., 2000 (abstract only); Krog-Mikkelsen et al., 2011; Krog-Mikkelsen et al., 2013; Liu et al., 2013b; Shibanuma et al., 2011; Yang et al., 2013).

# 6.3.1 Biodisposition: Absorption, Distribution, Metabolism, Kinetics and Excretion

Ramboll identified studies of arabinose biodisposition in humans (Table 6-1) though most focus on the effect arabinose has on sucrase activity in the small intestine. The studies did not evaluate absorption of L-arabinose from the stomach. In the small intestine, arabinose at sufficient levels (> 1% of the sucrose present) can inhibit the sucrase enzyme which hydrolyzes sucrose, resulting in lowered absorption of glucose and fructose into the blood stream (Osaki et al., 2001; Preuss et al., 2007). The exact metabolic pathway of L-arabinose has not been investigated, though a case report by Onkenhout et al. (2002) and a study by Segal & Foley (1959) suggest that L-arabitol dehydrogenase<sup>4</sup> plays a significant role in the catabolism of L-arabinose. According to Segal & Foley (1959), after intravenous injection, the disappearance of L-arabinose from the blood follows first-order kinetics with a rate of approximately 0.77% per minute (comparable to other pentoses) with greater than 85% of the injected L-arabinose excreted in urine within 24 hours and only 0.8% expired via respiration within six hours. In the colon, L-arabinose may also be fermented by gut bacteria, as demonstrated by Ramasamy et al. (2014), who reported that 99% of arabinose had disappeared after 24 hours of fermentation of soluble and insoluble fiber fractions from chicory root in an in vitro model of gut microbes. Thus, L-arabinose may be absorbed into the blood stream in the small intestine and excreted in urine or catabolized by L-arabitol dehydrogenase, or fermented by microbes in the colon.

# 6.3.2 Other Studies of Arabinose in Humans

Halschou-Jensen et al. (2014) conducted a pair of randomized, double-blind, cross-over trials to investigate the inhibiting effect of L-arabinose added in a mixed meal containing sucrose and/or starch from wheat flour on the blood glucose, insulin and C-peptide responses in humans. In the first study, 17 healthy, 23 year old males were given either 0, 5, or 10%

<sup>&</sup>lt;sup>4</sup> Also known as L-arabitinol 4-dehydrogenase; <a href="http://enzyme.expasy.org/EC/1.1.1.12">http://enzyme.expasy.org/EC/1.1.1.12</a>.



arabinose (0, 2.9, or 5.9 g) added to either Meal A (bun and muffin [sucrose and starch from wheat], jam, and butter) or Meal B (2 buns [starch from wheat], cheese and butter). The authors reported that for Meal A, no differences in glucose, insulin, or C-peptide were found in the subjects among the different levels of arabinose consumed and that for Meal B, insulin and C-peptide were higher for those who ate 0% arabinose compared to 10%.

In the second study, six healthy, 23 year old males were given either 0 or 20% arabinose (0 or 10.2 g) added to Meal B of the first study or to Meal B blended into a porridge-like consistency or 0 or 15 g arabinose added to a liquid meal of 75 g maltose in 300 mL of water. For this study, the authors reported that there were no differences in glucose, insulin, paracetamol, or C-peptide in subjects who ate the different meals. Both of the studies lasted for 3 hours.

Inoue et al. (2000) (abstract only) conducted three single-dose studies (cross-over for Study 1 and 3, randomized parallel for Study 2) to evaluate the effect of L-arabinose on blood glucose level after ingestion of sucrose-containing food. Study 1 involved eight healthy people aged 27 to 54 who were given 50 g sucrose in 300 mL water with 0 or 2 g L-arabinose. For Study 2, 40 healthy people over the age of 40 were given jelly with 30 g sucrose and either 0, 2, 3, or 4% L-arabinose (0, 0.6, 0.9, or 1.2 g L-arabinose) added. Study 3 involved 10 people aged 48-75 with Type 2 diabetes who were given 30 g sucrose and 0 or 3% L-arabinose (0 or 0.9 g L-arabinose) added. For all studies, exposure durations were two hours. The authors reported decreased blood glucose levels for the L-arabinose diets. They also reported no difference in insulin levels and no gastrointestinal (GI) symptoms in the subjects during or after completion of the study.

Kaats et al. (2011) conducted a pair of studies to evaluate the effects of L-arabinose and chromium on lowering blood glucose and insulin levels. Study 1 consisted of two phases. In the first phase, 20 people with an average age of 53.8 years were given 70 g sucrose in water on Day 1 and 70 g sucrose plus 1000 mg L-arabinose and 200 µg of a patented food source of chromium added on Day 2. The exposure duration was 90 minutes. For the second phase, 10 people with an average age of 53.7 years were given a diet with L-arabinose and chromium daily for 4 weeks. In Study 2, 50 people with an average age of 40.2 years were given 70 g sucrose in water (control) on Day 1 and 70 g sucrose in water with 1000 mg L-arabinose and 200 µg of a patented food source of chromium on Day 2. Exposure duration was 90 minutes. For both studies, the authors reported that there were decreased blood glucose and insulin circulation levels in the subjects after consuming the L-arabinose and chromium diets, compared to the control group. Additionally, there were no adverse effects reported in either study.

Krog-Mikkelsen et al. (2011) conducted a randomized, double-blind, cross-over, single-dose study to evaluate the effects of L-arabinose on intestinal sucrose activity in humans. 15 healthy, 25 year old males were given one sucrose beverage prepared with 75 g sucrose in 300 mL water, with the addition of 0 (control), 1, 2, or 3 g L-arabinose added. Each subject received one beverage on a weekly basis, until after four weeks they had all consumed each of the four beverages. The exposure duration was three hours. The authors reported that blood glucose levels, C-peptide, glucose dependent insulintropic polypeptide, and insulin levels all decreased for the L-arabinose diet. The authors also reported that glucagon-like-peptide-1 increased for the L-arabinose diet and that there were no differences for triacylglycerol, energy intake, or appetite among the diets. Finally, the researchers noted that there were a few mild GI symptoms reported: the 2 g L-arabinose treatment group had one subject report



mild diarrhea, and one reported mild distention followed by severe stomach ache and diarrhea; the 3 g L-arabinose treatment group had one report of mild flatulence and a report of mild heartburn moderate nausea, and mild stomach ache following consumption. The adverse effects did not differ between treatments and one subject reported mild distention after treatment with the 0 g L-arabinose treatment.

Krog-Mikkelsen et al. (2013) conducted another study involving L-arabinose and 14 healthy, 19-30 year old males. This was a randomized, double-blind, crossover, single-dose study to evaluate the effects of L-arabinose on intestinal sucrose activity in humans. The participants were given 75 g sucrose in 300 mL water with 0, 4, or 8% (0, 3, or 6 g) D-xylose or 8% (6 g) L-arabinose. The exposure duration was three hours. The authors reported that there were decreased blood glucose levels, C-peptide, and insulin for the L-arabinose diet, but increased glucagon-like-peptide-1 in the L-arabinose diet. They also reported that there were no differences in energy intake or appetite among the diets and that no differences in GI symptoms between treatments were reported.

Liu et al. (2013b) conducted a pair of parallel, randomized, repeated dose studies to evaluate the effects of L-arabinose on blood glucose and body weight in humans. In Study 1, 25 males and 25 females aged 22 to 24 years were split into groups of 10 people each. There were five groups total, each fed 45 g per day of sugars dissolved in water with one of the following breakdowns: 3% L-arabinose and 97% sucrose, 5% L-arabinose and 95% sucrose, 10% L-arabinose and 90% sucrose, 100% L-arabinose, or 100% sucrose. The exposure time for all treatments was 30 days. The authors reported that decreased blood glucose levels occurred for the L-arabinose diets and that three people in the 10% arabinose group experienced mild diarrhea which disappeared after four days with continued intake of L-arabinose.

In Study 2 by Liu et al. (2013b), 20 obese 18-23 year old people were given either 30 g L-arabinose/day or 30 g xylitol/day (control), taken as  $3 \times 10$  g, each time before a meal for a duration of 180 days. The authors reported that the body weight of the control group did not change over time but that the L-arabinose group experienced an average weight loss of 5.5 to 6 kg over the study period.

Ohki et al. (1999; cited in Wijlens & Mars, 2015) conducted a study involving 89 healthy females in order to evaluate the effect of sucrose-containing L-arabinose on fecal microflora, constituents, and characteristics in healthy women. The participants were given no supplement for three weeks to establish a baseline, and then 10 g sucrose with 3% L-arabinose twice daily for two weeks, followed by another 10 day period of no supplements. The authors reported that there were no differences observed in total anaerobic or aerobic bacteria, pH, moisture content, ammonia content, or organic acid content. They also reported an increased number of defecations per week and a decreased number of non-defecation days. No adverse effects were reported.

Shibanuma et al. (2011) conducted a double-blind controlled, cross-over, single-dose study to investigate the suppression of blood glucose levels by L-arabinose in healthy adults. Eighteen males and three females over the age of 20 were given 150 g drinks of 40 g sucrose and deionized water with 0 g (control) or 2 g L-arabinose added, followed by a 90 g bean paste jelly containing 40 g sucrose after two hours. The total exposure duration was two hours. The authors reported that there were decreased blood glucose levels for the L-arabinose diets.



Thondre and Lightowler (2014a) conducted a non-blind, crossover, single-dose trial to study the glycemic response to sucrose, sucrose with pectin oligosaccharides, sucrose with varying amounts of L-arabinose, and sucrose with L-arabinose and pectin oligosaccharides. The subjects were 19 healthy people between the ages of 18 and 65. They each received one or more of the following diets: 55 g reference glucose, 50 g sucrose, 49.73 g sucrose with 2.7 g pectin oligosaccharides, 50 g sucrose with 2.54 g L-arabinose, 50 g sucrose with 5.08 g L-arabinose, 50 g sucrose with 7.62 g L-arabinose, or 49.73 g sucrose with 2.54 g L-arabinose and 2.7 g pectin oligosaccharides. The researchers measured the subjects' blood glucose every 15 minutes for a 180 minute duration and reported that overall, there were decreased blood glucose levels for the L-arabinose diets compared to the diet with just sucrose. They also reported that no adverse effects occurred.

In another study conducted by Thondre and Lightowler (2014b), 11 healthy people with an average age of 24.8 years participated in a non-blind, repeat measure, crossover design trial to study the glycemic response to yogurt with sucrose and yogurt with sucrose and arabinose. The subjects received one of the following diets: 54.96 g reference glucose, 268.66 g yogurt with 29.85 g sucrose, or 285.71 g yogurt with 28.57 g sucrose and 3.17 arabinose. The researchers measured the subjects' blood glucose levels every 15 minutes for a 180 minute duration and reported that decreased blood glucose levels for the arabinose diet and that no adverse effects occurred.

In another study conducted by Thondre and Lightowler (2015a), 13 healthy people with an average age of 28.2 years participated in a non-blind, repeat measure, crossover design trial to study the glycemic responses to glucose, sucrose, sucrose with 10% arabinose, and sucrose with 10% xylose. The subjects received one of the following diets: 50 g glucose, 50 g sucrose, 55 g sucrose with 10% (5.5 g) arabinose, or 55 g sucrose with 10% xylose. The researchers measured the subjects' blood glucose levels every 15 minutes for a 180 minute duration and reported decreased blood glucose levels for the arabinose and xylose-added diets compared to the pure reference glucose and pure sucrose diets. Additionally, they reported that no adverse effects occurred.

In another study conducted by Thondre and Lightowler (2015b), 12 healthy people with an average age of 31.3 years participated in a non-blind, repeat measure, crossover design trial to study the glycemic responses to a tropical juice sweetened with sucrose and one sweetened with arabinose compared to a reference glucose dose. To do this, the subjects received one of the following diets: 54.96 g reference glucose, 467.3 g tropical juice drink with sucrose, or 491.5 g tropical juice drink with arabinose. The exposure duration was 180 minutes. The authors reported decreased blood glucose levels for subjects consuming the arabinose and sucrose drinks compared to the reference glucose, but that the difference in blood glucose effects between the drinks themselves was minimal. They also noted that no adverse effects occurred. In a similar study, conducted by the same team (Thondre and Lightowler, 2015c), the participants were provided muffins made with either sucrose or sucrose and 12.5% arabinose, and compared to participants who were provided muffins sweetened with just sucrose. The authors reported decreased blood glucose levels for the muffins compared to the reference glucose, and that the decrease was greater for the muffin with arabinose added compared to the muffin with just sucrose. Finally, they reported that no adverse effects occurred for any diets.

Yang et al. (2013) conducted a repeated-dose study to evaluate the effects of L-arabinose consumption on metabolic syndrome in humans. The study consisted of L-arabinose



consumption by 30 people aged 50 years (49.9 ±9.9 y) with metabolic syndrome for six months. There was no control group reported and the authors did not report that the study was blinded in any way. The participants were given L-arabinose dissolved in water at either 45 g per day (3 x 15 g) if they weighed more than 60 kg (625 mg L-arabinose/kg-bw/day based on the mean body weight of 72.2 ±13 kg), or 20 g per day (2 x 10 g) if they weighed less than 60 kg (338 mg L-arabinose/kg-bw/day for the lowest weight of the standard deviation at 59.2 kg). The authors reported that the participants' blood glucose levels, body weight, waist circumference, diastolic blood pressure, and total cholesterol decreased during the study, while systolic blood pressure, and either LDL or HDL cholesterol did not differ. Because the study was not blinded and did not have a control group, the results cannot be attributed to the test substance. Reported adverse effects included 13 people with mild diarrhea and one person with mild nausea after treatment with L-arabinose. The specifics of the severity or whether the effects were transient was not reported. The authors did note that 13 people were not included in study and of these 13, three people dropped from the study due to diarrhea. The authors do not report the body weight of those who reported the diarrhea and nausea, therefore it is unclear if they were receiving the low dose or the high dose.

# 6.3.3 Case Reports

Onkenhout et al. (2002) reported the case of a 16-month old female with high levels of arabinose in her urine, and high levels of L-arabitol, an arabinose metabolite, in her urine, plasma, and cerebrospinal fluid. The authors reported that this appeared to be a case of an inborn error in metabolism probably due to an L-arabitinol 4-dehydrogenase deficiency (though not confirmed). Onkenhout et al. note that the patient's high levels of urinary arabinose and was likely due to the fruit formula in her diet and that her clinical abnormalities were unlikely to be derived from this metabolic disorder.

Segal and Foley (1959), the researchers who evaluated the metabolic fate of pentoses, speculated that the low conversion of intravenously administered L-arabinose to  $O_2$  may be due to an enzymatic deficiency of their subject. They ultimately dismissed the idea because of the subject's ability to "handle the 20 g infusions of L-arabinose in a manner similar to other normal subjects." No toxicological consequences from such a metabolic disorder have been identified.

### 6.4 Other Studies Evaluating Arabinose in Animals and In Vitro

Table 6-2 presents summaries of animal arabinose studies identified in the publicly available scientific literature. The shortest studies were performed by Seri et al. (1996) with an exposure duration of two hours. Han et al. (2010) performed the studies of longest exposure duration (five months). Schutte et al. (1992) was the highest administered dose at 100 g L-arabinose/kg-bw to pigs. Several studies reported decreased blood glucose levels in diets containing arabinose (Han et al., 2010; He et al., 2009 (abstract only); Matsuura et al., 2001 (abstract only); Preuss et al., 2007; Seri et al., 1996; Wang et al., 2012 (abstract only); Zhou et al., 2008 cited in Wijlens & Mars, 2015).

Alhaidary et al. (2011) conducted a randomized, parallel, repeated-dose oral feeding study to compare the effects of five different dietary monosaccharides on mineral and nitrogen utilization. One hundred female rats were divided into five groups of 20, with each group given a different diet: a basal diet with one of the following ingredients added: 10% glucose, 9.2% xylose with 0.8% water, 9.2% arabinose with 0.8% water, 9.2% galacturonic acid with 0.8% water, or 9.2% galactose with 0.8% water. The authors reported that there were no



differences in body weight, body fat, water intake, or urine production and pH, but that cecal and fecal weight were higher for the arabinose diet compared to the glucose diet.

Fujii et al. (2000) (abstract only) conducted a study with two different experiments, both of which were parallel, repeated dose oral studies with the purpose of evaluating the physiological effects of L-arabinose in rats. In the first experiment, 54 male rats were divided into groups of six and each group was given a test diet for 10, 20, or 30 days. Each diet contained 20% sucrose and either 0% L-arabinose with 5% cellulose (control), 1% L-arabinose with 4% cellulose, or 2.5% L-arabinose with 2.5% cellulose. The authors reported that there were no differences in feed conversion rate, total cholesterol, blood glucose, or amount or composition of organic acids. They also reported reductions in the rats' body weight gains, retroperitoneal fat, epididymal fat, liver weight, triacylglycerol, and total liver lipids for rats on diets with higher concentrations of L-arabinose. An increase in cecum weight was also reported. For Experiment 2, 14 male rats were split into two groups which each received either a diet of only corn starch (no sucrose) with either 0% (control) or 2.5% arabinose added. The authors reported a reduced feed conversion rate and liver weight in the 2.5% arabinose group compared to the control group and that no other differences were found.

In a study by Han et al. (2010), 40 male obese rabbits were fed L-arabinose as part of a randomized, parallel, oral feeding study to evaluate L-arabinose's hypoglycemic and antiobesity effects. The rabbits were divided into five groups that were each given different diets over the course of five months. The rabbits had free access to the feed. The control group received an ordinary feed while the other four groups were provided high fat, high sugar (HFHS) diets with 308.5, 617, or 925.5 mg L-arabinose/kg-bw or no L-arabinose at all, as a control. The authors reported that the blood glucose, fat index, and body weight decreased for the diets involving L-arabinose compared with the control, while the amount of stool increased. They also noted that food intake did not differ between the groups.

Hao et al. (2015) conducted a randomized, parallel, repeated-dose oral study to investigate the effects of L-arabinose on hypertension, insulin resistance, and adipocytokines in rats with metabolic syndrome induced by a HFHS (fructose and sucrose) diet. Male Wistar rats were fed either a commercial pellet feed for the two control groups or an HFHS diet for 14 weeks to induce metabolic syndrome. The rats were then divided into four groups with 12 animals per group and the respective diets administered via gavage for six weeks: Control group (normal rats, normal chows); Control L-arabinose group (normal rats, normal chows, plus 400 mg L-arabinose/kg-bw/day); Model group (metabolic syndrome rats, HFHS diet); Model L-arabinose group (metabolic syndrome rats, HFHS diet, 400 mg L-arabinose/kg-bw/day). The authors reported statistically significant reductions in body weight, systolic and diastolic blood pressure, fasting blood glucose, triglycerides, total cholesterol, serum insulin, inflammatory cytokine (TNF- $\alpha$ ), and leptin in the rats fed the Model L-arabinose group compared to the Model group. The fasting blood glucose of the Control L-arabinose group did not significantly differ from the Control group. Compared to Model group, Model L-arabinose group also significantly increased expression of messenger ribonucleic acid (mRNA) for hepatic CPT-1α and PDK4, and downregulated hepatic ACCα. Compared to Model group, Model L-arabinose group also significantly reduced activity of blood urea nitrogen and creatine kinase. The authors concluded that L-arabinose consumption mediated the effects of metabolic syndrome in afflicted rats.

He et al. (2009) (abstract only) conducted a parallel, repeated-dose oral feeding study to evaluate the effects of L-arabinose on growth and metabolism of carbohydrates and lipids in



rats. Sixty male rats were split into six different groups, and each was given a different diet. The six diets were a blank control of just ordinary feed (A), 525 mg L-arabinose/kg-bw along with ordinary feed (B), a HFHS diet with no arabinose (C), a HFHS diet with 87.5 mg arabinose/kg-bw added (D), a HFHS diet with 175 mg arabinose/kg-bw added (E), and a HFHS diet with 525 mg arabinose/kg-bw weight added (F). Comparing treatment groups A to B, C to D, and E to F, the authors reported that body weight, feed intake, food utilization rates, fasting blood glucose levels, total cholesterol, and LDL cholesterol did not differ. They also reported that non-fasting blood glucose and triglycerides decreased, while HDL cholesterol increased when comparing treatment group A to treatment group B.

Iwata et al. (2007) (abstract only) conducted a parallel oral feeding study in order to evaluate the effect of sucrose with L-arabinose on the number of bifidobacteria in rat ceca. Fourteen male rats were split into two groups and given a diet of 20% sucrose with either 0 (control) or 1% L-arabinose added for a total of four weeks. The water and feed were freely consumed by the rats. The authors reported that there was no significant difference in body weight gain, abdominal fat, total organic acids in cecal content, fecal weight, and fecal moisture between the two groups. They also reported an increase in cecum weight and ammonia per cecum and a decrease in fecal dry weight for the rats fed the diet with L-arabinose included. Additionally, the researchers noted that bifidobacteria was observed in the L-arabinose group but not in the control.

Li et al. (2013; cited in Wijlens & Mars, 2015) conducted a randomized, parallel, repeated-dose intragastric feeding study in order to evaluate the effects of L-arabinose on glucolipid metabolism in both healthy rats and rats with metabolic syndrome. 52 male rats (12 healthy and 40 in metabolic syndrome) were split into five different groups. The first was a control group made up of the healthy rats who were given a blank control diet that included no added L-arabinose. The other 40 rats received a dose intragastrically of one of the following: 0 mg L-arabinose (as a model control), 87.5 mg L-arabinose/kg-bw, 175 mg L-arabinose/kg-bw, or 525 mg L-arabinose/kg-bw. The experiment lasted for six weeks during which time the rats also had free access to feed and water. The authors reported that diets with L-arabinose led to a reduction in body weight, fasting blood glucose, triglycerides, total cholesterol, LDL cholesterol, and serum free fatty acids when compared to the controls. They also reported that there was no change in HDL cholesterol among the groups. The authors also reported that rats in metabolic syndrome at the start exhibited excess eating, drinking, and urination, but that this subsided during the treatments with arabinose.

Liu et al. (2013a) conducted a parallel repeated-dose intragastric feeding study to evaluate the effects of L-arabinose on body weight reduction in obese mice. To do this, 50 male mice were made nutritionally obese over 70 days, while 10 other mice received ordinary feed for 70 days to establish them as a "no-treatment" group. After the initial 70 days, the newly obese mice received purified water intragastrically with either 0 (control), 1, 2, or 4 g L-arabinose/kg-bw daily for 45 days. The authors reported a reduction in body weight, lipid weight-body weight ratio, and triglyceride level for mice on the L-arabinose diets, along with an increased HDL cholesterol. They also reported that there were no significant differences in total cholesterol or organ indices.

Matsuura et al. (2001) (abstract only) conducted a randomized, parallel, single-dose intragastric feeding study in order to investigate the alpha-glucoside inhibitory activity of various sugars in rats with portal vein catheterization. This study involved two distinct experiments, each with 30 male rats. In the first, the researchers started by achieving stable



blood glucose concentrations in the rats via intragastric sucrose infusion, after which they were split into five different groups, each given a different test substance intragastrically. The five diets were D-xylose (0.24 g/kg-bw), L-arabinose (0.24 g/kg-bw), D-glucorono-6,3-lactone (0.24 g/kg-bw), acarbose (0.024 g/kg-bw), and voglibose (0.00024 g/kg-bw). The exposure duration was three hours. The authors reported that administration of L-arabinose inhibited blood glucose levels after continuous infusion of sucrose. In the second experiment, the experimental design was the same except that instead of sucrose, maltose was used stabilize the rats' initial blood sugar. The authors reported for this experiment that there was no change in blood glucose levels after continuous infusion of maltose with administration of arabinose.

Osaki et al. (2001) conducted a repeated-dose oral feeding study to investigate the effects of L-arabinose feeding on lipogenesis due to its inhibition of sucrose in male rats. To do this, the rats were split into groups of four and given a diet consisting of either 0, 0.5, or 1 g L-arabinose/100 g diet for 10 days, along with either no sucrose, a mix of 10 g glucose and 10 g fructose/100 g-bw, or 10, 20, or 30 g sucrose/100 g-bw. The authors reported that while overall body weight and blood glucose were not affected by L-arabinose, there was a decrease in adipose tissue and insulin levels and an increase in cecum weight for diets with L-arabinose. They also reported that there was no increase in activity of CoA carboxylase, fatty acid synthase, and ATP citrate lyase in diets with sucrose, and that no rats exhibited diarrhea.

Preuss et al. (2007a) conducted a single-dose oral feeding study to assess the ability of various natural dietary substances to influence starch and sucrose absorption in both rats and pigs. The animals received either no carbohydrates (control), rice starch, sucrose, or a combination of rice starch and sucrose, along with either water (control), or two doses of 0.5 g in 2 mL water of either bean extract, hibiscus extract, arabinose, or a formula with all three ingredients. The exposure duration was four hours. The authors reported that there was a decrease in circulating blood glucose levels for those subjects who consumed either arabinose, hibiscus, or bean extract with sucrose when compared to the control, with the most pronounced difference occurring with arabinose. The researchers noted similar effects for the subjects on the rice starch diet.

In another study by Preuss et al. (2007b) with a similar experimental design, study type, set of subjects, and diets for the subjects, the authors reported decreased blood glucose levels, HbA1C, and systolic blood pressure for animals on the arabinose diets. They also reported altered fluid-electrolyte balances for animals on the arabinose diets. Finally, the authors noted that there were no toxic hepatic, renal, or hematologic effects.

Preuss et al. (2013) conducted another L-arabinose study with rats. This was a repeated-dose oral feeding study to compare the effects of bean extract and L-arabinose on carbohydrate metabolism via different basic mechanisms in an effort to ameliorate insulin resistance and elevated blood pressure associated with heavy starch/sugar consumption. To do this, 48 male rats were split into four groups, each given one of the following diets: either a powdered baseline diet (control), a regular rat chow containing 20% sucrose and 20% rice starch, a regular rat chow containing 20% sucrose, 20% rice starch, 2% bean extract, and 3% arabinose, or regular rat chow containing 20% sucrose, 20% rice starch, and 25 mg trivalent chromium/kg-bw. The rats were on these diets for a total of 130 days, after which the non-control groups were all switched to a diet of regular rat chow containing 20% sucrose, 20% rice starch, 2% bean extract, 3% L-arabinose, and 25 mg trivalent chromium/kg-bw. This second diet phase lasted 45 days. The authors reported decreased blood glucose levels,



enhanced response to exogenous insulin, decreased systolic blood pressure, decreased reninangiotensin system activity, decreased serum angiotensin-converting enzyme activity, and enhanced nitric oxide activity for the arabinose and bean starch diet when compared to the diet with carbohydrates only. However, there was no significant difference when compared to the control diet.

Sanai (1997) conducted a parallel, single-dose oral feeding study to evaluate the inhibition of sucrose digestion and absorption by L-arabinose in rats. To do this, 20 rats were split into four different groups which were each fed a diet with different amounts of arabinose. All of the diets contained 2.5 g sucrose/kg-bw, combined with either 0, 1.5, 50, or 250 mg arabinose added. The exposure duration was six hours and the authors reported that sucrose digestion and absorption were inhibited by L-arabinose in a dose dependent manner.

Schutte et al. (1992) conducted a repeated-dose oral feeding study across two experiments to investigate the apparent ileal digestibility and urinary excretion of L-arabinose. In experiment 1, four male pigs received three treatments for 11 days in the following fixed order: a diet with 100 g glucose/kg-bw (reference), 50 g L-arabinose/kg-bw, and 100 g L-arabinose/kg-bw. The authors reported a dose-dependent increase in water intake, a decrease in ileal digestibility, and an increase in ileal flow of total volatile fatty acids for the L-arabinose diets, and that Lactic acid did not differ between treatments.

For experiment 2, Schutte et al. (1992) divided 10 male pigs into two groups and each group received four treatments for 11 days in the following fixed order: Either 25, 50, 75 or 100 g L-arabinose/kg-bw or 25, 50, 75 and 100 g D-glucose/kg-bw. The authors reported increased water intake for the L-arabinose diets and no difference between groups for urine and feces production or fecal digestibility.

Seri et al. (1986) conducted a group of parallel single or repeated-dose oral feeding studies to investigate the effects of L-arabinose on intestinal alpha-glucosidase activities in vitro and to evaluate its effects on postprandial glycemic responses. This consisted of five total experiments in which mice were split into groups of either three, five, or six and fed varying amounts of L-arabinose. Additionally, Experiment 1 consisted of two parts. In Experiment 1a, each group of mice was given 1 g sucrose/kg-bw with either 0, 12.5, 25, or 50 mg L-arabinose/kg-bw, along with either 0, 0.625, 1.25, or 2.5 mg acarbose/kg-bw and either 0, 12.5, 25, or 50 mg xylose/kg-bw. The exposure duration was two hours. The rest of the experiments were similar in that each group of mice was given varying amounts of xylose, arabinose, and/or acarbose in either single or repeated-dose situations. The authors reported a general decrease in blood glucose and insulin levels for the L-arabinose diets.

Wang et al. (2012) (abstract only) conducted a randomized, parallel, single-dose intragastric feeding study in Type 2 diabetic rats to evaluate the effects of L-arabinose on glucose and lipid metabolism. To do this, 50 male rats (10 in a blank control group, and eight per group in the diabetic groups) received dextrin (0.36 g/mL) and sucrose (0.04 g/mL) via gastric lavage. Additionally, rats in different groups received one of the following: a blank control with no L-arabinose, no L-arabinose, 50 mg L-arabinose/kg-bw, 150 mg L-arabinose/kg-bw, 500 mg L-arabinose/kg-bw, or 20 mg acarbose/kg-bw. The exposure duration was one week. The authors reported decreased blood glucose levels and increased cecum weight/body weight ratio for L-arabinose diets. They also noted that L-arabinose did not affect liver weight ratio, epididymal fat weight ratio, total cholesterol, triglycerides, or the insulin sensitivity index.



Zhou et al. (2008; cited in Wijlens & Mars, 2015) conducted a randomized, parallel, repeated-dose oral feeding study to evaluate the effects of L-arabinose as an inhibitor on body mass and sucrose tolerance in mice with on a high fat/high sugar diet. One hundred male mice were divided into four groups: 0, 30, 150, 250 mg total daily L-arabinose. All of the mice were put on a high fat/high sugar diet for 30 days, along with an oral dose the L-arabinose dissolved in 4 mL phosphoric acid buffer solution twice per day. The authors reported that food intake did not differ between the groups, but that body weight and blood glucose levels did decrease for those mice consuming L-arabinose diets.

# 6.5 International Regulations and Guidelines

Listings for arabinose were not identified in the following databases: Food Standards Australia New Zealand (FSANZ), Codex Alimentarius, and Joint FAO/WHO Expert Committee on Food Additives (JECFA).

L-Arabinose is designated as a Food for Specified Health Uses, or FOSHU, in Japan. Specifically, the L-arabinose approved FOSHU products are "foods related to blood sugar levels."<sup>5</sup>

### 6.6 Section 6 Summary

The toxicological studies performed with Sensus Betawell® Arabinose and the human, animal and in vitro studies in the publicly available scientific literature demonstrate the safety of the substance.

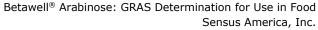
L-Arabinose ingested by humans is readily catabolized and exhaled, excreted in urine, or used as a carbon substrate by the microbiome. Only one case report suggests that there may be people with errors in metabolism that cannot metabolize arabinose; however, no adverse effect were reported in the only case identified/reported. In this subject arabinose was excreted in urine.

Numerous efficacy studies in humans and a variety of animal species and in vitro studies evaluating L-arabinose have reported that L-arabinose prevents, delays, or limits the uptake of glucose and fructose derived from the splitting of sucrose by the enzyme sucrase. L-arabinose appears to bind to the sucrase or sucrase-sucrose complex and prevent the enzymes activity for a short duration. The L-arabinose ultimately separates from the sucrase and normal enzymatic activity is restored.

These studies included short-term exposures to L-arabinose of up to 10 g in a single serving, and long-term exposures of up to 45 g/p/d for six months. These long term studies are of limited value due to poor study design and reporting. They do note that several subjects reported "mild" diarrhea and for some this was a transient effect that resolved after several days. There were no reports of persistent diarrhea with continued consumption of L-arabinose.

Toxicological studies with Sensus Betawell® Arabinose demonstrate the safety of L-arabinose generally but also demonstrate the safety of Betawell® Arabinose. The 90-day dietary toxicity study conducted in accordance with OECD test guidelines with Sensus Betawell® Arabinose reported NOAELs of 2218 mg Betawell® Arabinose/kg-bw/day in male rats and 2614 mg Betawell® Arabinose/kg-bw/day in female rats; these were the highest doses tested

<sup>&</sup>lt;sup>5</sup>Food for Specified Health Uses website, Japanese Ministry of Health, Labour and Welfare: http://www.mhlw.go.jp/english/topics/foodsafety/fhc/02.html; accessed 1-29-2017.







(30,000 ppm). Additional toxicology tests demonstrate that Sensus Betawell® Arabinose is neither mutagenic nor genotoxic under the test conditions.

The results from these studies demonstrate that Sensus Betawell® Arabinose is safe and suitable for its proposed uses.

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| Reference                                  | Substance   | Subjects  | Study Type   | Dose - Duration   | Reported Effects   |
|--|---|---|--|---|--|
| Halschou-Jensen L-arabinose<br>et al. 2014 | L-arabinose   | Study 1: 17 m<br>(23 y, healthy)<br>Study 2: 6 m<br>(23 y, healthy) | Randomized,<br>double-blind, cross-<br>over trial to<br>investigate the<br>inhibiting effect of    | Study 1: 0, 5 or 10% arabinose (0, 2.9, or 5.9 g) added to Meal A (bun and muffin [sucrose and starch from wheat], jam, and butter) or Meal B (2 buns | Study 1: For Meal A, no differences in glucose, insulin or C-peptide between 0, 5 or 10% arabinose diet. |
|  | L-arabinose added in a mixed meal containing sucrose and/or starch from |   | [starch from wheat], cheese and butter).  Study 2: 0 or 20% arabinose (0 or 10.2 g) added to solid | For Meal B, insulin and C-peptide were higher for 0% arabinose diet than for 10% arabinose diet.  |  |
|  |   |   | wheat flour on blood glucose, insulin and C-peptide responses in humans.                           | meal (Meal B of Study 1) or<br>semi-solid meal (Meal B<br>blended with part of the<br>drinks). Or 0 or 15 g arabinose<br>added to liquid meal (75 g   | Study 2: No differences in glucose, insulin, paracetamol or C-peptide between the 3 meals.               |
|  |   |   | maltose in 300 mL water).  |   | Results of the   |
|  |   |   |  | Duration for both studies was 3 hours.  | questionnaire on GI symptoms not reported.   |
| Inoue et al. 2000                          | L-arabinose   | Study 1: 8 people<br>(27-54 y, healthy)<br>Study 2: 40 people       | Single-dose study<br>(cross-over for<br>Study 1 and 3,   | Study 1: 50 g sucrose in 300 mL water with 0 or 2 g L-arabinose   | Decreased blood glucose levels for L-arabinose diets.  |
|  |   | (>40 y, healthy,<br>10 per group)                                   | randomized parallel<br>for Study 2) to<br>evaluate the effect                                      | Study 2: Jelly with 30 g sucrose and 0, 2, 3 and 4% L-arabinose   | No difference in insulin levels.   |
|  |   | Study 3: 10 people (48-75 y, diabetes type 2)                       | of L-arabinose on<br>blood glucose level   | (0, 0.6, 0.9 or 1.2 g<br>L-arabinose)   | No GI symptoms during or after completion of the   |
|  |   | Sexes not reported.   | after ingestion of sucrose-containing food in humans.  | Study 3: Jelly with 30 g sucrose and 0 or 3% L-arabinose (0 or 0.9 g L-arabinose).  | study.   |
|  |   |   |  | Exposure durations were 2 hours.  |  |



| Reference                     | Substance   | Subjects   | Study Type   | Dose - Duration   | Reported Effects   |
|-------------------------------|---|--|--|---|--|
| Kaats et al. 2011 L-arabinose | Study 1:  Phase 1: 20 people (6 m and 14 f, mean age at 53.8 y) | Randomized, blinded<br>studies (single-dose<br>for Study 1 and<br>repeated-dose for<br>Study 2) to evaluate<br>the effect of | Study 1:  Phase 1: 70 g of sucrose in water (control) on Day 1. On Day 2, 70 g of sucrose in water with 1 g of L-arabinose and | Decreased blood glucose and insulin levels for L-arabinose and chromium diets in both studies.  |  |
|                               |   | Phase 2: 10 people<br>(3 m and 7 f,<br>mean age at   | L-arabinose and<br>chromium on<br>lowering blood   | 200 µg of a patented food source of chromium.  Exposure duration is   | No adverse effects in either study.  |
|                               |   | 53.7 y)  | glucose and insulin levels.  udy 2: 50 people of m and 30 f, ean age at .2 y)  | 90 minutes.   |  |
|                               |   | Study 2: 50 people<br>(20 m and 30 f,<br>mean age at   |  | Phase 2: Diet with L-arabinose and a patented food source of chromium daily for 4 weeks.  |  |
|                               |   | 40.2 y)  |  | Study 2: 70 g of sucrose in water (control) on Day 1. On Day 2, 70 g of sucrose in water with 1 g of L-arabinose and 200 µg of a patented food source of chromium. Exposure duration is 90 minutes. |  |
| Krog-Mikkelsen<br>et al. 2011 | L-arabinose   | healthy) double-blind, cross<br>over, single-dose<br>study to evaluate<br>the effects of                                     | double-blind, cross-<br>over, single-dose<br>study to evaluate<br>the effects of<br>L-arabinose on                             | 4 sucrose beverages (75 g sucrose in 300 mL) with addition of 0 (control), 1, 2, or 3 g L-arabinose. Exposure duration was 3 hours.   | Decreased blood glucose levels, C-peptide, glucose-dependent insulintropic polypeptide and insulin for L-arabinose diet. |
|                               |   |  | intestinal sucrose activity in humans.   |   | Increased glucagon-like-<br>peptide-1 for L-arabinose<br>diet.   |
|                               |   |  |  |   | No differences for triacylglycerol, energy intake or appetite.   |
|                               |   |  |  |   | Adverse effects: A few mild GI symptoms; did   |



| Reference                       | Substance  | Subjects   | Study Type  | Dose - Duration  | Reported Effects  |  |  |  |
|---------------------------------|--|--|---|--|---|--|--|--|
|                                 |  |  |   |  | not differ between treatments.  |  |  |  |
| Krog-Mikkelsen l<br>et al. 2013 | L-arabinose  | 14 m (19-30 y,<br>healthy)                                   | Randomized,<br>double-blind,<br>crossover, single-                      | 75 g sucrose in 300 mL water with, 0, 4 or 8% (0, 3 or 6 g) D-xylose or 8% (6 g)   | Decreased blood glucose levels, C-peptide, insulin for L-arabinose diet.  |  |  |  |
|                                 |  |  | dose study to evaluate the effects of L-arabinose on intestinal sucrose | L-arabinose. Exposure duration was 3 hours.  | Increased glucagon-like-<br>peptide-1 for L-arabinose<br>diet.  |  |  |  |
|                                 |  |  | activity in humans.   |  | No differences in energy intake or appetite.  |  |  |  |
|                                 |  |  |   |  | Adverse effects: No differences in GI symptoms between treatments. Frequency and type of symptoms not reported. |  |  |  |
| Liu et al. 2013b                | L-arabinose  | <u>Study 1</u> : 25 m and<br>25 f (22-24 y,<br>10 per group) | 25 f (22-24 y, randomize  | Parallel,<br>randomized,<br>repeated-dose study                                    | randomized,<br>repeated-dose study  | randomized, (dissorrepeated-dose study 3 x 1 | Study 1: 45 g per day (dissolved in water, taken as 3 x 15 g) one of the following | Study 1: Decreased blood glucose levels for L-arabinose diets. |
|                                 |  | Study 2: 20  | to evaluate the effects of  | treatments:  | Three people in the   |  |  |  |
|                                 | (obese, 18-23 y, sex not mentioned, 10 per group)  3% L-arabinom 97% sucrose; 5% L-arabinom 95% sucrose; 10% L-arabinom 95% sucrose; | 3% L-arabinose (1.35 g) and 97% sucrose;                     | 10% L-arabinose group had mild diarrhea which                           |  |   |  |  |  |
|                                 |  | 10 per group)  |   | 5% L-arabinose (2.25 g) and 95% sucrose;   | disappeared after 4 days with continued intake of L-arabinose.  |  |  |  |
|                                 |  |  | 10% L-arabinose (4.5 g) and 90% sucrose;                                | Study 2: bw of the control group did not   |   |  |  |  |
|                                 |  |  |   | 100% L-arabinose (45 g); or  | change over time.   |  |  |  |
|                                 |  |  |   | 100% sucrose (control).<br>30 days exposure.                                       | L-arabinose group bw declined 5.5 to 6 kg over  |  |  |  |
|                                 |  |  |   | Study 2: Either 30 g<br>L-arabinose per day or 30 g<br>xylitol (control), taken as | the study period.   |  |  |  |



| Reference                | Substance  | Subjects                         | Study Type  | Dose - Duration   | Reported Effects  |
|--------------------------|--|----------------------------------|---|---|---|
|                          |  |                                  |   | 3 x 10 g, each dose before a meal. 180 day exposure.  | No adverse effects reported.  |
| Ohki 1999                | L-arabinose  | 89 f (healthy)                   | Repeated-dose study to evaluate the effect of sucrose-containing L-arabinose on fecal microflora, constituent and | 3 weeks no supplement, baseline period, then 10 g sucrose with 3% L-arabinose 2x daily for 2 weeks, then 10 days no supplement period.  | No differences were observed in total anaerobic or aerobic bacteria, pH, moisture content, ammonia content, or organic acid content.  |
|                          |  |                                  | characteristics in healthy women.   |   | Increased number of defecations per week and decreased non-defecation days.   |
|                          |  |                                  |   |   | No adverse effects reported.  |
| Segal & Foley<br>1959    | D- &<br>L-arabinose;<br>other<br>pentoses inc.<br>D-xylose,<br>D-lyxose, &<br>D-ribose | 5 m (18 – 21 y,<br>healthy)      | To observe the fate of C <sup>14</sup> labeled pentoses (inc. L-arabinose) administered intravenously.            | Five µc. of each sugar dissolved in 250 mL of saline infused over a 15 minute period (L-arabinose activity was 2.6 µc/mg). Expired air samples collected for 4 minutes at 15 to 60 minute intervals for 6 hours. Urine samples collected hourly for 6 hours and then pooled until 24 hours had elapsed. | First-order clearance of L-arabinose from blood at a rate of ~0.77% per minute (comparable to other pentoses) with >85% of L-arabinose excreted in urine within 24 hours; only 0.8% expired via respiration within 6 hours. |
| Shibanuma et al.<br>2011 | L-arabinose  | 18 m and 3 f<br>(>20 y, healthy) | Double-blind controlled, cross-over, single-dose study to investigate the suppression of blood glucose levels     | 150 g drinks of 40 g sucrose<br>and deionized water with 0 g<br>(control) or 2 g L-arabinose,<br>followed by 90 g bean paste<br>jelly containing 40 g sucrose   | Decreased blood glucose levels for L-arabinose diets.   |



| Reference                     | Substance                            | Subjects  | Study Type   | Dose - Duration   | Reported Effects  |
|-------------------------------|--------------------------------------|---|--|---|---|
|                               |                                      |   | by L-arabinose in healthy adults.  | after 2 hours. Exposure duration was 2 hours.   |   |
| Thondre &<br>Lightowler 2014a | Arabinose                            |   | A non-blind, crossover, singledose trial to study the glycemic response to sucrose, sucrose with pectin oligosaccharides, sucrose with L-arabinose, and sucrose with L-arabinose and pectin oligosaccharides | Subjects received one or more of the following diets:  55 g reference glucose (19 subjects)   | Decreased blood glucos<br>levels for L-arabinose<br>diets.  No adverse effects<br>reported. |
|                               |                                      |   |  | 50 g sucrose (11 subjects)  |   |
|                               |                                      |   |  | 49.73 g sucrose with 2.7 g pectin oligosaccharides (12 subjects)                              |   |
|                               |                                      |   |  | 50 g sucrose with 2.54 g<br>L-arabinose (10 subjects)   |   |
|                               |                                      |   |  | 50 g sucrose with 5.08 g<br>L-arabinose (12 subjects)   |   |
|                               |                                      |   |  | 50 g sucrose with 7.62 g<br>L-arabinose (10 subjects)   |   |
|                               |                                      |   |  | 49.73 g sucrose with 2.54 g<br>L-arabinose and 2.7 g pectin<br>oligosaccharides (10 subjects) |   |
|                               |                                      |   |  | Exposure duration = 180 minutes.  |   |
| Thondre &<br>Lightowler 2014b | Arabinose<br>(provided by<br>Sensus) | 11 people<br>y (healthy, 4 m and<br>7 f, mean age at<br>24.8 y) | A non-blind, repeat<br>measure, crossover<br>design trial to study<br>the glycemic<br>response to yogurt<br>with sucrose and   | Subjects received one of the following diets:   | Decreased blood glucose levels for arabinose diet.  |
|                               |                                      |   |  | 54.96 g reference glucose   | No adverse effects  |
|                               |                                      |   |  | 268.66 g yogurt with 29.85 sucrose  | reported.   |



| Reference                     | Substance                            | Subjects  | Study Type  | Dose - Duration   | Reported Effects                                   |
|-------------------------------|--------------------------------------|---|---|---|--|
|                               |                                      |   | yogurt with sucrose and arabinose.  | 285.71 g yogurt with 28.57 g sucrose and 3.17 g arabinose |  |
|                               |                                      |   |   | Exposure duration = 180 minutes.                          |  |
| Thondre &<br>Lightowler 2015a | Arabinose<br>(provided by<br>Sensus) | 13 people<br>(healthy, 5 m and<br>8 f, mean age at<br>28.2 y)   | A non-blind, repeat measure, crossover design trial to study the glycemic response to sucrose, sucrose with 10% arabinose and sucrose with 10% xylose           | Subjects received one of the following diets:             | Decreased blood glucose levels for arabinose diet. |
|                               |                                      |   |   | 54.96 g reference glucose                                 | No adverse effects reported.                       |
|                               |                                      |   |   | 50 g sucrose  |  |
|                               |                                      |   |   | 55 g sucrose with 10% arabinose                           |  |
|                               |                                      |   |   | 55 g sucrose with 10% xylose                              |  |
|                               |                                      |   |   | Exposure duration is 180 minutes.                         |  |
| Thondre &<br>Lightowler 2015b | Arabinose<br>(provided by<br>Sensus) | 12 people<br>(healthy, 6 m and<br>6 f, mean age at<br>31.3 y)   | A non-blind, repeat measure, crossover design trial to study the glycemic response to tropical juice drink with sucrose and tropical juice drink with arabinose | Subjects received one of the following diets:             | Decreased blood glucose levels for arabinose diet. |
|                               |                                      |   |   | 54.96 g reference glucose                                 | No adverse effects reported.                       |
|                               |                                      |   |   | 467.3 g tropical juice drink with sucrose                 |  |
|                               |                                      |   |   | 491.5 g tropical juice drink with arabinose               |  |
|                               |                                      |   |   | Exposure duration = 180 minutes.                          |  |
| Thondre &<br>Lightowler 2015c | (provided by (<br>Sensus)            | 12 people<br>y (healthy, 6 m and<br>6 f, mean age at<br>26.8 y) | A non-blind, randomized, crossover, single- dose trial to study the glycemic response to muffin with sucrose and muffin with sucrose                            | Subjects received one of the following diets:             | Decreased blood glucose levels for arabinose diet. |
|                               |                                      |   |   | 54.96 g reference glucose                                 | No adverse effects reported.                       |
|                               |                                      |   |   | 106.94 g muffin with sucrose                              |  |
|                               |                                      |   |   | 113.5 g muffin with sucrose and 12.5% arabinose           |  |



| Reference            | Substance   | Subjects  | Study Type  | Dose - Duration  | Reported Effects  |
|----------------------|-------------|---|---|--|---|
|                      |             |   | and 12.5%<br>arabinose  | Exposure duration is 180 minutes.                            |   |
| Yang et al.,<br>2013 | L-arabinose | 30 subjects, 19 m and 11 f (50 y, with metabolic syndrome) (13 additional subjects had dropped out for a variety of reasons.) | Single arm, repeated-dose study to evaluate the effects of L-arabinose consumption on metabolic syndrome in humans. | L-arabinose doses per day for 6 months (dissolved in water): | Decreased blood glucose<br>levels, bw, waist<br>circumference, diastolic<br>blood pressure, and total   |
|                      |             |   |   | 45 g (3 x 15 g) if bw > 60 kg;                               |   |
|                      |             |   |   | $20 g (2 \times 10 g) \text{ if bw } < 60 \text{ kg}.$       | cholesterol.  |
|                      |             |   |   |  | Systolic blood pressure, and LDL-cholesterol or HDL-cholesterol did not differ.   |
|                      |             |   |   |  | Adverse effects: 13 people reported diarrhea and 1 person reported mild nausea. Additionally, 3 failed to complete the study due to diarrhea and were not evaluated as part of the 30 subjects. |

List of Supporting Data and Information (in accordance with 21 CFR §170.255)

lipoprotein; m = male; mL = milliliter(s); y = year(s).



| Reference                | Substance   | Subjects   | Study Type  | Dose - Duration   | Reported Effects  |
|--------------------------|-------------|--|---|---|---|
| Alhaidary et al.<br>2011 | arabinose   | 100 f rats<br>(20 per group)   | Randomized,<br>parallel, repeated-<br>dose oral feeding<br>study to compare the<br>effects of five<br>different dietary<br>monosaccharides on<br>mineral and nitrogen<br>utilization. | Rats received a basal diet with one of the following ingredients added for 28 days:  A) 10% glucose. B) 9.2% xylose, 0.8% water C) 9.2% arabinose, 0.8% water D) 9.2% galacturonic acid, 0.8% water E) 9.2% galactose, 0.8% water   | No differences in: bw; body fat; water intake; urine production and pH; higher cecal and fecal weight for diet with arabinose.  |
| Fujii et al. 2000        | L-arabinose | Experiment 1: 54 m Wistar rats (6 per group)  Experiment 2: 14 m Wistar rats (7 per group) | Parallel, repeated-<br>dose oral feeding<br>study to evaluate the<br>physiological effects<br>of L-arabinose on<br>rats   | Experiment 1: Rats were given a test diet for 10, 20 or 30 days. The diets contained 20% sucrose and:  A) 0% L-arabinose, 5% cellulose (control)  B) 1% L-arabinose, 4% cellulose C) 2.5% L-arabinose and 2.5% cellulose  Experiment 2: For 20 days rats received a diet of only corn starch (no sucrose) with either 0% (control) or 2.5% L-arabinose. | Experiment 1: No differences in feed conversion rate, total cholesterol, blood glucose or amount or composition of organic acids.  Reduced bw gain, increased cecum weight, reduced retroperitoneal fat pad, reduced epididymal fat pad, reduced liver weight, reduced triacylglycerol, and reduced total liver lipids for diets with higher concentrations of L-arabinose. |
|                          |             |  |   |   | Experiment 2: Reduced feed conversion rate and liver weight in 2.5% L-arabinose group than in control, no other differences were found.   |



| Reference       | Substance   | Subjects   | Study Type  | Dose - Duration  | Reported Effects  |
|-----------------|-------------|--|---|--|---|
| Han et al. 2010 | L-arabinose | 40 m obese<br>rabbits (8 per<br>group)   | Randomized,<br>parallel, repeated-<br>dose oral feeding<br>study to evaluate<br>L-arabinose's<br>hypoglycemic and<br>anti-obesity effects   | For 5 months one group received ordinary feed (blank control) and four other groups received HFHS feed with:  A) 0.3085 g/kg L-arabinose per day B) 0.617 g/kg L-arabinose per day C) 0.9255 g/kg L-arabinose per day D) no L-arabinose (control)  | Reduced blood glucose, fat index and bw and increased stool amount for diet with L-arabinose when compared with control.  Food intake did not differ between groups.  |
| Hao et al. 2015 | L-arabinose | 56 m Wistar<br>rats; induced<br>metabolic<br>syndrome (using<br>HCHF diet)<br>(12 per group) | Randomized, parallel, repeated- dose oral study to investigate the effects of L-arabinose on hypertension, insulin resistance, and adipocytokines in rats with metabolic syndrome induced by a HCHF diet. | For 6 weeks groups received diet by gavage: Control: normal rats, normal chows Control L-arabinose: normal rats, normal chows, 400 mg L-arabinose/kg-bw/day Model: metabolic syndrome rats, HCHF diet Model L-arabinose: metabolic syndrome rats, HCHF diet, 400 mg L-arabinose/kg-bw/day                | Reduction in: bw, systolic and diastolic blood pressure, fasting blood glucose, triglycerides, total cholesterol, serum insulin, TNF-a, and leptin.  Increased expression of mRNA for hepatic CPT-1a and PDK4, reduced expression of mRNA for hepatic ACCa. |
| He et al. 2009  | L-arabinose | 60 m Wistar rats<br>(10 per group)   | Parallel, repeated-dose oral feeding study to evaluate the effects of L-arabinose on growth and carbohydrate, lipid metabolism in Wistar rats.  | Rats received one of the following diets for 6 weeks:  A) 0 L-arabinose, ordinary feed (blank control)  B) 525 mg L-arabinose/kg-bw, ordinary feed  C) 0 L-arabinose, HFHS diet  D) 87.5 mg L-arabinose/kg-bw, HFHS diet  E) 175 mg L-arabinose/kg-bw, HFHS diet  F) 525 mg L-arabinose/kg-bw, HFHS diet | bw, feed intake, food utilization rates, fasting blood glucose levels, total cholesterol and LDL-cholesterol did not differ. Reduced fat index, reduced blood glucose, increased HDL-cholesterol, and reduced triglycerides for diets with L-arabinose.     |



| Reference         | Substance  | Subjects  | Study Type  | Dose - Duration  | Reported Effects  |
|-------------------|--|---|---|--|---|
| Iwata et al. 2007 | al. 2007 L-arabinose 14 m rats (7 per group)   | Parallel, repeated-<br>dose oral feeding<br>study to evaluate the<br>effect of sucrose with<br>L-arabinose on the | 4-week diet of 20% sucrose with 0 (control) or 1% L-arabinose.  | No significant difference in bw gain, abdominal fat, total organic acids in cecal content, fecal weight, and fecal moisture.                 |   |
|                   |  | number of bifidobacteria in the rat cecum.  |   | Increased cecum weight and ammonia per cecum in 1% L-arabinose group than in control.  |   |
|                   |  |   |   |  | Reduced fecal dry weight in 1% L-arabinose group than in control.   |
|                   |  |   |   |  | Bifidobacteria was observed in 1% L-arabinose group but not in control.   |
| Li et al. 2013    | (12 healthy m parallel, repeated- rats in blank dose intragastric control, 10 m feeding study to rates in evaluate effect of metabolic L-arabinose on syndrome each glucolipid in groups B,C,D metabolism of | parallel, repeated-<br>dose intragastric<br>feeding study to<br>evaluate effect of                                | For 6 weeks, rats received a daily dose of L-arabinose in distilled water intragastrically:  A) blank control: 0 mg L-arabinose B) model control: 0 mg L-arabinose C) 87.5 mg L-arabinose/kg-bw D) 175 mg L-arabinose/kg-bw E) 525 mg L-arabinose/kg-bw | Reduced bw, fasting blood glucose, triglycerides, total cholesterol, LDL-cholesterol, and serum free fatty acids for diets with L-arabinose. |   |
|                   |  |   |   | No differences in HDL-cholesterol.   |   |
|                   |  |   | rats.   |  | Rats in metabolic syndrome first exhibited excess eating, drinking and urination, but this subsided during the treatments with arabinose. |
| Liu et al. 2013a  | L-arabinose  | 60 m mice.<br>50 were made<br>nutritionally   | Parallel, repeated-<br>dose intragastric<br>feeding study to  | The no-treatment group continued on ordinary feed. The obese mice received purified water  | Reduced bw, lipid-body ratio, and triglyceride level, and increased HDL-  |



| Reference               | Substance     | Subjects  | Study Type                                   | Dose - Duration  | Reported Effects   |
|-------------------------|---------------|---|--|--|--|
|                         |               | obese in<br>70 days; the  | evaluate effects of<br>L-arabinose on body   | intragastrically with 0 (control), 1,<br>2 or 4 g L-arabinose/kg-bw daily for  | cholesterol for diets with L-arabinose.  |
|                         |               | other 10 received 70-day ordinary feed (no- treatment group)              | weight reduction in obese mice.              | 45 days  | No significant differences in total cholesterol or organ indices.  |
| Matsuura et al.<br>2001 | L-arabinose   | Experiment 1:  30 m rats (6 per group)                                    | study to investigate                         | Experiment 1: After stable blood glucose concentrations were obtained with intragastric sucrose infusion, rats received one of the following test substances | Experiment 1: Administration of L-arabinose inhibited blood glucose levels after continuous infusion of                |
|                         | Experiment 2: | the alpha-<br>glucosidase   | intragastrically:                            | sucrose.   |  |
|                         |               | It is not clear if inhibitory activity of the same rats various sugars in | rats with portal vein                        | A) D-xylose 0.24 g/kg-bw B) L-arabinose 0.24 g/kg-bw C) D-glucorono-6, 3-lactone 0.24 g/kg-bw D) Acarbose 0.024 g/kg E) Voglibose 0.00024 g/kg               | Experiment 2: No change in blood glucose levels after continuous infusion of maltose with administration of arabinose. |
|                         |               |   |  | Exposure duration was 3 hours.   |  |
|                         |               |   |  | Experiment 2: The same as Experiment 1, but maltose instead of sucrose. No exposure duration given.  |  |
| Osaki et al. 2001       | L-arabinose   | 4 m rats per<br>group   | Repeated-dose oral feeding study (mixture of | Rats were fed 0, 0.5, or 1 g<br>L-arabinose/100 g diet in one of the<br>following diets for 10 days:   | Body weight and blood glucose not affected by L-arabinose.   |
|                         |               | not clear) to<br>investigate the<br>effects of                            | investigate the effects of                   | C: no sucrose CS10: 10 g sucrose/100 g bw CS20: 20 g sucrose/100 g bw CS30: 30 g sucrose/100 g bw  | Decreased adipose tissue, increased cecum weight, and decreased insulin levels for diets with L-arabinose.             |
|                         |               |   | L-arabinose feeding on lipogenesis due to    | CGF20: 10 g glucose and 10 g fructose/100 g bw   | No increase in activity of CoA carboxylase, fatty acid   |



| Reference              | Substance   | Subjects  | Study Type  | Dose - Duration   | Reported Effects  |
|------------------------|-------------|---|---|---|---|
|                        |             |   | its inhibition of sucrose.  |   | synthase and ATP citrate lyase in diets with sucrose.   |
|                        |             |   |   |   | No rats exhibited diarrhea.   |
| Preuss et al.<br>2007a | arabinose   | 96 m Sprague-<br>Dawley rats<br>and 2 Yorkshire<br>pigs | Single-dose oral feeding study (mixture of parallel/cross-over for rats, not clear; cross-over for pigs) to assess the ability of various natural dietary substances to influence starch and                  | Rats and pigs received: -no carbohydrate (control), rice starch, sucrose, or combined rice starch with sucrosewater (control), or two doses of 0.5 g in 2 mL water of: bean extract, hibiscus extract, arabinose, or formula with all 3 ingredients.  | Decreased blood glucose levels for arabinose combined with sucrose compared to control.  Decreased blood glucose levels for arabinose combined with rice starch compared to control.                        |
|                        |             |   | sucrose absorption in rats and pigs.  | Exposure duration was 4 hours.  |   |
| Preuss et al.<br>2007b | L-arabinose | 16 Sprague-<br>Dawley rats<br>(8 per group)             | Repeated-dose oral feeding study (mixture of parallel/cross-over for rats, not totally clear) to assess the ability of various natural dietary substances to influence starch and sucrose absorption in rats. | Rats received one of the following diets twice daily over 9 weeks:  - 2 mL of water with no carbohydrate (control), 2 g glucose, 2 g rice starch, 2 g sucrose, or 2 g of combined rice starch and sucrose.  - 4 mL of water (control), or 4 mL of water with 1 g of a formula containing bean extracts (19%), hibiscus extracts (31%), and L-arabinose (31%). | Decreased blood glucose levels, decreased HbA1C, lowered systolic blood pressure and altered fluid-electrolyte balance for arabinose diets.  No toxic hepatic, renal, or hematologic effects were reported. |
| Preuss et al. 2013     | L-arabinose | 48 m Sprague-<br>Dawley rats<br>(12 per group)          | Repeated-dose oral feeding study to compare the effects of bean extract and L-arabinose on carbohydrate metabolism via  | Phase 1: Rats received one of the following diets for 130 days: - Powdered baseline diet (control)  | Decreased blood glucose levels, enhanced response to exogenous insulin, decreased blood pressure, decreased renin-angiotens system activity, decreased serum angiotensin-                                   |



| Reference          | Substance   | Subjects                                    | Study Type   | Dose - Duration   | Reported Effects  |
|--------------------|-------------|---|--|---|---|
|                    |             |   | different basic<br>mechanisms to   | - Regular rat chow containing 20% sucrose and 20% rice starch   | converting enzyme activity, and enhanced nitric oxide   |
|                    |             |   | ameliorate insulin<br>resistance and<br>elevated blood   | istance and - Regular rat chow containing 20% when composed blood sucrose and 20% rice starch with carbohydra   | activity for arabinose diet when compared to diet with carbohydrates only.  |
|                    |             |   | pressure associated with heavy   | 2% bean extract and 3%<br>L-arabinose   | No significant difference when compared to control.   |
|                    |             |   | sugar/starch<br>consumption.   | <ul> <li>Regular rat chow containing 20% sucrose and 20% rice starch with</li> <li>mg/kg trivalent chromium</li> </ul>  | when compared to control.   |
|                    |             |   |  | Phase 2:<br>The above three treatment groups<br>(no control group) continued to<br>receive the following diet for<br>45 days:   |   |
|                    |             |   |  | <ul> <li>Regular rat chow containing 20% sucrose and 20% rice starch with 2% bean extract, 3% L-arabinose, and 25 mg/kg trivalent chromium</li> </ul>   |   |
| Sanai 1997         | L-arabinose | 20 m rats (5 per<br>group)                  | Parallel, single-dose oral feeding study to evaluate inhibition of sucrose digestion and absorption by L-arabinose in rats.                | 2.5 g sucrose/kg-bw combined with either 50 mg L-arabinose, 250 mg L-arabinose, 1.5 mg acarbose, or water (control)  Exposure duration was 6 hours.   | Sucrose digestion and absorption were inhibited by L-arabinose in a dosedependent manner.   |
| Schutte et al.1992 | L-arabinose | Experiment 1:<br>4 m pigs                   | Repeated-dose oral feeding study (cross-   | Experiment 1: Pigs received 3 treatments for 11 days in the   | Experiment 1: Increased water intake, decreased   |
|                    |             | Experiment 2:<br>10 m pigs (5 per<br>group) | over for Experiment 1 and parallel for Experiment 2) to investigate the apparent ileal digestibility and urinary excretion of L-arabinose. | following fixed order: a diet with 100 g glucose/kg-bw (control), 50 g L-arabinose/kg-bw, and 100 g L-arabinose/kg-bw.  Experiment 2: Pigs divided in 2 groups. Each group received 4 treatments for 11 days in the following fixed order: Either 25, 50, | ileal digestibility, and increased ileal flow of total volatile fatty acids for L-arabinose diets. Lactic acid did not differ between treatments.  Experiment 2: Increased water intake for the |

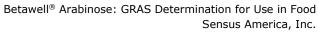


| Reference        | Substance   | Subjects                       | Study Type                            | Dose - Duration   | Reported Effects   |                      |  |
|------------------|-------------|--------------------------------|---------------------------------------|---|--|----------------------|--|
|                  |             |                                |                                       | 75 or 100 g L-arabinose/kg-bw or 25, 50, 75 and 100 g D-glucose/kg-bw (control).  | L-arabinose diets. No difference between groups for urine and feces production or fecal digestibility. |                      |  |
| Seri et al. 1996 | L-arabinose | Experiment 1:                  | Parallel single or                    | Experiment 1a: 0, 12.5, 25 or 50 mg   | Decreased blood glucose  |                      |  |
|                  |             | 6 mice per group               | repeated-dose oral feeding studies to | L-arabinose/kg-bw; 0, 12.5, 25 or 50 mg xylose/kg-bw; 0, 0.625, 1.25  | levels and insulin levels for L-arabinose diets.   |                      |  |
|                  |             | Experiment 2:                  | investigate the                       | or 2.5 mg acarbose/kg-bw with 1 g   |  |                      |  |
|                  |             | 5 rats per group               | L-arabinose on intestinal alpha-      | effects of<br>L-arabinose on  | sucrose/kg-bw. The exposure duration was 2 hours.  |                      |  |
|                  |             | Experiment 3: 6 mice per group |                                       | Experiment 1b: 0, 25, 50 or 100 mg  |  |                      |  |
|                  |             | Experiment 4:                  |                                       | L-arabinose/kg-bw; 0, 0.625, 1.25 or 2.5 mg acarbose/kg-bw with 1 g   |  |                      |  |
|                  |             | 3 rats per group               |                                       |   |  | evaluate its effects | soluble starch/kg-bw. The exposure duration was 2 hours. |
|                  |             | Experiment 5:                  | glycemic responses.                   | Experiment 2: 0, 50, 100 mg/kg-bw   |  |                      |  |
|                  |             | 6 rats per group               |                                       | L-arabinose with 2.5 g/kg sucrose. The exposure duration was 2 hours.   |  |                      |  |
|                  |             |                                |                                       | Experiment 3: Consecutive 0 or 25 mg/kg L-arabinose per day for 3 weeks with 1 g/kg sucrose.  |  |                      |  |
|                  |             |                                |                                       | Experiment 4: 6 groups received 1000 mg/kg-bw L-arabinose. 1 control group received no L-arabinose. The exposure duration was 24 hours. |  |                      |  |
|                  |             |                                |                                       | Experiment 5: Rats received 1000 mg L-arabinose, xylose or water (control). Exposure duration was 24 hours.                             |  |                      |  |



| Reference   | Substance       | Subjects   | Study Type  | Dose - Duration   | Reported Effects   |
|---|-----------------|--|---|---|--|
| Wang et al. 2012  | L-arabinose     | 50 m rats (10 in<br>blank control,<br>and 8 per group<br>in the diabetes | Randomized,<br>parallel, single-dose<br>intragastric feeding  | Rats received dextrin (0.36 g/mL) and sucrose (0.04 g/mL) via gastric lavage, with:   | Decreased blood glucose levels and increased cecum weight/bw ratio for L-arabinose diets.  |
|   |                 | type 2 groups B,<br>C, D, E, F)  | study to evaluate the<br>effect of L-arabinose<br>on glucose and lipid<br>metabolism in type 2<br>diabetic rats | A) blank control, no L-arabinose B) no L-arabinose C) 50 mg L-arabinose/kg-bw D) 150 mg L-arabinose/kg-bw E) 500 mg L-arabinose/kg-bw F) 20 mg acarbose/kg-bw Exposure duration was one week. | L-arabinose diets. L-arabinose did not affect liver weight ratio, epididymal fat weight ratio, total cholesterol, triglycerides, or the insulin sensitivity index. |
| Zhou et al. (2008;<br>cited in Wijlens &<br>Mars, 2015) | L-arabinos<br>e | 100 m mice<br>(25 per group)   | Randomized parallel,<br>repeated-dose oral<br>feeding study to<br>evaluate the effects<br>of L-arabinose as     | Mice were put on a HFHS diet for 30 days with an oral dose of arabinose dissolved in 4 mL phosphoric acid buffer solution twice per day:  | Food intake did not differ between the groups. Decreased bw and blood glucose levels for L-arabinose diets.  |
|   |                 |  | inhibitor on body<br>mass and sucrose<br>tolerance in mice<br>with HFHS feeding                                 | <ul><li>A) 250 mg L-arabinose</li><li>B) 150 mg L-arabinose</li><li>C) 30 mg L-arabinose</li><li>D) 0 mg L-arabinose (control)</li></ul>  |  |

ATP = adenosine triphosphate; bw = body weight; f = female; g = gram(s); GI = gastrointestinal; HDL = high-density lipoprotein; HCHF = high-carbohydrate, high-fat; HFHS = high-fat high-sucrose; kg = kilogram(s); LDL = low-density lipoprotein; m = male; mg = milligram(s); mL = milliliter(s)



4

RAMBOLL

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# 7 List of Supporting Data and Information (in accordance with 21 CFR §170.255)

Part 7 provides lists of all of the data and information discussed in Part 6 to provide a basis for our view that the notified substance is safe under the conditions of its intended use as described in accordance with 21 CFR §570.250(a)(1). Section 7.1 presents a list of the publicly available published literature. Section 7.2 provides a list of the literature presented in the Appendices of this dossier.

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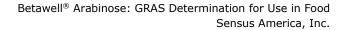


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# 7.2 List of Exhibits (Appendices)

Information is generally available unless noted otherwise.

- Appendix A Specifications and Batch Data (generally available)
- Appendix B Residual and Contaminants Analyses (not generally available)
  - B1 Residuals and Contaminants Analyses: Alkaline Process
  - B2 Residuals and Contaminants Analyses: Enzymatic Process
  - B3 Residuals and Contaminants Analyses: Pesticides
- Appendix C Toxicological Studies (generally available)
  - C1 90-Day Oral Tox Study with Betawell L-Arabinose by Dietary Administration in the Rat
  - C2 Evaluation of the Mutagenic Activity of Betawell L-Arabinose in the Salmonella typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay (Plate Incorporation and Pre-Incubation Methods)
  - C3 An In Vitro Micronucleus Assay with Betawell L-Arabinose in Cultured Peripheral Human Lymphocytes
  - C4 Development of an Analytical Method for the Analysis of Betawell L-Arabinose in Diet
- Appendix D Selected Food Codes and Categories
- Appendix E Reference Literature: Copies (PDF on CD)
- Appendix F GRAS Expert Panel Report





APPENDIX A SPECIFICATIONS AND BATCH DATA



Subject : Arabinose powder – batch analysis for alkaline

process

: Greg Sower, Gavin Thompson

Copy : Anton Kemmeren

Sender : Alex Benschop

Date : 05-09-2016

Reference: YJ
Archive: F22090
Doc.no: 160618.9620

Page : 1

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# Data for three batches for GRAS determination:

|                                  | Arabinose             | Arabinose             | Arabinose             |                    |
|----------------------------------|-----------------------|-----------------------|-----------------------|--------------------|
|                                  | powder<br>batch C61-1 | powder<br>batch C62-1 | powder<br>batch C65-1 | Method of analysis |
| Arabinose (wt%)                  | >99.5                 | >99.9                 | >99.9                 | Dionex-PAD         |
| Fucose (wt%)                     | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Rhamnose (wt%)                   | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Galactose (wt%)                  | 0.13                  | < 0.01                | 0.03                  | Dionex-PAD         |
| Glucose (wt%)                    | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Mannose (wt%)                    | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Xylose (wt%)                     | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Fructose (wt%)                   | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Sucrose (wt%)                    | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Galacturonic acid (wt%)          | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Glucuronic acid (wt%)            | < 0.01                | < 0.01                | < 0.01                | Dionex-PAD         |
| Dry matter (wt%)                 | 99.9                  | 99.95                 | 99.98                 | 3 hours 105 °C     |
| Apha color (Hazen)               | 0                     | <1                    | 0                     | 10% solution       |
| Turbidity (FNU)                  | 2.7                   | 1.50                  | 1.2                   | 10% solution       |
| Aerobic plate count 30°C / 10 g  | 316                   | 67                    | 63                    |                    |
| Moulds/10 g                      | 0                     | 0                     | 0                     |                    |
| Yeasts / 10 g                    | 0                     | 0                     | 0                     |                    |
| Clostridium perfringens/10 g     | 0                     | 0                     | 0                     |                    |
| Listeria / 10 g                  | Absent                | Absent                | Absent                |                    |
| Bacillus cereus/ g               | 0                     | 0                     | 0                     |                    |
| Staph. aureus/ g                 | Absent                | Absent                | Absent                |                    |
| Enterobacteriaceae (kwal) / 10 g | Absent                | Absent                | Absent                |                    |
| Salmonella / 10 g                | Absent                | Absent                | Absent                |                    |
| E. coli / 10 g                   | Absent                | Absent                | Absent                |                    |
| Coliforms/10 g                   | Absent                | Absent                | Absent                |                    |
| Faecal Streptococci (cfu/g)      | <10                   | <10                   | <10                   | KF agar method     |
| Antimony (mg/kg)                 | <0.005                | <0.005                | <0.005                | ICP-MS             |
| Arsenic (mg/kg)                  | <0.01                 | <0.01                 | <0.01                 | ICP-MS             |
| Cadmium (mg/kg)                  | <0.005                | <0.005                | <0.005                | ICP-MS             |
| Copper(mg/kg)                    | 0.066                 | 0.02                  | 0.027                 | ICP-MS             |
| Lead (mg/kg)                     | <0.01                 | <0.01                 | <0.01                 | ICP-MS             |
| Mercury (μg/kg)                  | <0.5                  | <0.5                  | <0.5                  | ICP-MS             |
| Molybdene (mg/kg)                | <0.01                 | <0.01                 | 0.03                  | ICP-MS             |
| Tin (mg/kg)                      | <0.01                 | <0.01                 | <0.01                 | ICP-MS             |
| Bismuth (mg/kg)                  | <0.2                  | <0.2                  | <0.2                  | Analog §64 LFGB    |
| Silver(mg/kg)                    | <0.05                 | <0.05                 | <0.05                 | Analog §64 LFGB    |
| Aflatoxin B1 (μg/kg)             | <0.05                 | <0.05                 | <0.05                 | IM W8333           |
| Aflatoxin B2 (µg/kg)             | <0.02                 | <0.02                 | <0.02                 | IM W8333           |
| Aflatoxin G1 (μg/kg)             | <0.05                 | <0.05                 | <0.05                 | IM W8333           |
| Aflatoxin G2 (μg/kg)             | <0.03                 | <0.03                 | <0.03                 | IM W8333           |
| AflatoxinsTotal (µg/kg)          | <0.15                 | <0.15                 | <0.15                 | IM W8333           |



: Arabinose powder – Stability data Subject Reference: YJ

: F22090 Archive

Doc.no : 160618.9620 : Greg Sower, Gavin Thompson То

: 1 Page

: Anton Kemmeren Сору

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Sender : Alex Benschop E yvonne.joosse@cosun.com

: 15-11-2016 Date

Data for batch C7-1(enzymatic process) analysed in November 2012 and November 2016:

|                                  | Arabinose  | Arabinose  | Method of analysis |
|----------------------------------|------------|------------|--------------------|
|                                  | powder     | powder     | Method of analysis |
|                                  | batch C7-1 | batch C7-1 |                    |
|                                  | 7-11-2012  | 4-11-2016  |                    |
| Arabinose (wt%)                  | 99.9       | 99.8       | Dionex-PAD         |
| Fucose (wt%)                     | < 0.01     | < 0.01     | Dionex-PAD         |
| Rhamnose (wt%)                   | 0.01       | 0.01       | Dionex-PAD         |
| Galactose (wt%)                  | 0.04       | 0.04       | Dionex-PAD         |
| Glucose (wt%)                    | < 0.01     | < 0.01     | Dionex-PAD         |
| Mannose (wt%)                    | < 0.01     | < 0.01     | Dionex-PAD         |
| Xylose (wt%)                     | 0.03       | 0.03       | Dionex-PAD         |
| Fructose (wt%)                   | < 0.01     | < 0.01     | Dionex-PAD         |
| Sucrose (wt%)                    | < 0.01     | < 0.01     | Dionex-PAD         |
| Galacturonic acid (wt%)          | < 0.01     | < 0.01     | Dionex-PAD         |
| ( ,                              |            | < 0.01     |                    |
| Glucuronic acid (wt%)            | < 0.01     |            | Dionex-PAD         |
| Dry matter (wt%)                 | 99.9       | 99.9       | 3 hours 105 °C     |
| Apha color (Hazen)               | 0          | 0          | 10% solution       |
| Turbidity (FNU)                  | <1         | <1         | 10% solution       |
| Aerobic plate count 30°C / 10 g  | <1000      | <1000      | ISO 4833:2003      |
| Moulds/10 g                      | 0          | 0          | ISO 7954:1987      |
| Yeasts / 10 g                    | <20 CFU/g  | <20 CFU/g  | ISO 7954:1987      |
| Clostridium perfringens/10 g     | <20 CFU/g  | <20 CFU/g  | ISO 7937:2004      |
| Listeria / 10 g                  | Absent     | Absent     | ISO 11290-1:1997   |
| Bacillus cereus / g              | <100 CFU/g | <100 CFU/g | ISO 7932:2004      |
| Staph. aureus/ g                 | Absent     | Absent     | ISO 6888-3 :2003   |
| Enterobacteriaceae (kwal) / 10 g | Absent     | Absent     | ISO 21528-1:2004   |
| Salmonella / 10 g                | Absent     | Absent     | ISO 6579:2002      |
| E. coli / 10 g                   | Absent     | Absent     | ISO 16649-2:2001   |
| Coliforms/10 g                   | Absent     | Absent     | ISO 4832:2006      |
| Cronobacter Sakazakii            | Absent     | Absent     | ISO 22964:2006     |
| Faecal Streptococci (cfu/g)      | Absent     | Absent     | KF agar method     |
| Antimony (mg/kg)                 | <0.005     | <0.005     | ICP-MS             |
| Arsenic (mg/kg)                  | <0.01      | <0.01      | ICP-MS             |
| Cadmium (mg/kg)                  | <0.005     | <0.005     | ICP-MS             |
| Copper (mg/kg)                   | 0.011      | 0.011      | ICP-MS             |
| Lead (mg/kg)                     | <0.01      | <0.01      | ICP-MS             |
| Mercury (μg/kg)                  | <0.5       | <0.5       | ICP-MS             |
| Molybdene (mg/kg)                | <0.01      | <0.01      | TCP-MS             |
| Tin (mg/kg)                      | <0.01      | <0.01      | ICP-MS             |
| Bismuth (mg/kg)                  | <0.2       | <0.2       | Analog §64 LFGB    |
| Silver (mg/kg)                   | <0.05      | <0.05      | Analog §64 LFGB    |
| AflatoxinB1 (µg/kg)              | <0.05      | <0.05      | IM W8333           |
| Aflatoxin B2 (μg/kg)             | <0.02      | <0.02      | IM W8333           |
| Aflatoxin G1 (μg/kg)             | <0.05      | <0.05      | IM W8333           |
| Aflatoxin G2 (µg/kg)             | <0.03      | <0.03      | IM W8333           |
| Aflatoxins Total (µg/kg)         | <0.15      | <0.15      | IM W8333           |



Datum 15 Nov ember 2016

Pagina

Data for batch C61-1 (alkaline process) analysed in Januari 2016 and November 2016:

|                                  | Arabinasa           | Arabinasa           | Mothod at analysis |
|----------------------------------|---------------------|---------------------|--------------------|
|                                  | Arabinose<br>powder | Arabinose<br>powder | Method of analysis |
|                                  | batch C61-1         | batch C61-1         |                    |
|                                  | 4-1-2016            | 4-11-2016           |                    |
| Arabinose (wt%)                  | >99.5               | 99.8                | Dionex-PAD         |
|                                  | >99.5<br>< 0.01     | 11 00.0             |                    |
| Fucose (wt%)                     |                     | < 0.01              | Dionex-PAD         |
| Rhamnose (wt%)                   | < 0.01              | < 0.01              | Dionex-PAD         |
| Galactose (wt%)                  | 0.13                | <0.1                | Dionex-PAD         |
| Glucose (wt%)                    | < 0.01              | < 0.01              | Dionex-PAD         |
| Mannose (wt%)                    | < 0.01              | < 0.01              | Dionex-PAD         |
| Xylose (wt%)                     | < 0.01              | < 0.01              | Dionex-PAD         |
| Fructose (wt%)                   | < 0.01              | < 0.01              | Dionex-PAD         |
| Sucrose (wt%)                    | < 0.01              | < 0.01              | Dionex-PAD         |
| Galacturonic acid (wt%)          | < 0.01              | < 0.01              | Dionex-PAD         |
| Glucuronic acid (wt%)            | < 0.01              | < 0.01              | Dionex-PAD         |
| Dry matter (wt%)                 | 99.9                | 99.96               | 3 hours 105 °C     |
| Apha color (Hazen)               | 0                   | 46                  | 10% solution       |
| Turbidity (FNU)                  | 2.7                 | 5                   | 10% solution       |
| Aerobic plate count 30°C / 10 g  | 316                 | 744                 | ISO 4833:2003      |
| Moulds/ 10 g                     | 0                   | 0                   | ISO 7954:1987      |
| Yeasts / 10 g                    | 0                   | 0                   | ISO 7954:1987      |
| Clostridium perfringens/10 g     | 0                   | 0                   | ISO 7937:2004      |
| Listeria / 10 g                  | Absent              | Absent              | ISO 11290-1:1997   |
| Bacillus cereus/ g               | 0                   | 0                   | ISO 7932:2004      |
| Staph. aureus/ g                 | Absent              | Absent              | ISO 6888-3 :2003   |
| Enterobacteriaceae (kwal) / 10 g | Absent              | Absent              | ISO 21528-1:2004   |
| Salmonella / 10 g                | Absent              | Absent              | ISO 6579:2002      |
| E. coli / 10 g                   | Absent              | Absent              | ISO 16649-2:2001   |
| Coliforms/10 g                   | Absent              | Absent              | ISO 4832:2006      |
| Cronobacter Sakazakii            | Absent              | Absent              | ISO 22964:2006     |
| Faecal Streptococci (cfu/g)      | <10                 | <10                 | KF agar method     |
| Antimony (mg/kg)                 | <0.005              | <0.005              | TCP-MS             |
| Arsenic (mg/kg)                  | <0.01               | <0.01               | ICP-MS             |
| Cadmium (mg/kg)                  | <0.005              | <0.005              | ICP-MS             |
| Copper (mg/kg)                   | 0.066               | 0.062               | ICP-MS             |
| Lead (mg/kg)                     | <0.01               | <0.01               | ICP-MS             |
| Mercury (µg/kg)                  | <0.5                | <0.5                | ICP-MS             |
| Molybdene (mg/kg)                | <0.01               | <0.01               | ICP-MS             |
| Tin (mg/kg)                      | <0.01               | <0.01               | ICP-MS             |
| Bismuth (mg/kg)                  | <0.2                | <0.2                | Analog §64 LFGB    |
| Silver (mg/kg)                   | <0.05               | <0.05               | Analog §64 LFGB    |
| Aflatoxin B1 (µg/kg)             | <0.05               | <0.05               | IM W8333           |
| Aflatoxin B2 (μg/kg)             | <0.02               | <0.02               | IM W8333           |
| Aflatoxin G1 (µg/kg)             | <0.05               | <0.05               | IM W8333           |
| Aflatoxin G2 (µg/kg)             | <0.03               | <0.03               | IM W8333           |
| Aflatoxins Total (µg/kg)         | <0.15               | <0.15               | IM W8333           |

# Memo



Subject : GRAS Batch data Enzymatic Referentie : \aafi\science

Archiefcode:

To : Gavin Thompson

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Date : September 05, 2015

Attachment : 1

# 1. Purity

Water – Max. 0.3% (Karl Fischer Method) Other saccharides – Max. 1% on the dry weight basis (HPLC) Ash – Max. 0.01% on the dry weight basis (Conductivity Ash Method) Heavy metals -  $\leq$  0.3 ppm ( $\leq$  0.3 mg/kg) Aflatoxin and biological contaminants

| Test                          | Method              | Maximum        |
|-------------------------------|---------------------|----------------|
| Total Viable Count / g (30°C) | ISO 4833:2003       | ≤ 1000 CFU / g |
| Yeasts / g                    | ISO 7954:1987       | ≤ 20 CFU / g   |
| Moulds / g                    | ISO 7954:1987       | ≤ 20 CFU / g   |
| Staph. aureus / g             | ISO 6888-3 :2003    | Absent         |
| Salmonella / 50g              | ISO 6579:2002       | Absent         |
| E. coli / g                   | ISO 16649-2:2001    | Absent         |
| Bacillus cereus / g           | ISO 7932:2004       | ≤ 100 CFU / g  |
| Coliforms / g                 | ISO 4832:2006       | Absent         |
| Enterobacteria / g            | ISO 21528-1:2004    | Absent         |
| Listeria / g                  | ISO 11290-1:1997    | Absent         |
| Clostridium perfringens/g     | ISO 7937:2004       | Absent         |
| Cronobacter Sakazakii         | ISO 22964:2006      | Absent         |
| Faecal Streps/g               | External laboratory | Absent         |
| Aflatoxins                    | External laboratory | < 0.1 μg/kg    |

Pesticide contaminants – Not detectable

#### 2. Analytical Aspects

Several batches were analyzed to validate and verify the process. The analytical results of 3 typical batches are listed in table 1 below. The data show compliance with the specification as given above.



Datum 5 March 2015 Referentie \aafi\science

Pagina 2

Table 1: Typical analyses of three arabinose batches from Cosun Biobased Products

| Batch              | C7-1    | C12-1   | C15-1   |
|--------------------|---------|---------|---------|
| Copper             | 0.011   | 0.11    | 0.03    |
| Antimony           | <0.005  | <0.005  | <0.005  |
| Arsenic            | <0.01   | <0.01   | <0.01   |
| Bismuth            | <0.2    | <0.2    | <0.2    |
| Cadmium            | <0.005  | <0.005  | <0.005  |
| Mercury            | <0.0005 | <0.0005 | <0.0005 |
| Lead               | <0.01   | <0.01   | <0.01   |
| Molybdene          | 0.01    | <0.01   | 0.03    |
| Tin                | <0.01   | <0.01   | <0.01   |
| Silver             | <0.05   | <0.05   | <0.05   |
| Total heavy metals | 0.021   | 0.11    | 0.06    |
| Arabinose, wt%     | >99.9   | 99.5    | >99.0   |
| Other sugars, wt%  | 0.1     | 0.22    | 0.11    |
| Water, wt%         | 0.1     | 0.4     | 0.2     |

| Component                            | Value           |
|--------------------------------------|-----------------|
| Arabinose                            | 99.9 wt%        |
| Glucose                              | <0.01 wt%       |
| Mannose                              | <0.01 wt%       |
| Rhamnose                             | 0.01 wt%        |
| Xylose                               | 0.03 wt%        |
| Fucose                               | <0.01 wt%       |
| Galactose                            | 0.04 wt%        |
| Galacturonic acid                    | <0.01 wt%       |
| Beet pectin derived oligosaccharides | 0.02 wt%        |
| Water content                        | 0.1 wt%         |
| Solubility ( 10% in water)           | < 20 Hazen      |
| Clarity                              | 0.85 – 0.90 FNU |



Subject Arabinose poeder

To S. Bink, H. van Nispen, A. van Kemmeren

Archiefcode : F22090 Doc.nr. : 152244.9620

Pagina : 1

Referentie: YJ

Copy T 0165-582844

F

Date : 4-22-2015

#### **Results:**

|                          | 1.<br>Ara C7-1<br>Analysis<br>per 10 g | 2.<br>Ara 12-1<br>Analysis per 10 g | 3.<br>Ara 15-1<br>Analysis per 10 g |
|--------------------------|--|-------------------------------------|-------------------------------------|
| Aerobic plate count 30   | 0                                      | 250                                 | 25                                  |
| Moulds                   | 0                                      | 25                                  | 0                                   |
| Yeasts                   | 0                                      | 0                                   | 0                                   |
| Clostridium perfringens  | 0                                      | 0                                   | 0                                   |
| Listeria monocytogenes   | Absent                                 | Absent                              | Absent                              |
| Bacillus cereus          | 0                                      | 0                                   | 0                                   |
| Staphylococcus aureus    | Absent                                 | Absent                              | Absent                              |
| Enterobacteriaceae(kwal) | Absent                                 | Absent                              | Absent                              |
| Salmonella               | Absent                                 | Absent                              | Absent                              |
| Escherichia coli         | Absent                                 | Absent                              | Absent                              |
| Coliforms                | Absent                                 | Absent                              | Absent                              |
| Fecal Streptococci       | Absent                                 | Absent                              | Absent                              |
| Cronobacter sakazakii    | Absent                                 | Absent                              | Absent                              |

Referentie: YJ Archiefcode: F22090 Doc.nr.: 152244.9620

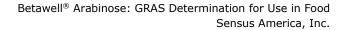
(b) (6)

Pagina : 1

T 0165-582844

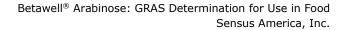
F

E yvonne.joosse@cosun.com





APPENDIX B RESIDUALS AND CONTAMINANTS ANALYSES





APPENDIX B1
RESIDUALS AND CONTAMINANTS ANALYSES:
ALKALINE PROCESS



Cosun (CFTC sectie analyse) Attention Renate Bremen Oostelijke Havendijk 15 4704 RA ROOSENDAAL Certificate of analysis

Analytical Service Manager

Client id

Tjitte Douma HE0000060

Your project name

Your project number

F22091

Your order number

Quotationcode RER&2013007762
Batchcode EUNLHE-00124355

Number of samples

Enclosure

Report date 8 July 2016
Date sampling Unknown
Time sampling Unknown
Samples received on 29 June 2016

Sample taking Eurofins No

Sample taker Renate Bremen

Certificate number:AR-16-HE-026080-01Sample number:888-2016-06290608Your sample number:Arabinose batch C61Sample description:Arabinose batch C61

Limit criteria:

Reception condition Uncooled

| Lab    | тс      |     | Analysis   | Unit  | Result |
|--------|---------|-----|--|-------|--------|
| Q EUNI | LHE UM: | 3L5 | Faecal Streptococci E <10 >300000 /G (1-3) KF Agar Internal Method |       |        |
|        |         |     | Faecal Streptococci  | cfu/g | < 10   |
| Q EUNI | LHE HEN | M70 | Antimony (ICP-MS) Internal Method                                  |       |        |
|        |         |     | Antimony (Sb)  | mg/kg | <0.005 |
| Q EUNI | LHE HEM | M54 | Arsenic (ICP-MS) Internal Method                                   |       |        |
|        |         |     | Arsenic  | mg/kg | <0.01  |
| Q EUNI | LHE HEM | M57 | Cadmium (ICP-MS) Internal Method                                   |       |        |
|        |         |     | Cadmium  | mg/kg | <0.005 |
| Q EUNI | LHE HEN | MD8 | Copper (ICP-MS) Internal Method                                    |       |        |
|        |         |     | Copper (Cu)  | mg/kg | 0.066  |
| Q EUNI | LHE HEN | M68 | Lead (ICP-MS) Internal Method                                      |       |        |
|        |         |     | Lead   | mg/kg | <0.01  |
| Q EUNI | LHE HEN | ME1 | Mercury (ICP-MS) Internal Method                                   |       |        |
|        |         |     | Mercury  | μg/kg | <0.5   |
| Q EUNI | LHE HEN | M64 | Molybdene (ICP-MS) Internal Method                                 |       |        |
|        |         |     | Molybdenum (Mo)  | mg/kg | <0.01  |
| Q EUNI | LHE HEN | M71 | Tin (ICP-MS) Internal Method                                       |       |        |
|        |         |     | Tin (Sn)   | mg/kg | <0.01  |
| Q EUNI | LBA3 RM | M02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)                    |       |        |
|        |         |     | Aflatoxin B1   | μg/kg | < 0.05 |
|        |         |     | Aflatoxin B2   | μg/kg | < 0.02 |
|        |         |     | Aflatoxin G1   | μg/kg | < 0.05 |
|        |         |     |  | •     |        |

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

1/2

Eurofins Food Testing Netherlands B.V.

Leeuwarderstraatweg 129

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Batchcode EUNLHE-00124355

Number of samples

Enclosure

Certificate number: AR-16-HE-026080-01 Sample number: 888-2016-06290608 Your sample number: Arabinose batch C61 Arabinose batch C61 Sample description:

Limit criteria:

| Lab       | TC    | Analysis  | Unit  | Result |
|-----------|-------|---|-------|--------|
| Q EUNLBA3 | RMM02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)           |       |        |
|           |       | Aflatoxin G2  | μg/kg | < 0.03 |
|           |       | Aflatoxins total  | μg/kg | < 0.15 |
| Q EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |       |        |
|           |       | Bismuth (Bi)  | mg/kg | <0.2   |
| Q EUHAWE3 | J1002 | Silver (AAS-Graphite food) analog §64 LFGB L 00.00-19/3   |       |        |
|           |       | Silver (Ag)   | mg/kg | <0.05  |

Legend

Lab Laboratory

EUNLHE Eurofins Food Testing Netherlands B.V. **EUNLBA3** Eurofins Food Testing Rotterdam BV EUHAWE3 Eurofins WEJ Contaminants GmbH

Q = Operation accredited in accordance with ISO/IEC 17025;2005

## Accreditation

Q NEN EN ISO/IEC 17025:2005 RVA L154 Q NEN EN ISO/IEC 17025:2005 RVA L076

Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

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Cosun (CFTC sectie analyse) Attention Renate Bremen Oostelijke Havendijk 15 4704 RA ROOSENDAAL

Certificate of analysis

Analytical Service Manager

Client id

Tjitte Douma HE0000060

Your project name

Your project number

F22091

Your order number

Quotationcode RER&2013007762 EUNLHE-00124359 Batchcode

Number of samples

Enclosure

8 July 2016

Report date Date sampling Unknown Time sampling Unknown 29 June 2016 Samples received on

Sample taking Eurofins No

Renate Bremen Sample taker

Certificate number: AR-16-HE-026081-01 Sample number: 888-2016-06290613 Your sample number: Arabinose Batch C62 Arabinose Batch C62 Sample description:

Limit criteria:

Reception condition Uncooled

| Lab     | TC    | Analysis   | Unit  | Result |
|---------|-------|--|-------|--------|
| EUNLHE  | UM3L5 | Faecal Streptococci E <10 >300000 /G (1-3) KF Agar Internal Method |       |        |
|         |       | Faecal Streptococci  | cfu/g | < 10   |
| EUNLHE  | HEM70 | Antimony (ICP-MS) Internal Method                                  |       |        |
|         |       | Antimony (Sb)  | mg/kg | <0.005 |
| EUNLHE  | HEM54 | Arsenic (ICP-MS) Internal Method                                   |       |        |
|         |       | Arsenic  | mg/kg | <0.01  |
| EUNLHE  | HEM57 | Cadmium (ICP-MS) Internal Method                                   |       |        |
|         |       | Cadmium  | mg/kg | <0.005 |
| EUNLHE  | HEMD8 | Copper (ICP-MS) Internal Method                                    |       |        |
|         |       | Copper (Cu)  | mg/kg | 0.020  |
| EUNLHE  | HEM68 | Lead (ICP-MS) Internal Method                                      |       |        |
|         |       | Lead   | mg/kg | <0.01  |
| EUNLHE  | HEME1 | Mercury (ICP-MS) Internal Method                                   |       |        |
|         |       | Mercury  | μg/kg | <0.5   |
| EUNLHE  | HEM64 | Molybdene (ICP-MS) Internal Method                                 |       |        |
|         |       | Molybdenum (Mo)  | mg/kg | <0.01  |
| EUNLHE  | HEM71 | Tin (ICP-MS) Internal Method                                       |       |        |
|         |       | Tin (Sn)   | mg/kg | <0.01  |
| EUNLBA3 | RMM02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)                    |       |        |
|         |       | Aflatoxin B1   | μg/kg | < 0.05 |
|         |       | Aflatoxin B2   | μg/kg | < 0.02 |
|         |       | Aflatoxin G1   | μg/kg | < 0.05 |

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

1/2

Eurofins Food Testing Netherlands B.V.

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A. A. Kuneman General manager





Batchcode EUNLHE-00124359

Number of samples

Enclosure

Certificate number:AR-16-HE-026081-01Sample number:888-2016-06290613Your sample number:Arabinose Batch C62Sample description:Arabinose Batch C62

Limit criteria:

| Lab       | TC    | Analysis  | Unit  | Result |
|-----------|-------|---|-------|--------|
| Q EUNLBA3 | RMM02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)           |       |        |
|           |       | Aflatoxin G2  | μg/kg | < 0.03 |
|           |       | Aflatoxins total  | μg/kg | < 0.15 |
| Q EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |       |        |
|           |       | Bismuth (Bi)  | mg/kg | <0.2   |
| Q EUHAWE3 | J1002 | Silver (AAS-Graphite food) analog §64 LFGB L 00.00-19/3   |       |        |
|           |       | Silver (Ag)   | mg/kg | <0.05  |

Legend

Lab Laboratory

EUNLHE Eurofins Food Testing Netherlands B.V.
EUNLBA3 Eurofins Food Testing Rotterdam BV
EUHAWE3 Eurofins WEJ Contaminants GmbH

Q = Operation accredited in accordance with ISO/IEC 17025;2005

AWE3 Eurotins Wej Contaminants GmbH

Accreditation

Q NEN EN ISO/IEC 17025:2005 RVA L154 Q NEN EN ISO/IEC 17025:2005 RVA L076

Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

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A. A. Kuneman General manager



000095



Cosun (CFTC sectie analyse) Attention Renate Bremen Oostelijke Havendijk 15 4704 RA ROOSENDAAL Certificate of analysis

Analytical Service Manager

e Manager Tjitte Douma HE0000060

Client id Your project name

Your project number

F22091

Your order number

Quotationcode RER&2013007762
Batchcode EUNLHE-00124371

Number of samples

Enclosure

Report date 8 July 2016
Date sampling Unknown
Time sampling Unknown
Samples received on 29 June 2016

Sample taking Eurofins No

Sample taker Renate Bremen

Certificate number:AR-16-HE-026082-01Sample number:888-2016-06290633Your sample number:Arabinose batch C65Sample description:Arabinose batch C65

Limit criteria:

Reception condition Uncooled

| Lab       | тс    | Analysis   | Unit           | Result           |
|-----------|-------|--|----------------|------------------|
| Q EUNLHE  | UM3L5 | Faecal Streptococci E <10 >300000 /G (1-3) KF Agar Internal Method |                |                  |
|           |       | Faecal Streptococci  | cfu/g          | < 10             |
| Q EUNLHE  | HEM70 | Antimony (ICP-MS) Internal Method                                  |                |                  |
|           |       | Antimony (Sb)  | mg/kg          | <0.005           |
| Q EUNLHE  | HEM54 | Arsenic (ICP-MS) Internal Method                                   |                |                  |
|           |       | Arsenic  | mg/kg          | <0.01            |
| Q EUNLHE  | HEM57 | Cadmium (ICP-MS) Internal Method                                   |                |                  |
|           |       | Cadmium  | mg/kg          | <0.005           |
| Q EUNLHE  | HEMD8 | Copper (ICP-MS) Internal Method                                    |                |                  |
|           |       | Copper (Cu)  | mg/kg          | 0.027            |
| Q EUNLHE  | HEM68 | Lead (ICP-MS) Internal Method                                      |                |                  |
|           |       | Lead   | mg/kg          | <0.01            |
| Q EUNLHE  | HEME1 | Mercury (ICP-MS) Internal Method                                   |                |                  |
|           |       | Mercury  | μg/kg          | <0.5             |
| Q EUNLHE  | HEM64 | Molybdene (ICP-MS) Internal Method                                 |                |                  |
|           |       | Molybdenum (Mo)  | mg/kg          | 0.03             |
| Q EUNLHE  | HEM71 | Tin (ICP-MS) Internal Method                                       |                |                  |
|           |       | Tin (Sn)   | mg/kg          | <0.01            |
| Q EUNLBA3 | RMM02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)                    |                |                  |
|           |       | Aflatoxin B1   | μg/kg          | < 0.05           |
|           |       | Aflatoxin B2   | μg/kg          | < 0.02           |
|           |       | Aflatoxin G1   |                | < 0.05           |
|           |       | Aflatoxin B2<br>Aflatoxin G1                                       | µg/kg<br>µg/kg | < 0.02<br>< 0.05 |

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

1/2

Eurofins Food Testing Netherlands B.V.

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NL-8440 AT Heerenveen NL

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Batchcode EUNLHE-00124371

Number of samples

Enclosure

Certificate number:AR-16-HE-026082-01Sample number:888-2016-06290633Your sample number:Arabinose batch C65Sample description:Arabinose batch C65

Limit criteria:

| Lab       | TC    | Analysis  | Unit  | Result |
|-----------|-------|---|-------|--------|
| Q EUNLBA3 | RMM02 | Aflatoxin (B1.B2.G1.G2) Internal Method (W8333)           |       |        |
|           |       | Aflatoxin G2  | μg/kg | < 0.03 |
|           |       | Aflatoxins total  | μg/kg | < 0.15 |
| Q EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |       |        |
|           |       | Bismuth (Bi)  | mg/kg | <0.2   |
| Q EUHAWE3 | J1002 | Silver (AAS-Graphite food) analog §64 LFGB L 00.00-19/3   |       |        |
|           |       | Silver (Ag)   | mg/kg | <0.05  |

Legend

Lab Laboratory

EUNLHE Eurofins Food Testing Netherlands B.V.
EUNLBA3 Eurofins Food Testing Rotterdam BV
EUHAWE3 Eurofins WEJ Contaminants GmbH

Q = Operation accredited in accordance with ISO/IEC 17025;2005

Accreditation

Q NEN EN ISO/IEC 17025:2005 RVA L154 Q NEN EN ISO/IEC 17025:2005 RVA L076

Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

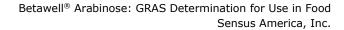
The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

Eurofins Food Testing Netherlands B.V.

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APPENDIX B2
RESIDUALS AND CONTAMINANTS ANALYSES:
ENZYMATIC PROCESS



Cosun (CFTC sectie analyse) Attention Judith van der Berg Postbus 1308 4700 BH Roosendaal

Certificate number: AR-13-HE-048013-02 Sample number: 888-2013-10170595

Your sample number: Arabinose, batch C7-1, 05.11.2012 Sample description: Arabinose, batch C7-1, 05.11.2012

#### Certificate of analysis

Analytical Service Manager Tjitte Douma Client id HE0000060

Sandra van der Borst Your project name Your project number Sandra van der Borst

Your order number F22091

RER&2013007702 Quotationcode EUNLHE-00026550 Batchcode

Number of samples

Enclosure

Report date 30 October 2013 Date sampling 17 October 2013 Time sampling Unknown Samples received on 17 October 2013

Sample taking Eurofins

Sample taker

Sandra van der Borst

| Lab       | TC    | Analysis                                | Unit  | Result |
|-----------|-------|---|-------|--------|
| Q EUNLBA3 | NLM05 | Aflatoxin (B1.B2.G1.G2) Internal Method |       |        |
|           |       | Aflatoxin B1                            | μg/kg | < 0.05 |
|           |       | Aflatoxin B1                            | μg/kg | < 0.05 |
|           |       | Aflatoxin B2                            | μg/kg | < 0.02 |
|           |       | Aflatoxin B2                            | μg/kg | < 0.02 |
|           |       | Aflatoxin G1                            | μg/kg | < 0.05 |
|           |       | Aflatoxin G1                            | μg/kg | < 0.05 |
|           |       | Aflatoxin G2                            | μg/kg | < 0.03 |
|           |       | Aflatoxin G2                            | μg/kg | < 0.03 |
|           |       | Aflatoxins total                        | μg/kg | < 0.15 |
|           |       | Aflatoxins total                        | μg/kg | < 0.15 |

Legend

Accreditation Lab Laboratory

**EUNLBA3** Eurofins Food Testing Rotterdam BV Q NEN EN ISO/IEC 17025:2005 RVA L076

Q = Operation accredited in accordance with ISO/IEC 17025;2005

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retreivable from the ASM department Opinions and interpretations in this certificate are outside the scope of accreditation. The samples will be stored until 21 days after date of reception.

Eurofins Food Testing Netherlands B.V.

Leeuwarderstraatweg 129 P.O. Box 766 NL-8440 AT Heerenveen NL Tel.: +31 88 83 10 000 Fax : +31 88 83 10 100 E-mail: ASM-Food-NL@eurofins.com www.eurofins.nl

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S.L.M. Meersseman Managing Director



Cosun (sectie analyse) Attention de heer M. Leijdekkers PO Box 1308 4700 BH Roosendaal

#### Certificate of analysis

Certificate number : 2012197180
Report date : 29-11-2012
Start date : 19-11-2012
Samples received on : 16-11-2012
Date sampling : Unknown
Client id : 738

Customer name : Co

: Cosun (CFTC sectie analyse)

Location

Your project number

: F22090

Your project name

:

Project Coordinator :

: Tjitte Douma

Sampled by : S Bink

Contact person : de heer M. Leijdekkers

No. Sample description Time sampling EOL sample number

1 Arabinose batch C7-1 888-2012-ST-7250925

| MTH  | Analysis           | Unit<br>Analytico-# | <b>1</b> 7250925 |
|------|--------------------|---------------------|------------------|
|      |                    | Analytico-#         | 1200920          |
| M1 Q | Copper (ICP-MS)    | mg/kg               | 0.011            |
| M2 Q | Antimony (ICP-MS)  | mg/kg               | <0.005           |
| M3 Q | Arsenic (ICP-MS)   | mg/kg               | <0.01            |
| Υ    | Bismuth (AAS-oven) | mg/kg               | < 0.2            |
| M4 Q | Cadmium (ICP-MS)   | mg/kg               | <0.005           |
| M5 Q | Mercury (ICP-MS)   | μg/kg               | <0.5             |
| M6 Q | Lead (ICP-MS)      | mg/kg               | < 0.01           |
| M7 Q | Molybdene (ICP-MS) | mg/kg               | 0.01             |
| M8 Q | Tin (ICP-MS)       | mg/kg               | <0.01            |
| QY   | Silver (Ag)        | mg/kg               | <0.05            |
|      | ( 3)               |                     |                  |

#### Legend

Q: Operation accredited in accordance with ISO/IEC 17025

Y: performed by Eurofins wej CONTAMINANTS (DAR D-PL-14602-01-00) at Hamburg.D-21079

See enclosure for general remarks.

 $^{\star}$  Indicative value.  $\mid$  \*\* Without confirmation.

The results are only valid for the sample. The uncertainty of measurement for the applied methods of analysis are retrievable from the ASM department. The samples will be stored until three weeks after date of receipt

Enclosure: C

#### Eurofins Food Testing Netherlands B.V.

Leeuwarderstraatweg 129 8441 PK Heerenveen P.O. Box 766 8440 AT Heerenveen NL Bijdorpplein 21-23 2992 LB Barendrecht P.O Box 510 2990 AM Barendrecht NL Tel. +31 (0)88 831 0000 Fax +31 (0)88 831 0100 E-mail service@eurofins.nl Site www.eurofins.nl

Eurofins Food Testing Netherlands B.V. is certified by the COKZ (EG/92/46) and by the PDV (GMP10). All offers and agreements are subject to our General Conditions directly available upon request. Initials S.L.M. Meersseman Managing Director (b) (6)

Page 1/1





#### Enclosure (C) concerning method references referring to certificate of analysis 2012197180

Page 1/1

| MTH | Analysis           | Method | Technique | Conformity | Method reference |
|-----|--------------------|--------|-----------|------------|------------------|
| M2  | Antimony (ICP-MS)  | W5430  | ICP-MS    | -          | Own method       |
| M1  | Copper (ICP-MS)    | W5430  | ICP-MS    | -          | Own method       |
| M3  | Arsenic (ICP-MS)   | W5430  | ICP-MS    | -          | Own method       |
| M4  | Cadmium (ICP-MS)   | W5430  | ICP-MS    | -          | Own method       |
| M5  | Mercury (ICP-MS)   | W5430  | ICP-MS    | -          | Own method       |
| M6  | Lead (ICP-MS)      | W5430  | ICP-MS    | -          | Own method       |
| M7  | Molybdene (ICP-MS) | W5430  | ICP-MS    | -          | Own method       |
| M8  | Tin (ICP-MS)       | W5430  | ICP-MS    | -          | Own method       |

our General Conditions directly available upon request.



Cosun (CFTC sectie analyse) T.a.v. Sandra Van der Borst Oostelijke Havendijk 15 4704 RA ROOSENDAAL

#### Analysecertificaat

Analytical Service Manager Tjitte Douma Klantcode HE0000060 F22091 Uw projectnaam Uw projectnummer F22091

Uw ordernummer

RER&2013007713 Quotationcode EUNLHE-00054603 Batchcode

Aantal monsters

Bijlage

Rapportagedatum 16 september 2014 Datum monstername Onbekend Tijd monstername Onbekend

Monster(s) ontvangen 1 september 2014

Monstername Eurofins

Sandra van der Borst Monsternemer

Certificaatnummer: AR-14-HE-022403-01 Monsternummer: 888-2014-09010088

Uw monsternummer: Arabinose, batch C12-1 15-07-2013 Arabinose, batch C12-1 15-07-2013 Monsteromschrijving:

| Lab     | TC    | Analyse   | Eenheid            | Resultaat |
|---------|-------|---|--------------------|-----------|
| EUNLHE  | HEM70 | Antimoon (ICP-MS) Eigen methode                           |                    |           |
|         |       | Antimoon (Sb)   | mg/kg              | <0.005    |
| EUNLHE  | HEM54 | Arseen (ICP-MS) Eigen methode                             |                    |           |
|         |       | Arseen (As)   | mg/kg              | <0.01     |
| EUNLHE  | HEM57 | Cadmium (ICP-MS) Eigen methode                            |                    |           |
|         |       | Cadmium (Cd)  | mg/kg              | <0.005    |
| EUNLHE  | HEMD8 | Koper (ICP-MS) Eigen methode                              |                    |           |
|         |       | Koper (Cu)  | <sup>1</sup> mg/kg | 0.11      |
| EUNLHE  | HEME1 | Kwik (ICP-MS) Eigen methode                               |                    |           |
|         |       | Kwik (Hg)   | μg/kg              | <0.5      |
| EUNLHE  | HEM68 | Lood (ICP-MS) Eigen methode                               |                    |           |
|         |       | Lood (Pb)   | mg/kg              | <0.01     |
| EUNLHE  | HEM64 | Molybdeen (ICP-MS) Eigen methode                          |                    |           |
|         |       | Molybdeen (Mo)  | mg/kg              | <0.01     |
| EUNLHE  | HEM71 | Tin (ICP-MS) Eigen methode                                |                    |           |
|         |       | Tin (Sn)  | mg/kg              | <0.01     |
| EUNLBA3 | NLM05 | Aflatoxine (B1.B2.G1.G2) Eigen methode                    |                    |           |
|         |       | Aflatoxine B1   | μg/kg              | < 0.05    |
|         |       | Aflatoxine B2   | μg/kg              | < 0.02    |
|         |       | Aflatoxine G1   | μg/kg              | < 0.05    |
|         |       | Aflatoxine G2   | μg/kg              | < 0.03    |
|         |       | Aflatoxins (sum B1, B2, G1, G2)                           | μg/kg              | < 0.15    |
| EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |                    |           |
|         |       | Bismuth (Bi)  | mg/kg              | <0.2      |
| EUHAWE3 | JJ0CP | Zilver (Ag) EN ISO 17294-2-E29                            |                    |           |
|         |       | Zilver (Ag)   | mg/kg              | <0.05     |

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

Eurofins Food Testing Netherlands B.V.

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Tel.: +31 88 83 10 000 Fax: +31 88 83 10 100 Email: ASM-Food-NL@eurofins.com www.eurofins.nl

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TESTING RvA L154



Batchcode

EUNLHE-00054603

Aantal monsters Bijlage

 Certificaatnummer:
 AR-14-HE-022403-01

 Monsternummer:
 888-2014-09010088

Uw monsternummer:Arabinose, batch C12-1 15-07-2013Monsteromschrijving:Arabinose, batch C12-1 15-07-2013

# <u>Opmerkingen</u>

Monster 888-2014-09010088

1 Resultaat is het gemiddelde van 3 afzonderlijke waarden: 0.07 mg/kg, 0.16 mg/kg en 0.11 mg/kg

Legenda

**EUNLHE** 

EUNLBA3

Lab Laboratorium

Eurofins Food Testing Netherlands B.V.

Q NEN EN ISO/IEC 17025:2005 RVA L154
Eurofins Food Testing Rotterdam BV

Q NEN EN ISO/IEC 17025:2005 RVA L076

EUHAWE3 Eurofins WEJ Contaminants GmbH Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

Q = geaccrediteerde verrichting conform ISO/IEC 17025;2005

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

Accreditatie

Eurofins Food Testing Netherlands B.V.

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000103



Cosun (CFTC sectie analyse) T.a.v. Sandra Van der Borst Oostelijke Havendijk 15 4704 RA ROOSENDAAL

Analysecertificaat

Analytical Service Manager Tjitte Douma Klantcode HE0000060 F22090 Uw projectnaam Uw projectnummer F022090

Uw ordernummer

RER&2013007711 Quotationcode EUNLHE-00041263 Batchcode

Aantal monsters

Bijlage

Rapportagedatum 18 april 2014 Datum monstername Onbekend Tijd monstername Onbekend 2 april 2014 Monster(s) ontvangen Nee

Monstername Eurofins

Sandra van der Borst Monsternemer

Certificaatnummer: AR-14-HE-009556-01 Monsternummer: 888-2014-04020425

Uw monsternummer: Arabinose batch C15-1, 17-03-2014 Arabinose batch C15-1, 17-03-2014 Monsteromschrijving:

| Lab     | TC    | Analyse   | Eenheid | Resultaat |
|---------|-------|---|---------|-----------|
| EUNLHE  | HEM70 | Antimoon (ICP-MS) Eigen methode                           |         |           |
|         |       | Antimoon (Sb)   | mg/kg   | <0.005    |
| EUNLHE  | HEM54 | Arseen (ICP-MS) Eigen methode                             |         |           |
|         |       | Arseen (As)   | mg/kg   | <0.01     |
| EUNLHE  | HEM57 | Cadmium (ICP-MS) Eigen methode                            |         |           |
|         |       | Cadmium (Cd)  | mg/kg   | <0.005    |
| EUNLHE  | HEMD8 | Koper (ICP-MS) Eigen methode                              |         |           |
|         |       | Koper (Cu)  | mg/kg   | 0.030     |
| EUNLHE  | HEME1 | Kwik (ICP-MS) Eigen methode                               |         |           |
|         |       | Kwik (Hg)   | μg/kg   | <0.5      |
| EUNLHE  | HEM68 | Lood (ICP-MS) Eigen methode                               |         |           |
|         |       | Lood (Pb)   | mg/kg   | <0.01     |
| EUNLHE  | HEM64 | Molybdeen (ICP-MS) Eigen methode                          |         |           |
|         |       | Molybdeen (Mo)  | mg/kg   | 0.03      |
| EUNLHE  | HEM71 | Tin (ICP-MS) Eigen methode                                |         |           |
|         |       | Tin (Sn)  | mg/kg   | <0.01     |
| EUNLBA3 | NLM05 | Aflatoxine (B1.B2.G1.G2) Eigen methode                    |         |           |
|         |       | Aflatoxine B1   | μg/kg   | < 0.05    |
|         |       | Aflatoxine B2   | μg/kg   | < 0.02    |
|         |       | Aflatoxine G1   | μg/kg   | < 0.05    |
|         |       | Aflatoxine G2   | μg/kg   | < 0.03    |
|         |       | Aflatoxine (som B1.B2.G1.G2)                              | μg/kg   | < 0.15    |
| EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |         |           |
|         |       | Bismuth (Bi)  | mg/kg   | <0.2      |
| EUHAWE3 | J1002 | Zilver analog §64 LFGB L 00.00-19/3                       |         |           |
|         |       | Zilver (Ag)   | mg/kg   | <0.05     |

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

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TESTING RvA L154



 Certificaatnummer:
 AR-14-HE-009556-01

 Monsternummer:
 888-2014-04020425

Uw monsternummer:Arabinose batch C15-1, 17-03-2014Monsteromschrijving:Arabinose batch C15-1, 17-03-2014

Legenda

Lab Laboratorium

EUNLHE Eurofins Food Testing Netherlands B.V.

EUNLBA3 Eurofins Food Testing Rotterdam BV

EUHAWE3 Eurofins WEJ Contaminants GmbH

Q = geaccrediteerde verrichting conform ISO/IEC 17025;2005

Accreditatie

Q NEN EN ISO/IEC 17025:2005 RVA L154 Q NEN EN ISO/IEC 17025:2005 RVA L076

Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

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000105



Cosun (CFTC sectie

analyse)

Analytical Service Manager Tjitte Douma Klantcode HE0000060 Uw projectnaam F22090 Uw projectnummer F022090

Uw ordernummer

RER&2013007711 Quotationcode Batchcode EUNLHE-00041263

Aantal monsters

Bijlage

18 april 2014 Rapportagedatum Datum monstername Onbekend Tijd monstername Onbekend Monster(s) ontvangen 2 april 2014 Monstername Eurofins Nee

Monsternemer Sandra van der Borst

Certificaatnummer: AR-14-HE-009556-01 888-2014-04020426 Monsternummer:

Arabinose batch C16-1, 17-03-2014 2 Uw monsternummer: Arabinose batch C16-1, 17-03-2014 2 Monsteromschrijving:

|   | Lab     | тс    | Analyse   | Eenheid | Resultaat |
|---|---------|-------|---|---------|-----------|
| Q | EUNLHE  | HEM70 | Antimoon (ICP-MS) Eigen methode                           |         |           |
|   |         |       | Antimoon (Sb)   | mg/kg   | <0.005    |
| Q | EUNLHE  | HEM54 | Arseen (ICP-MS) Eigen methode                             |         |           |
|   |         |       | Arseen (As)   | mg/kg   | <0.01     |
| Q | EUNLHE  | HEM57 | Cadmium (ICP-MS) Eigen methode                            |         |           |
|   |         |       | Cadmium (Cd)  | mg/kg   | <0.005    |
| Q | EUNLHE  | HEMD8 | Koper (ICP-MS) Eigen methode                              |         |           |
|   |         |       | Koper (Cu)  | mg/kg   | 0.75      |
| Q | EUNLHE  | HEME1 | Kwik (ICP-MS) Eigen methode                               |         |           |
|   |         |       | Kwik (Hg)   | μg/kg   | <0.5      |
| Q | EUNLHE  | HEM68 | Lood (ICP-MS) Eigen methode                               |         |           |
|   |         |       | Lood (Pb)   | mg/kg   | <0.01     |
| Q | EUNLHE  | HEM64 | Molybdeen (ICP-MS) Eigen methode                          |         |           |
|   |         |       | Molybdeen (Mo)  | mg/kg   | 0.04      |
| Q | EUNLHE  | HEM71 | Tin (ICP-MS) Eigen methode                                |         |           |
|   |         |       | Tin (Sn)  | mg/kg   | <0.01     |
| Q | EUNLBA3 | NLM05 | Aflatoxine (B1.B2.G1.G2) Eigen methode                    |         |           |
|   |         |       | Aflatoxine B1   | μg/kg   | < 0.05    |
|   |         |       | Aflatoxine B2   | μg/kg   | < 0.02    |
|   |         |       | Aflatoxine G1   | μg/kg   | < 0.05    |
|   |         |       | Aflatoxine G2   | μg/kg   | < 0.03    |
|   |         |       | Aflatoxine (som B1.B2.G1.G2)                              | μg/kg   | < 0.15    |
| Q | EUHAWE3 | J1022 | Bismuth (AAS-Graphite, food) analog §64 LFGB L 00.00-19/3 |         |           |
|   |         |       | Bismuth (Bi)  | mg/kg   | <0.2      |
|   |         |       |   |         |           |

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

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Certificaatnummer: AR-14-HF-009556-01 888-2014-04020426 Monsternummer:

J1002

Q EUHAWE3

Arabinose batch C16-1, 17-03-2014 2 Uw monsternummer: Arabinose batch C16-1, 17-03-2014 2 Monsteromschrijving:

Zilver analog §64 LFGB L 00.00-19/3

Resultaat Lab TC Analyse Eenheid

<0.05 Zilver (Ag) mg/kg

Legenda

Lab Laboratorium

**EUNLHE** Eurofins Food Testing Netherlands B.V. **EUNLBA3** Eurofins Food Testing Rotterdam BV EUHAWE3 Eurofins WEJ Contaminants GmbH

Q = geaccrediteerde verrichting conform ISO/IEC 17025;2005

Accreditatie

Q NEN EN ISO/IEC 17025:2005 RVA L154 Q NEN EN ISO/IEC 17025:2005 RVA L076

Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

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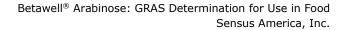
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TESTING RvA L154 000107





APPENDIX B3
RESIDUALS AND CONTAMINANTS ANALYSES:
PESTICIDES

Eurofins | Dr. Specht Laboratorien GmbH Großmoorbogen 25 D-21079 Hamburg GERMANY

> Tel: +49 40 881 448 0 Fax: +49 40 881 448 101

pesticides@eurofins.de www.eurofins.de

Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg

Eurofins Food Testing Netherlands B.V. P.O. Box 766 8444 AT Heerenveen NIEDERLANDE

Hamburg, 01.11.2013

**Analytical report** 

Sample Code

Order from: Reception date time: Sample name:

Client sample code: Organic:

Start analysis: End analysis:

Analysis of pesticides

AR-13-SP-035135-01

388-2013-00035236

21.10.2013 23.10.2013

Perspulp SU Dinteloord 888-2013-10160603

No

23.10.2013 01.11.2013

# Analysis of pesticides

Pesticide-Screening Quechers-LC-MS/MS (QuLC-99-01-alle) SP911 EN 15662:2008 Organochlorine Pesticides and Pyrethroids (OC-00-01-OUG) SP001 ASU L00.00-34



The results of examination refer exclusively to the checked samples.

Duplicates - even in parts - must be authorized by the test laboratory in written form.

Eurofins | Dr. Specht Laboratorien GmbH - Postfach 90 02 64 · D-21079 Hamburg

General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner, Dr. Matthias Sauer.

VAT No.: DE 238466739

HRB 91731 AG Hamburg

NordLB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code



D-PL-14198-01-00

Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory

The accreditation is valid for the analytical methods which are marked in the analytical report.

**Analytical report**: AR-13-SP-035135-01 **Sample Code**: 388-2013-00035236

## **Test results**

| Parameter    | Measurement | Dimension | Result | MRL | LOQ  |
|--------------|-------------|-----------|--------|-----|------|
| Epoxyconazol | LC-MS/MS    | mg/kg     | 0.01   |     | 0.01 |

No further pesticides/parameters of above mentioned scope of analysis are detectable.

LOQ = Limit of Quantification

MRL = Maximum Residue Level according to Regulation (EC) NO 396/2005

n.n. = not detectable

This test report has been created electronically and has been verified and authorised.

Jochen Riehle - Head of Analytical Service Management/Sales

### Page 2/2

The results of examination refer exclusively to the checked samples. Duplicates - even in parts - must be authorized by the test laboratory in written form. Eurofins | Dr. Specht Laboratorien GmbH - Postfach 90 02 64 · D-21079 Hamburg General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner, Dr. Matthias Sauer. VAT No.: DE 238466739 HRB 91731 AG Hamburg NordLB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code



Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory

The accreditation is valid for the analytical methods which are marked in the analytical report.

D-PL-14198-01-00

Eurofins | Dr. Specht Laboratorien GmbH Großmoorbogen 25 D-21079 Hamburg GERMANY

> Tel: +49 40 881 448 0 Fax: +49 40 881 448 101

pesticides@eurofins.de www.eurofins.de

Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg

Eurofins Food Testing Netherlands B.V. P.O. Box 766 8444 AT Heerenveen **NIEDERLANDE** 

Hamburg, 01.11.2013

**Analytical report** 

Sample Code 388-2013-00035237

Order from: 21.10.2013 Reception date time: 23.10.2013

Sample name: Perspulp SU Vierverlaten Client sample code: 888-2013-10160604

Organic:

Start analysis: 23.10.2013 End analysis: 01.11.2013

**Analysis of pesticides** 

# Analysis of pesticides

Pesticide-Screening Quechers-LC-MS/MS (QuLC-99-01-alle) SP911 EN 15662:2008 Organochlorine Pesticides and Pyrethroids (OC-00-01-OUG) SP001 ASU L00.00-34

No

AR-13-SP-035136-01



The results of examination refer exclusively to the checked samples. Ine results of examination refer exclusively to the checked samples.

Duplicates - even in parts - must be authorized by the test laboratory in written form.

Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg

General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner, Dr. Matthias Sauer.

VAT No.: DE 238466739

HRB 91731 AG Hamburg

NordLB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code



D-PL-14198-01-00

Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory The accreditation is valid for the analytical methods which are marked in the analytical report.

**Analytical report**: AR-13-SP-035136-01 **Sample Code**: 388-2013-00035237

## **Test results**

| Parameter   | Measurement | Dimension | Result | MRL | LOQ  |
|-------------|-------------|-----------|--------|-----|------|
| Fenpropidin | LC-MS/MS    | mg/kg     | 0.01   |     | 0.01 |

No further pesticides/parameters of above mentioned scope of analysis are detectable.

LOQ = Limit of Quantification

MRL = Maximum Residue Level according to Regulation (EC) NO 396/2005

n.n. = not detectable

This test report has been created electronically and has been verified and authorised.

Jochen Riehle - Head of Analytical Service Management/Sales

### Page 2/2

The results of examination refer exclusively to the checked samples. Duplicates - even in parts - must be authorized by the test laboratory in written form. Eurofins | Dr. Specht Laboratorien GmbH - Postfach 90 02 64 · D-21079 Hamburg General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner, Dr. Matthias Sauer. VAT No.: DE 238466739 HRB 91731 AG Hamburg NordLB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code



Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory

The accreditation is valid for the analytical methods which are marked in the analytical report.

D-PL-14198-01-00

Eurofins | Dr. Specht Laboratorien GmbH Großmoorbogen 25 D-21079 Hamburg **GERMANY** 

> Tel: +49 40 881 448 0 Fax: +49 40 881 448 101

pesticides@eurofins.de www.eurofins.de

Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg

Eurofins Food Testing Netherlands B.V. P.O. Box 766 8444 AT Heerenveen **NIEDERLANDE** 

Hamburg, 08.10.2014

AR-14-SP-079888-01 **Analytical report** 

Sample Code 388-2014-00079017

Reception date time: 30.09.2014

Sample name: Perspulp SU Dinteloord camp. week 3

Client sample code: 888-2014-09240118

Organic:

Start analysis: 30.09.2014 End analysis: 08.10.2014

Pesticides Result **MRL** RL Unit

SP001 Organochlorine Pesticides and Pyrethroids (#)

Method ASU L00.00-34, DFG-S19, GC-ECD

Screened pesticides Not Detected

SP911 Pesticide-Screening Quechers-LC-MS/MS (#)

EN 15662:2008, P-14.141, LC-MS/MS Method

Screened pesticides Not Detected

MRL = Maximum Residue Level RL = Reporting Limit

(b) (6)

Analytical Service Manager (Sandra Kobüssen)

### Page 1/1

The results of examination refer exclusively to the checked samples. Duplicates - even in parts - must be authorized by the test laboratory in written form. Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner.
VAT No.: DE 238466739
HRB 91731 AG Hamburg
Nord/LB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code

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DAkkS

Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory

The accreditation is valid for the analytical methods which are marked in the analytical report.

Akkreditierungsstelle D-PL-14198-01-00



Cosun (CFTC sectie analyse) T.a.v. Sandra Van der Borst Oostelijke Havendijk 15 4704 RA ROOSENDAAL

AR-14-HE-025727-01 888-2014-09240370

Uw monsternummer:

Certificaatnummer:

Monsternummer:

Perspulp SU Vierverlaten Camp. week 3 Monsteromschrijving: Perspulp SU Vierverlaten Camp. week 3

## Analysecertificaat

Analytical Service Manager Tjitte Douma Klantcode HE0000060 Uw projectnaam F031040 F031040 Uw projectnummer

Uw ordernummer

Quotationcode RER&2013007719 EUNLHE-00056905 Batchcode

Aantal monsters

Bijlage Extern(e) certifica(a)t(en)

21 oktober 2014 Rapportagedatum Datum monstername Onbekend Tijd monstername Onbekend

Monster(s) ontvangen 24 september 2014

Monstername Eurofins

Monsternemer Sandra van der Borst

|   | Lab     | тс    | Analyse                      | Eenheid | Resultaat  |
|---|---------|-------|------------------------------|---------|------------|
|   | EUNLHE  | HEX05 | Extern onderzoek             |         |            |
|   |         |       | Externe analyse              |         | Op bijlage |
| Q | EUNLHE  | HEMD8 | Koper (ICP-MS) Eigen methode |         |            |
|   |         |       | Koper (Cu)                   | mg/kg   | 1.00       |
| Q | EUNLHE  | HEB65 | Vocht 102 °C Eigen methode   |         |            |
|   |         |       | Vocht 102 °C                 | % (m/m) | 79.2       |
| Q | EUNLHE  | HEME6 | Zink (ICP-MS) Eigen methode  |         |            |
|   |         |       | Zink (Zn)                    | mg/kg   | 8.3        |
| Q | EUHAWE2 | FIN0N | Fluor                        |         |            |
|   |         |       | Fluoride                     | mg/kg   | <10        |
| Q | EUNLBA3 | NLM09 | Ochratoxine A Eigen methode  |         |            |
|   |         |       | Ochratoxine A                | μg/kg   | < 0.4      |
| Q | EUHAWE3 | JJ0JS | Roquefortine C Eigen methode |         |            |
|   |         |       | Roquefortine C               | μg/kg   | <10        |
| Q | EUHAWE3 | A7193 | Zearalenon Eigen methode     |         |            |
|   |         |       | Zearalenon                   | μg/kg   | <10        |

# Legenda

Accreditatie Lab Laboratorium **EUNLHE** Eurofins Food Testing Netherlands B.V. Q NEN EN ISO/IEC 17025:2005 RVA L154

EUNLBA3 Eurofins Food Testing Rotterdam BV Q NEN EN ISO/IEC 17025:2005 RVA L076 EUHAWE2 Eurofins Consumer Product Testing GmbH Q DIN EN ISO/IEC 17025:2005 D-PL-14435-01-00 EUHAWE3 Eurofins WEJ Contaminants GmbH Q EN ISO/IEC 17025:2005 DAKKS D-PL-14602-01-00

Q = geaccrediteerde verrichting conform ISO/IEC 17025;2005

Dit certificaat mag uitsluitend in zijn geheel worden gereproduceerd. De analyseresultaten hebben alleen betrekking op het monster. De meetonzekerheden van de analysemethoden zijn opvraagbaar bij de afdeling ASM. Opinies en interpretaties in dit certificaat vallen buiten de scope van de accreditatie. De analysemonsters worden tot 21 dagen na de datum ontvangst bewaard.

Eurofins Food Testing Netherlands B.V.

Leeuwarderstraatweg 129 P.O. Box 766 NL-8440 AT Heerenveen NL Tel.: +31 88 83 10 000 Fax: +31 88 83 10 100 Email: ASM-Food-NL@eurofins.com

Op al onze leveringen zijn onze algemene voorwaarden van toepassing te vinden op www.eurofins.nl





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Eurofins | Dr. Specht Laboratorien GmbH Großmoorbogen 25 D-21079 Hamburg **GERMANY** 

> Tel: +49 40 881 448 0 Fax: +49 40 881 448 101

pesticides@eurofins.de www.eurofins.de

Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg

Eurofins Food Testing Netherlands B.V. P.O. Box 766 8444 AT Heerenveen **NIEDERLANDE** 

Hamburg, 09.10.2014

AR-14-SP-080597-01 **Analytical report** 

Sample Code 388-2014-00079010

Reception date time: 30.09.2014

Sample name: Perspulp SU Vierverlaten Camp. week 3

Client sample code: 888-2014-09240370

Organic:

Start analysis: 30.09.2014 End analysis: 09.10.2014

Pesticides Result **MRL** RL Unit

SP001 Organochlorine Pesticides and Pyrethroids (#)

ASU L00.00-34, DFG-S19, GC-ECD Method

Screened pesticides Not Detected

SP911 Pesticide-Screening Quechers-LC-MS/MS (#)

EN 15662:2008, P-14.141, LC-MS/MS Method

Screened pesticides Not Detected

MRL = Maximum Residue Level RL = Reporting Limit

(b) (6)

Analytical Service Manager (Svenja Maurer)

### Page 1/1

The results of examination refer exclusively to the checked samples. Duplicates - even in parts - must be authorized by the test laboratory in written form. Eurofins | Dr. Specht Laboratorien GmbH · Postfach 90 02 64 · D-21079 Hamburg General Managers: Dr. Thomas Anspach, Dr. Manfred Linkerhägner.
VAT No.: DE 238466739
HRB 91731 AG Hamburg
Nord/LB 135024461 (BLZ 250 500 00) IBAN DE82 2505 0000 0135 0244 61, BIC-/SWIFT-Code



Accreditated by DAkkS according to

DIN EN ISO/IEC 17025 accreditated laboratory

The accreditation is valid for the analytical methods which are marked in the analytical report.

D-PL-14198-01-00



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| Z"'0\$"                       | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |
| W&/7"')534                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| WAW:%&/)>&B                   | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| WAW:%6"\$&B                   | %J <jji%< td=""><td>1,E+,</td></jji%<> | 1,E+, |
| WAW:%("/\$&B                  | %J <jji%< td=""><td>1,E+,</td></jji%<> | 1,E+, |
| WAW:%")#0/3'B                 | %J <jji%< td=""><td>1,E+,</td></jji%<> | 1,E+, |
| W")\$&*>/35                   | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| W")\$&*>/35%")340(":%*0#B     | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| W")\$&*>/35%")340(":%\$5&'#B  | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| W"4&*>/3536""T"""%9WA[=       | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| M342'0/BF*\$&'3&\$"           | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |

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| M#3   | 86"'T&'                  |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
|---|--------------------------|----------------------|--|--|--|-------|
| M#3   | 3(50'                    |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| M#3   | 3)53)&/0'                |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| @0'   | (&'"%9,&11&BW            | AW=                  |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| C"\$  | >342*>/35                |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| C05   | "4                       |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| V0\$  | 5&)250'                  |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| V0\$  | 537"'                    |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| V3'8  | k*>/35:%*0#B             |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| V3'8  | k*>/35:%\$5& <b>'</b> #B |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| F*\$8   | &*>/35#\$25"'"           |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| F\$>  | "5%#*5"""(%)"#\$         | \$0*0("#             |  |  |  |       |
| F42   | 7/.357"'                 |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| -"'(0   | 1"\$>&/0'                |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| -"'\$8  | &*>/35&'0#3/"            |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| -"'\$8  | &*>/353&'0/0'"           |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| -""\$8  | &*>/3536"'T""            |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| -"'\$8  | &*>/353\$>03&'0#         | <b>‡</b> 3/"         |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| -"51  | "\$>50'                  |                      |  |  | %J <jk%< th=""><th>1,E+,</th></jk%<>   | 1,E+, |
| -/07  | "'&\$"                   |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| -3/2  | *>/353\$"5)"""%9         | <b>4</b> &1)>"*>/35= |  |  | %J <j^%< th=""><th>1,E+,</th></j^%<>   | 1,E+, |
| -537  | 7/.5&/0'                 |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| G.0'  | \$3T"'"                  |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| D% <sup>4</sup>   | ΊK                       |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| D*5'  | """(%)"#\$0*0("#         |                      |  |  |  |       |
| \$&.E   | 3U/.8&/0'&\$"            |                      |  |  | %J <jk%< th=""><th>1,E+,</th></jk%<>   | 1,E+, |
| !"*'&   | Т""                      |                      |  |  | %J <jjk%< th=""><th>1,E+,</th></jjk%<> | 1,E+, |
| !"7/.   | \$>50'                   |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| !"\$5   | &(073'                   |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| !"\$5   | &#./                     |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| !5&/  | 31"\$>50'                |                      |  |  | %J <jk%< th=""><th>1,E+,</th></jk%<>   | 1,E+, |
| !5&';   | #7/.\$>50'               |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| !508  | k//&\$"                  |                      |  |  | %J <jjl%< th=""><th>1,E+,</th></jjl%<> | 1,E+, |
| !50*  | >/353'&\$                |                      |  |  | %J <jji%< th=""><th>1,E+,</th></jji%<> | 1,E+, |
| !507  | 7/.5&/0'                 |                      |  |  | %J <jjk%< td=""><td>1,E+,</td></jjk%<> | 1,E+, |
| <\$""#&#/(+=(*"01%2</th><th>F)\$01&/</th><th>%^JJ ,</th><th>C0'01</th><th>&/</th><th>%IJJ,</th><th></th></tr><tr><th>>2=2.2'?2(:2#;+,</th><th>;DI%@JJ<J</th><th>JBQ^%</th><th></th><th></th><th></th><th></th></tr><tr><th>!.21"."#&+'- >2%"#2,((<br>#2*#*</th><th>B%,"'"5&//2</th><th>2%5"a.05"(%735%</th><th>\$>0#%\$"#\$</th><th>DJK</th><th>X4\$5&*\$03'%</th><th>NUZ%DK_</th></tr></tbody></table> |                          |                      |  |  |  |       |

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!3% )5380("%&%a.0\*+%&'(% \*>"&)% 1"\$>3(% \$3%#\*5""'% 5"#0(."#% \*.55""\$/2%.#" (% )"#\$0\*0("#%&'(% 1"\$&63/0\$"#%''% #"/"\*\$"(%75.0\$#%&'(%8","\$&6/"#<

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!>"% )53\*"(.5"% 0'83/8"#% 0'0\$0&/#0',/" B>&#"% "4\$5&\*\$03'%37%KJ,% #&1)/"% \$0\$>%KJ%1@% &\*"\$3'0\$50/":%3/3\$"(%62%0a.0(B0a.0(%&5\$0\$03'0',%51"(% 62%&((0\$03'%7%&,"#0.1% D./7&\$"%)/.#% D3(0.1% A>/350("<%Y"138&/% 37%5"#0(.&/% \$&\$"5%&'(% \*/"&'.)% &5"%)"57351"(% #01./\$&""3.#/2% 62%.#0',% &%5\$0)(%)53\*"(.5"% \*&//"(% (0#)"5#08"%#3/0(%)>&#"% "4\$5&\*\$03'% 9(0#)"5#08"%D-X =%0'%\$>0'\*>%C&,""#0.1% D./7&\$"%&'(%) )501&529#"\*3'(&52% &10' "% 9-D;=% #356""\$%&5"%#01)/2%104"(% \$0\$>\%'\@\%\*\*"\$3'0\$\$50/"\\$5\$&\*\$\\$'\%'(%) )501&529#"\*3'(&52% &10' "% 9-D;=% #356""\$%&5"\\$#01)/2%104"(% \$0\$>\%'\@\%\*\*"\$3'0\$\$50/"\\$5\$&\*\$\\$\%''(%) (0#)"5#08"\\$0-X%\$\$0\$>\\$\\$0;%5"138"\\$% 1&'2%) )3/&5%\&\$504\\$01)3""\$\\$#% #.\*>% &#\%35,&'0\*\%\*\*0(#:\%"5\$&0'\%3/&5\)0,1""\$\\$% &'(% #.,&5#%\$3'\\$3'1"% "4\$""\$%7531\\$>"\%735\\$a.\\$/0\$&\$\$\$\$8.\\$0\$&\$08.\\$%(% a.\\$'\$0\$&\$08.\\$0\$"\\$"510'\\$\$03'\%37% @AB&1""\\$6/"\%)"\\$\$0\*0(#<

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;@!XYXN% ZY; -X% CID!:% ;',"/0\*&:% ;'0#&\$"(% (50'+%S0\$>3.\$%&/\*3>3/:%;531&\$0T"(%S&\$"5% (50'+:%;5\$0\*>3+"%.0\*":%;#)&5&,.#:% [&62%\*31)3\$":% [&/1% /"&8"#:%[&1633% #>33\$#:%&#"% 735%\*\$&5:%[&#0/:%[&2%/"&8"#%9@&.5"/%[""\$533\$:%[""\$533\$%?.0\*":%["550"#%E9#1&//%75.0\$#:% [0\$\$"\$**!**B'0\*%#3(&:% [/&\*+% 5&(0#>:%//&\*+% D&/#072:%&\*+6"552%?.0\*":% [/&\*+\*.55&'\$ %?.0\*":% [/."6"550"#% ?.0\*":%[35&,":% [3\$\$/"(% S&\$"5:%5&##0\*&#:%\*+\$>35'% 9#"&%#&/3S\$>35'=%.0\*":% &)50\*3\$%>&/8"#:% A&""(% &5\$0\*>3+"%>"&5\$#:%A&""(% &5\$0\*>3'#:% A&''''(% &#)&5&,,#:% A&""(% 6&1633% #>33\$#:%A&""(% 6""\$533\$#:%A&""(% 60,&55"&.4:%A&""(% 6/&\*+6"550"#:%A&""(% 6/."6"550"#% E%60/6"550"#:%\&""(% 653\*\*3/0:%A&""(% [5.##"/#% #)53.\$#:%A&""(% \*&553\$#:%A&""(% \*&./07/3S"5:%A&""(% \*"/"52:% A&' ""(% \*>"552%)/.1#:% A&""(% \*>0\*352%"&(#:%A&""(% A>0\*352%"&(#:%A&""(% \*.5/2%+&/":%A&""(% 7/&,"3/"\$#:% A&""(% U5""\*>E% S&4% 6"&'#:% A&""(% 75.0\$%3\*+\$&0/:%A&""(% 75.\$%#&/&(:% A&""(% ,5&)"75.0\$#:9\\dag{""}(% /""\$0/:\%A\\dag{""}(% /"\$\$.\*"\%>"\&5\$#:\\dag{\dag{A}}\dag{""}(\left \gamma/2\*>"":\% A\dag{\dag{A}}\t"(\left \gamma 2\*>\text{"}:\% A\dag{\dag{A}}\t"(\left \gamma 1\dag{\dag{A}}\text{"}(\left \gamma 2\*)\text{"}). \*/"1""\$0""#:% A&""(% 1&',3:% A&""(% 1"/3':% A&""(% 1.#>5331#:% A&""(% 35&',":% A&""(% )&/1% >"&5\$#:%A&""(% )"&\*>% >&/8"#:%A&""(% )"&#:% A&" "(% )"&#% z%\*&553\$#:% A&""(% )0"%))/":% A&""(% )0)"5&(":% A&""(% )3\$&\$3"#:%A;VVXN% Y;D-[XYYc:% A&""(% 5"(\*.55&'\$#:%A&""(% #&/#070"##\&""(% #3&+"(%(52%6"\&'#:% A\&""(% #3\&+"(%(52\% )"&#:%A&""(% #32&%6"&'#%#)53.\$:%A&""(% #)0'&#>:%A&""(% #\$5&\$1650"#:%A&""(% #\$""\$% \*35':% A&""(% #\$""\$%)"))"5:% A&""(% \$31&\$3"#:%A&""(% \$5.77**#**:%A&""(% 8","\$&6/"% 6/"'(:% A&""(% `0//0&1#% )"&5#:% A&5&S&2%/"&8"#:% A&563'&\$"(% ).5" % &))/"% ?.0\*":% A&5(33'#:%A&553\$:**%**&##&8&:**%**"/"50&\*:%A"/"52:%A"/"52%?.0\*":%A"/"52%/"&8"#:%A"5"&/%,5&0'#:% A>"552%.0\*":%A>"552%\$31&\$3:%A>"580/:%A>08"#:%A>3+"6"550"#%.0\*":%A0\$5.#%5.0\$#:%/3.(2% &))/"% ?.0\*":%A31)3\$":% A31)3\$"% /0,>\$:%A31)3\$"% #.,&5"(:% A35**&**'("5% /"&8"#:% A3S6"552% 95"(% 60/6"552=%.0\*":% A5"1"% ("% 1&553':% A.\*.560\$#% 9'(06/"% #+0'#=:% A. 55&\\$#:\%N&\$":% N&.)>0""% )3\$&\$3%753T"":% NEZ/.\*3#"% 9("4\$53#"=% N50"(% &))/":% N50"(% &)50\*3\$:%N50"(% &5\$0\*>3+":%150"(%&#)&5&, #:% N50"(%6&'&'&:% N50"(%6""\$533\$:%N50"(% 6/&\*+\*.55&'\$:% N50"(% 6/."6"550"#:%N50"(%653\*\*3/0:%N50"(%\*&553\$:%N50"(%\*&./07/3\$"5:%N50\\% \*"/"52:% N50"(%\*"/"52:% /"&8"#:% N50"(%\*>"552:%N50"(%\*>0\*352:%N50"(%\*3\*3'.\$:% N50"(%\*35':% N50"(%\*3S6"552%95"(% "/("56"550"#:%N50"(%7"""/:% N50"(%70,:%N50"(%70,%#./)>.5&\$"(:%N50"(%.&8&:% N50"(%"13':% N50"(%"13'% )""/:% N50"(%/38&,"% /"&8"#:%N50"(%1&'(&50':%N50"(%1&',3:%N50"(%1"/3':% N50"(%35&',":% N50"(%)&)&2&:% N50"(%)&##03'% 75.0\$:%150"(%)"&\*>: % N50"(%)"&5:% N50"(%) )0"'&))/":% N50"(%).1)+0':% N50"(%5&#)6"550"#:%N50"(%5"(\*.55&'\$:% N5α(% 5>.6&56:%N50"(% 53#"%0):%N50"(%#\$5&S6"552**N5**0"(%\$31&\$3:%N50"(%T.\*\*>0'0:%N50'+%&(" %S0\$>%0\*":%X,,)/&'\$:% X/("56"550"#%.0\*":%U"""/:% U"""/% /"&8"#:%U0,:%J0,%\&#\$":%U5""\*>% 750"#%"\*33+"(% 753T"':% U5""\*>% U50"#%5"\*33+"(% 753T"":%U5"#>%0//:%U5"#>%""\$0/#:%U5"#>%1.,\$ 35\$:%U5"#>%1.#\$:% U5.\*\$3#":%J5.0\$%./0#:%J5.0\$*\"*##"5\$:%J5.0\$*\"*##"5\$:%J5.0\$*\"*\$60'+#:%J5.0\$\"% \*3'\*""\$5&\$":%U5.0\$%&#\$":%U5.0\$%3S("5E7/3.5:%U5.0\$%5""%S(\$>%#..&5%E%31)3\$":%U5.0\$% #)"\*0&/\$2:%J5.0\$\$3))0',:% U5.0\$\$6\\$>\%06\"%)""/:% U5.0\$B","\$&6\"%?.0\*":%U5.0\$B","\$&6\"%?.0\*"% 7531%3'\*"\$5&\$":% U5.0\$#\$\frac{4}{975}"#>\%5\%753T"\=\%'.\$#:\% U5.0\$#\frac{4}{825}.):\% U.'.0:\% Z/36\"\% &5\$0\*>3+\":\% Z/.\*3#":% Z.&8&%?.0\*":%W"&(%65&##0\*&:W3""2:% W35#"5&(0#>:W35#"5&(0#%)./):% W2##3):% O&163/&':% O&)&"#"% 5&(0#>:%0"5.#&/"1% &5\$0\*>3+":%3>/5&60:%1.1a.&\$:% @&72%65&##0\*&:% @",.1"% 8","\$&6/"#:% @"13'&(":% @"13',5&##:% @"\$\$.\*"%%%3\$>"5%#&/&(%)/&'\$#:%@BZ/.\*3#":% @01"%.0\*":%@38&,":%C&5?35&1:%&51&/&(":%C&#>"(%)3\$&\$3"#:%C0/+"(%1&#>"(%)3\$&\$3"#:% C0'\$:%/"\*\$&5:%F5",&'3:% F\$>"5%&)0&\*"&:%&/1% >"&5\$#:%&5#/"2:%&5#/"2%533\$:%&5#'0):%-"&5% ?.0\*":%-""/"(% )3\$&\$3"#:%"))"5:% -"))"510'\$:% -"5#0113':% -XD!% W3"'2:% -XD! %O&1:% ).5"":% \*31)3\$"% %7531%U5.0\$#:9&D!% O.0\*"#%9z\*3'\*""\$5&\$"# =%7531%U5.0\$#:9&D!% S>"&\$:% 52":%%<<%M!WFI!% ;NNM!MjX:%->2#&/0#:%31"% 75.0\$#:%3\$&\$3%3\$&\$3%653S'%)5"\*33+"(% 753T":% -3\$&\$3% 7/&+"#:% -3\$&\$3% 7/3.5:% -3\$&\$3% 3\$>"5% )5"\*33+"(% 753T".% -3\$&\$3% D&.\$""E-&50#0"""%-5"\*33+"(

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| KBV&)>\$>2/&*"\$0*%&*0(    | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| I:^:LB!                    | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| I:^BN                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| I:^BN[                     | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| I:^~BU351342/0(0(          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| I:PBN0*>/3536"'T&10("      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| IBV&)>\$>2/342&*"\$0*%&*0( | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| QBW2(5342*&5637.5&'        | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
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| ;6&1"*\$0'                              | %J <l%< th=""><th>1,E+,</th></l%<>                               | 1,E+,         |
|---|--|---------------|
| ;*")>&\$"                               | %J <k%< td=""><td>1,E+,</td></k%<>                               | 1,E+,         |
| ;*"\$&10)50(                            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| :*"\$3*>/35                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;*06"T3/&5B#B1"\$>2/                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;*07/.357"'                             | %J <jl%< td=""><td>1,E+,</td></jl%<>                             | 1,E+,         |
| ;*50'&\$>50'                            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;/&'2*&56                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;/(0*&56                                | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| ;/(0*&56B#./73'''                       | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;/(0*&56B#./7340("                      | %J <jl%< td=""><td>1,E+,</td></jl%<>                             | 1,E+,         |
| ;1"\$3*\$5&(0'                          | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;10'3*&56                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;10#./6531                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;10\$5&T                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;'0/373#                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;\$5&T0':%("#0#3)53)2/B                 | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;\$5&T0'"                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
|   | %J <jk%< td=""><td></td></jk%<>                                  |               |
| ;T&*3'&T3/"<br>:T\$ (05.8 *> \$0.1      |  | 1,E+,         |
| ;T&(05&*>\$0'<br>:T0'\>2#P1"\$>2/       | %J <jl%<br>%J<jk%< td=""><td>1,E+,<br/>1 ⊑±</td></jk%<></jl%<br> | 1,E+,<br>1 ⊑± |
| ;T0')>3#B1"\$>2/                        |  | 1,E+,         |
| ;T3*2*/3\$0'                            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ;T342#\$5360'                           | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["8/&42/                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["'(03*&56                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["'7.5"#&\$"                            | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| ["'3(&'0/                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["'312/                                 | %J <jjl%< td=""><td>1,E+,</td></jjl%<>                           | 1,E+,         |
| ["34&*35                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["#./0("                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["\$&T3"                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [""\$>0&8&/0*&56:%0#3)53)2/B            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["T&/+3'0.1%*>/350("%9\$3\$&/=%9[;A=    |  | 1,E+,         |
| ["'T"\$>3'0.1%A>/350("                  | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| ["T3401&\$"                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| ["T2/(01"\$>2/(3("*2/&113'0.1%*>/350("% | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| 9[;ABAKI=                               |  |               |
| [07"'&T&\$"                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [0\$"5\$&'3/                            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [04&7"                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [3#*&/0(                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [531342'0/                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [531.*3'&T3/":%*0#B                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [531.*3'&T3/":%\$5&'#B                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [!D%I\I\K                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [!D%^^L_L                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [!D%^^L_P                               | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [.)0501&\$"                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [.)537"T0'                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [.\$3*&563401B#./7340("                 | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [.\$.53'                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| [.\$2/&\$"                              | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| A&(.#&)>3#                              | %J <ji%< td=""><td>1,E+,</td></ji%<>                             | 1,E+,         |
| A&56&52/                                | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| A&56"'(&T01                             | %J <jjl%< td=""><td>1,E+,</td></jjl%<>                           | 1,E+,         |
| A&56"'(&T01E["'312/%9#.1=               | %J <jjl%< td=""><td>1,E+,</td></jjl%<>                           | 1,E+,         |
| A&56"\$&10("                            | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| A&5637.5&'                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
| A&563#./7&'                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                             | 1,E+,         |
|   |  |               |





| A&56340'                         | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
|----------------------------------|--|-------|
| A&57"\\$5&T3"\B"\\$>2/           | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A&5)53)&10(                      | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A"\$&/+3'0.1%*>/350("%9[;ABAKP=  | %J <ji%< td=""><td>1,E+,</td></ji%<>   | 1,E+, |
| A>/35&'\$5&'0/0)53/"             | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/356531.53'                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/356.7&1                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/357/.&T.53'                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/350(&T3'"                     | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/353\$3/.53'                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/3534.53'                      | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/35)53)>&1                     | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>/35)25073#%9B"\$>2/=           | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |
| A>/35)25073#B1"\$>2/             | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A>531&7"'3T03(                   | %J <k%< td=""><td>1,E+,</td></k%<>     | 1,E+, |
| A0'0(3'B"\$>2/                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/"7342(01                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/"\$>3(01                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/016&T3/"                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/37"'\$"T0""                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/31&T3'"                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/31")53)                        | %J <k%< td=""><td>1,E+,</td></k%<>     | 1,E+, |
| A/3)53)                          | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A/3)25&/0(                       | %J <k%< td=""><td>1,E+,</td></k%<>     | 1,E+, |
| A/3\$>0&'0(0'                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A3.1&)>3#                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A5010(0'"                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2&'37"")>3#                     | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2&T37&10(                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2*/3&\$"                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2*/342(01                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A27/.1"\$37"'                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2>&/373)B6.\$2/                 | %J <jl%< td=""><td>1,E+,</td></jl%<>   | 1,E+, |
| A2>"4&\$0'                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2>"4&\$0'E;T3*2*/3\$0'%9D.1=    |  | 1,E+, |
| A2134&'0/                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2)>"'3\$>50'                    | %J <jl%< td=""><td>1,E+,</td></jl%<>   | 1,E+, |
| A2)53*3'&T3/"                    | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2)53(0'0/                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| A2531&T0"                        | %J <k%< td=""><td>1,E+,</td></k%<>     | 1,E+, |
| N&T31"\$                         | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| NN; A%AKJ%B%                     | %J <ji%< td=""><td>1,E+,</td></ji%<>   | 1,E+, |
| N0("*2/(01"\$>2/&113'0.1*>/350(" | 0/ 1 - 11 0/                           | 4 = . |
| N"1"\$3'BDB1"\$>2/               | %J <jl%< td=""><td>1,E+,</td></jl%<>   | 1,E+, |
| N"1"\$3'BDB1"\$>2/B#./73'"       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N"#1"(0)>&1                      | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0&7"'\$>0.53'                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0&//&\$"                        | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0&T0'3'                         | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0*&16&                          | %J <k%< td=""><td>1,E+,</td></k%<>     | 1,E+, |
| N0*>/37"'\$>03'                  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0*>/3510(                       | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0*>/35)53)                      | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0*>/3583#                       | %J <ji%< td=""><td>1,E+,</td></ji%<>   | 1,E+, |
| N0*53\$3)>3#                     | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| NO"\$>37"'*&56                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N0"\$>2/\$3/.&10("               | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N07'''&*3.1                      | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| N07"'3*3'&T3/"                   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |





| NOTING 4 TO                                    | 0/ 1 11/0/  | 4 =            |
|--|---|----------------|
| N07"'34.53'                                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N07/.6"T.53'                                   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N07/.7"'0*&'                                   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"7.53'                                      | %J <k%< td=""><td>1,E+,</td></k%<>                      | 1,E+,          |
| N01")0)"5&\$"                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"\$>&*>/35                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"\$>"'&10(                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"\$>3&\$"                                   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"\$>3135)>                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01"\$0/&'                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N01342#\$5360'                                 | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0'0*3'&T3/"                                   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0'3*&)  | %J <jl%< td=""><td>1,E+,</td></jl%<>                    | 1,E+,          |
| N0'3#"6  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0'3\$"7.5&'                                   | %J <jl%< td=""><td>1,E+,</td></jl%<>                    | 1,E+,          |
| N0'3\$"56                                      | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N034&*&56                                      | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0)>"'&10(                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0)>"'2/&10""                                  | %J <ji%< td=""><td>1,E+,</td></ji%<>                    | 1,E+,          |
| N0#./73\$3'                                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0#./73\$3'%9#.1=                              | 700 01170   | 1,E+,          |
| N0#./73\$3'B#./73'                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0#./73\$3'B#./7340("                          | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N0.53'   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N3("1357                                       | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| N3(0""   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X1&1"*\$0'                                     | %J <jk%< td=""><td>1,⊑+,<br/>1,E+,</td></jk%<>          | 1,⊑+,<br>1,E+, |
| X-V  | %J <jk%< td=""><td>1,⊑+,<br/>1,E+,</td></jk%<>          | 1,⊑+,<br>1,E+, |
| X)340*3'&T3/"                                  | %J <jk%< td=""><td>1,⊑+,<br/>1,E+,</td></jk%<>          | 1,⊑+,<br>1,E+, |
| X-!A   | %J <jk%< td=""><td>1,⊑+,<br/>1,E+,</td></jk%<>          | 1,⊑+,<br>1,E+, |
| X\$>037""*&56                                  | %J <jk%< td=""><td>1,⊑+,<br/>1,E+,</td></jk%<>          | 1,⊑+,<br>1,E+, |
|  | %J <jk%< td=""><td></td></jk%<>                         |                |
| X\$>037""*&56B#./73""  X\$>037""*&56B#./7340/" |   | 1,E+,          |
| X\$>037""*&56B#./7340("<br>X\$>03'             | %J <jk%<br>%J<jk%< td=""><td>1,E+,</td></jk%<></jk%<br> | 1,E+,          |
|  | %J <jk%<br>%J<jk%< td=""><td>1,E+,</td></jk%<></jk%<br> | 1,E+,          |
| X\$>0)53/"                                     |   | 1,E+,          |
| X\$>05013/                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X\$>37.1"#&\$"                                 | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X\$>3)53)>3#                                   | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X\$>342a.0'                                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X\$>2*>/3T&\$"                                 | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| X\$37")534                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&10(3'"                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&10)>3#                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&10)>3#%9#.1=                               |   | 1,E+,          |
| U"'&10)>3#B#./73"                              | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&10)>3#B#./7340("                           | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&5013/                                      | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'&T&a.0'                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'6.*3'&T3/"                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'6.\$&\$0'%340("                             | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'>"4&10(                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'36.*&56                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U""3)53)                                       | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'34&)53)B -                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"'342*&56                                     | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"")0*/3'0/                                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"")53)0(0'                                    | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
| U"")53)0135)>                                  | %J <jk%< td=""><td>1,E+,</td></jk%<>                    | 1,E+,          |
|  |   |                |

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| U"')25&T&10'"   | %J <jk%< th=""><th>1,E+,</th></jk%<>   | 1,E+, |
|---|--|-------|
| U"')253401&\$"  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'#./73\$>03'  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$>03'   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$>03'%9#.1=   | 700 01170                              | 1,E+, |
| U"'\$>03'B343'  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$>03'B343'B#./73'"  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$>03'B343'B#./7340("  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$>03'B#./73"  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"\\$>03'B#./7340("   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U"'\$0'%&*"\$&\$"   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U0)53'0/  | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |
| U0)53'0/:%("#./70'2/B   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U0)53'0/B#./70("  | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |
| U0)53'0/B#./73'"  | %J <jjl%< td=""><td>1,E+,</td></jjl%<> | 1,E+, |
| U/3'0*&10(  | %J <jl%< td=""><td>1,E+,</td></jl%<>   | 1,E+, |
| U/.&T073)B  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.&T073)B-B6.\$2/  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.&T0'&1   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.&T.53'   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.6"'(0&10("   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.*2*/34.53'   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.(0343'0/   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.7"'&*"\$   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.7"'34.53'  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.7"'T0'"  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.31"\$.53'  | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.3)0*3/0(   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.3)25&1   | %J <jk%< td=""><td>1,E+,</td></jk%<>   | 1,E+, |
| U/.34&#\$5360'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.5342)25</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.5342)25BC"\$>2/>")\$2/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.5)5010(3/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.5\$&13'"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.#0/&T3/"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.\$>0&*"\$B1"\$>2/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.\$0&'0/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.\$3/&'0/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U/.\$50&73/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>UCBPBK</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U31"#&7"'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U35*>/357"'.53'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U351"\$&'&\$"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U3#\$>0&T&\$"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U.6"50(&T3/"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U.5&/&42/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U.5&1"\$)25</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>U.5&\$>03*&56</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W&/34273)</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W")\$"'3)>3#</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W"4&*3'&T3/"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W"4&7/.1.53'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W"4&T0'3""</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>W"42\$>0&T34</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>M1&T&/0/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>M1&T&)25</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>M1&T&a.0'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>M1&T"\$>&)25</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td></td><td></td><td></td></tr></tbody></table> |  |       |

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| M106"'*3'&T3/"                     | %J <jk%< th=""><th>1,E+,</th></jk%<> | 1,E+, |
|------------------------------------|--------------------------------------|-------|
| M10(&*/3)50(                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M'(&T07/&1                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M'(34&*&56                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M3(3#./7.53'%1"\$>2/               | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M342'0/                            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M)53(03'"                          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M)538&/0*&56                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#&T3)>3#                          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#37"')>3#                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#3)53*&56                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#3)53\$>03/&'''                   | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#3)53\$.53'                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#3)25&T&1                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#3.53'                            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#34&6"                            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| M#34&7/.\$3/"                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| {5"#3401B1"\$>2/                   | %J <jl%< td=""><td>1,E+,</td></jl%<> | 1,E+, |
| @"&*0/                             | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| @0'.53'                            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| @.7"'.53'                          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C&/&343'                           | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C&/&\$>03'                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C&/&\$>03'EC&/&343'%9#.1=          | 700 -01770                           | 1,E+, |
| C&'(0)53)&10(                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| CA-;                               | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| CA-[                               | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"*3)53)                           | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C")&'0)2501                        | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"#3\$503""                        | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| C"\$&7/.10T3'"                     | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$&/&42/                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$&10\$53'                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$*3'&T3/"                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>&6"T\$>0&T.53'                | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>&*50)>3#                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>&10(3)>3#                     | %J <jl%< td=""><td>1,E+,</td></jl%<> | 1,E+, |
| C"\$>0(&\$>03'                     | %J <jl%< td=""><td>1,E+,</td></jl%<> | 1,E+, |
| C"\$>03*&56                        | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>03*&56B#./73"                 | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>03*&56B#./7340("              | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>312/                          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$>3427"'3T0("                   | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$36531.53'                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$3/&*>/35                       | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$3/*&56                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$3#./&1                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$34.53'                         | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C"\$506.T0'                        | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C0/6"1"*\$0'%;Q                    | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| C0/6"1"*\$0'%;^                    | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| C050#\$&/+3'0.1%*>/350("%9[;ABAK^= | %J <ji%< td=""><td>1,E+,</td></ji%<> | 1,E+, |
| C3/0'&\$"                          | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C3'3*53\$3)>3#                     | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C3'3/0'.53'                        | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C3'.53'                            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| C2*/36.\$&'0/                      | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| V&)>\$>&/"""%;*"\$&10("            | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
|                                    |                                      |       |





| V&)53)&10("  | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
|--|--------------------------------------|-------|
| V"6.53'  | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| V0*3#./7.53'   | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| V0\$"')25&1  | %J <k%< td=""><td>1,E+,</td></k%<>   | 1,E+, |
| V38&/.53'  | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| V3807/.1.53'   | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| V.&5013/   | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| F7.5&*"  | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| F1"\$>3&\$"  | %J <jk%< td=""><td>1,E+,</td></jk%<> | 1,E+, |
| F52#&#\$5360'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F52T&/0'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F4&(0&T3'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F4&(042/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F4&12/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F4&12/B3401"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F4&T0*/31"73'"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F47"(&T3/"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>· ·</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>F42*&56340'</td><td></td><td></td></tr><tr><td>F42("1"\$3'B1"\$>2/</td><td>%J<JI%</td><td>1,E+,</td></tr><tr><td>-&*/36.\$5&T3/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-&5&343'B"\$>2/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-&5&343'B1"\$>2/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"6./&\$"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'*3'&T3/"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-""*2*.53'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'(01"\$>&/0'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'7/.7"'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'34#./&1</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'\$&*>/353)>"'3/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'\$&'3*>/35</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"'\$>03)25&(</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-"\$>34&10(</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->"'1"(0)>&1</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->""\$>3&\$"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->35&\$"%9#.1=</td><td></td><td>1,E+,</td></tr><tr><td>->35&\$"B#./73""</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->35&\$"B#./7340("</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->3#&/3"</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->3#1"\$</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->3#1"\$%9D.1=</td><td>7.22</td><td>1,E+,</td></tr><tr><td>->3#1"\$B343'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->3#)>&10(3'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>->3401</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-0*&50(0'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-0*/35&1</td><td>%J<I%</td><td>1,E+,</td></tr><tr><td>-0'34&("'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>•</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-0)"53'2/%6.\$340("</td><td></td><td></td></tr><tr><td>-05010*&56</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-05010*&56:%("#1"\$>2/B</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-05010*&56:%("#1"\$>2/B7351&10(3B</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-05010)>3#B1"\$>2/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-53*>/35&T</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-53*210(3'''</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-537"'373#</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-531"*&56</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-531"\$3'</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-53)&13*&56</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td>-53)&'0/</td><td>%J<JK%</td><td>1,E+,</td></tr><tr><td></td><td></td><td></td></tr></tbody></table> |                                      |       |

IKBO./2BIJKL YCJ!- ^QELP





| F3\8 a 0T8.73\   | 0/ 1~ 11/0/                                    | 4 -            |
|--|--|----------------|
| -53)&a.0T&73)  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53)&5,0\$"<br>53)>\$1   | %J <jk%< td=""><td>1,E+,<br/>1 ⊑±</td></jk%<>  | 1,E+,<br>1 ⊑±  |
| -53)>&1  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53)0*3'&T3/"  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53)34.5<br>-53)342*&56&T3'E-53)342*&56&T3'BIB>2(5342%   | %J <jk%< td=""><td>1,E+,<br/>1,E+,</td></jk%<> | 1,E+,<br>1,E+, |
| 9D.1=  |  | 1,⊑⊤,          |
| -53)342*&56&T3'BIB>2(5342  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53)342*&56&T3'"   | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53)2T&10("  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53a.0'&T0(  | %J <ji%< td=""><td>1,E+,</td></ji%<>           | 1,E+,          |
| -53#./73*&56   | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53\$>03*3'&T3/"   | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
| -53\$>03*3'&T3/"B("#\$>03  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
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| -25&*/3#\$5360'  | %J <jk%< td=""><td>1,E+,</td></jk%<>           | 1,E+,          |
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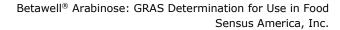
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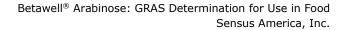
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APPENDIX C TOXICOLOGICAL STUDIES





APPENDIX C1
90-DAY ORAL TOXICITY STUDY WITH
BETAWELL L-ARABINOSE BY DIETARY
ADMINISTRATION IN THE RAT

# **FINAL REPORT**

# Study Title

# 90-DAY ORAL TOXICITY STUDY WITH BETAWELL L-ARABINOSE BY DIETARY ADMINISTRATION IN THE RAT

# <u>Author</u>

C.G.M. Beerens - Heijnen, PhD.

# **Test Facility**

Charles River Laboratories Den Bosch BV Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

**Laboratory Project Identification** 

Project 509991 Substance 206781/A+B

# 1. CONTENTS

| 1.      | CONTENTS   |    |
|---------|--|----|
| 2.      | STATEMENT OF GLP COMPLIANCE                                      | 4  |
| 3.      | QUALITY ASSURANCE STATEMENT                                      |    |
| 4.      | SUMMARY  |    |
| 5.      | INTRODUCTION   |    |
| 5.      |  |    |
|         | 5.1. Preface   |    |
|         | 5.2. Study plan  |    |
|         | 5.3. Aim of the study  |    |
|         | 5.4. Guidelines  |    |
|         | 5.5. Storage and retention of records and materials              |    |
| 6.      | MATERIALS AND METHODS  |    |
|         | 6.1. Test substance  |    |
|         | 6.1.1. Test substance information 206781/A                       | 11 |
|         | 6.1.2. Study specific test substance information (Batch A and B) | 11 |
|         | 6.1.3. Diet preparation  | 11 |
|         | 6.2. Chemical analysis of diet preparations                      |    |
|         | 6.3. Test system   |    |
|         | 6.4. Allocation  |    |
|         | 6.5. Animal husbandry  |    |
|         | 6.6. Treatment   |    |
|         | 6.7. Observations  |    |
|         | 6.8. Clinical laboratory investigations                          |    |
|         | 6.9. Pathology   |    |
|         | 6.9.1. Necropsy  |    |
|         | 6.9.2. Organ weights   |    |
|         | 6.9.3. Histotechnology   |    |
|         | 6.9.4. Histopathology  | 17 |
|         | 6.10. Electronic data capture                                    | 17 |
|         |  |    |
|         | 6.11. Interpretation   |    |
|         | 6.12. List of deviations   |    |
|         | 6.12.1. List of protocol deviations                              |    |
| _       | 6.12.2. List of standard operating procedures deviations         |    |
| 7.      | RESULTS  |    |
|         | 7.1. Analysis of dose preparations                               |    |
|         | 7.2. Observations  |    |
|         | 7.2.1. Mortality   |    |
|         | 7.2.2. Clinical signs  |    |
|         | 7.2.3. Functional observations                                   |    |
|         | 7.2.4. Body weights  |    |
|         | 7.2.5. Food consumption  | 20 |
|         | 7.2.6. Test article intake                                       | 20 |
|         | 7.2.7. Ophthalmoscopic examination                               | 20 |
|         | 7.3. Clinical laboratory investigations                          |    |
|         | 7.3.1. Haematology   |    |
|         | 7.3.2. Clinical biochemistry                                     |    |
|         | 7.4. Pathology   |    |
|         | 7.4.1. Macroscopic examination                                   |    |
|         | 7.4.2. Organ weights   |    |
|         | 7.4.3. Microscopic examination                                   |    |
| 8.      | DISCUSSION AND CONCLUSION  |    |
| ٥.<br>۵ | DEFEDENCES   | 22 |

# **APPENDICES**

APPENDIX 1 FIGURES AND SUMMARY TABLES
APPENDIX 2 INDIVIDUAL DATA TABLES
APPENDIX 3 CERTIFICATE OF ANALYSIS
APPENDIX 4 PHASE REPORT DIET ANALYSIS
APPENDIX 5 PHASE REPORT HISTOPATHOLOGY
APPENDIX 6 SUMMARY OF DOSE RANGE FINDING STUDY

Final Report - Page 3 -

## 2. STATEMENT OF GLP COMPLIANCE

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with:

OECD Principles of Good Laboratory Practice.

EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).

## Except for the following:

- The characterisation of the test item was conducted in a ISO environment.
- Diet Analysis was performed at the Sponsor under non-GLP conditions and was therefore excluded from the QA inspections. It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V. The external lab is specialized in sugar analysis and therefore is well-found with necessary equipment for the analysis of Betawell L-Arabinose in diet. The analysis was evaluated by the principle scientist.

The data generated and reported are considered to be valid.

Charles River Den Bosch

C.G.M. Beerens - Heijnen, PhD. Study Director



Date: 11 November 2016

# 3. QUALITY ASSURANCE STATEMENT

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands.

Study title: Repeated dose 90-day oral toxicity study with Betawell L-Arabinose by dietary administration in the rat.

This report was inspected by the Charles River Den Bosch Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s).

The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected.

The dates of Quality Assurance inspections are given below.

| Project | 509991 |
|---------|--------|
|---------|--------|

| Type of<br>Inspections | Phase/Process   | Start<br>Inspection<br>date  | End<br>Inspection<br>date  | Reporting date to TFM and SD*  |
|------------------------|---|--|--|--|
| Study                  | Protocol Test substance preparation Study Plan Amendment 01 Study Plan Amendment 02 Study Plan Amendment 03 Observations /measurements biological test system Study Plan Amendment 04 Study Plan Amendment 05 | 06-Oct-2015<br>03-Nov-2015<br>04-Nov-2015<br>04-Nov-2015<br>12-Nov-2015<br>20-Nov-2015<br>18-Dec-2015<br>27-Jan-2016 | 06-Oct-2015<br>03-Nov-2015<br>04-Nov-2015<br>04-Nov-2015<br>12-Nov-2015<br>20-Nov-2015<br>18-Dec-2015<br>27-Jan-2016 | 06-Oct-2015<br>03-Nov-2015<br>04-Nov-2015<br>04-Nov-2015<br>12-Nov-2015<br>20-Nov-2015<br>18-Dec-2015<br>27-Jan-2016 |
|                        | Necropsy Specimen sampling Study Plan Amendment 06 Study Plan Amendment 07 Report   | 04-Feb-2016<br>04-Feb-2016<br>04-Feb-2016<br>09-Mar-2016<br>07-Oct-2016  | 04-Feb-2016<br>04-Feb-2016<br>04-Feb-2016<br>09-Mar-2016<br>07-Oct-2016  | 04-Feb-2016<br>04-Feb-2016<br>04-Feb-2016<br>09-Mar-2016<br>17-Oct-2016  |
| Process                | Animal Facilities Test Substance Handling Exposure Observations/Measurements Specimen Handling  | 19-Oct-2015  | 30-Oct-2015  | 04-Nov-2015  |
|                        | <b>Test Substance Receipt</b> Test Substance Handling   | 09-Nov-2015  | 20-Nov-2015  | 20-Nov-2015  |
|                        | Clinical pathology Observations/Measurements Specimen Handling  | 18-Nov-2015  | 26-Nov-2015  | 26-Nov-2015  |
|                        | Analytical and physical chemistry Test Substance Handling Exposure  | 30-Nov-2015  | 14-Dec-2015  | 17-Dec-2015  |

Final Report - Page 5 -

Observations/Measurements Specimen Handling

**Test Substance** 

**Formulation** 02-Dec-2015 11-Dec-2015 18-Dec-2015

**Test Substance Handling** 

**Histology** 07-Dec-2015 18-Dec-2015 18-Dec-2015

Specimen Handling

**Necropsy** 07-Dec-2015 18-Dec-2015 18-Dec-2015

Observations/Measurements

Specimen Handling

The facility inspection program is conducted in accordance with Standard Operating Procedure.

The review of the final report was completed on the date of signing this QA statement.

Charles River Den Bosch

Name: Maaike van Dooren, BSc Quality Assurance Auditor

Date: 11 - 10 - 2016

<sup>\*</sup>TFM=Test Facility Management SD = Study Director

## 4. SUMMARY

#### Title

90-Day oral toxicity study with Betawell L-Arabinose by dietary administration in the rat.

## Guidelines

The study was based on the following guidelines:

- EC No 440/2008, B.26 Repeated Dose (90 days) Toxicity (oral), 2008.
- OECD 408, Repeated Dose 90-day Oral Toxicity Study in Rodents, 1998.
- OPPTS 870.3100, EPA 712-C-98-199, 90-Day Oral Toxicity in Rodents, 1998.
- Japanese Chemical Substances Control Law 1973, Notification of Mar. 31 2011 by MHLW (0331 No.7), METI (H23.03.29 SeiKyoku No. 5) and MOE (No. 110331009).

#### Rationale for dose levels

Based on the results of a 14-day range finding study (Project 509992; See APPENDIX 6), the dose levels for this 90-day oral study by dietary administration were selected to be 0, 3000, 10000 and 30000 mg/kg.

#### Study outline

The test substance, was administered for at least 90 days by dietary administration to SPF-bred Wistar rats. One control group and three treated groups were tested, each consisting of 10 males and 10 females.

#### Evaluated parameters

Chemical analyses of dietary preparations were conducted during Weeks 1, 6 and 13 to assess accuracy, homogeneity and stability over 9 days at room temperature under normal laboratory light conditions.

The following parameters were evaluated: clinical signs daily; functional observation tests in Week 12-13; body weight and food consumption weekly; ophthalmoscopy at pretest and in Week 13; clinical pathology and macroscopy at termination; organ weights and histopathology on a selection of tissues.

### Results

Dietary analyses, conducted (non-GLP) by the Sponsor and evaluated by Principle Scientist, confirmed that preparations of test substance in diets were prepared accurately and homogenously, and were stable over at least 9 days.

Mean test article intake over the study period was as follows:

| group | Nominal dietary inclusion level [ppm] | Average intake [mg test substance/kg body weight] (range indicated within brackets) |             |         |             |
|-------|---------------------------------------|---|-------------|---------|-------------|
|       |                                       | males   |             | females |             |
| 2     | 3000                                  | 216   | (183-289)   | 251     | (227-290)   |
| 3     | 10000                                 | 760   | (608-984)   | 872     | (755-997)   |
| 4     | 30000                                 | 2218  | (1859-2833) | 2614    | (2319-3062) |

No toxicologically significant changes were noted in any of the parameters investigated in this study (i.e. clinical appearance, functional observations, ophthalmoscopy, body weight, food consumption, clinical laboratory investigations, macroscopic examination, organ weights, and microscopic examination).

### Conclusion

From the results presented in this report a No Observed Adverse Effect Level (NOAEL) for Betawell L-Arabinose of at least 30000 ppm was established, which corresponded to 2218 mg/kg body weight in males and 2614 mg/kg body weight in females.

Final Report - Page 7 -

## 5. INTRODUCTION

Due to the acquisition of WIL Research by Charles River, the name of the WIL Research facility in Den Bosch, has been changed to Charles River Laboratories Den Bosch BV, Hambakenwetering 7, 5231 DD, 's-Hertogenbosch, The Netherlands. Study documents may contain both names and both names are considered equivalent and may be used as the name of WIL Research transitions to Charles River.

## 5.1. Preface

Information concerning the dose range finding study (Project 509992) is given in APPENDIX 6.

Two Project numbers were used to collect online data (Project 509993 (arena observations) and 509991 (other data)). All data was reported under Project 509991.

Sponsor Cosun Biobased Products B.V. As part of Royal Cosun

Postbus 3411 4800 MG Breda Netherlands

Study Monitor Alex Benschop and Diederick Meyer

Study Director C.G.M. Beerens - Heijnen, PhD.

Charles River Laboratories Den Bosch BV

Hambakenwetering 7 5231 DD 's-Hertogenbosch

The Netherlands Tel: +31.73 640 6700 Fax: +31.73 640 6799

Email: chantal.beerens@crl.com

Coordinating Biotechnician Dose range finding study

N.E.J. Duijts (Charles River Den Bosch)

Main study

H. Raaso (Charles River Den Bosch)

Clinical Pathology C.W. Koot, BSc. (Charles River Den Bosch)

Necropsy M. Schelling (Charles River Den Bosch)

Histotechnology W. Verhoef (Charles River Den Bosch)

Histopathology J.F.M. Lensen, PhD., CRP/TP (Principal Scientist, Charles

River Den Bosch)

Analytical Chemistry J. Ciric, PhD. (Principal Scientist, Charles River Den Bosch)

QA C.J. Mitchell, BSc. (Charles River Den Bosch):

Email: <a href="mailto:christine.mitchell@crl.com">christine.mitchell@crl.com</a>

Test facility Management H.H. Emmen, MSc. (Charles River Den Bosch):

Email: harry.emmen@crl.com

Test Facility Charles River Laboratories Den Bosch BV

Hambakenwetering 7 5231 DD 's-Hertogenbosch

The Netherlands

Final Report - Page 8 -

## 5.2. Study plan

Experimental starting date 06 October 2015 (allocation dose range finding study: see

APPENDIX 6)

Treatment 04 November 2015 to 03 February 2016 (all females + first 5

males/dose group)

04 November 2015 to 04 February 2016 (last 5 males/dose

group)

Clinical Pathology 04 February 2016 (all females + first 5 males/dose group)

05 February 2016 (last 5 males/dose group)

Necropsy 04 February 2016 (all females + first 5 males/dose group)

05 February 2016 (last 5 males/dose group)

Experimental completion date 05 February 2016 (end of in-life phase)

## 5.3. Aim of the study

The nature and purpose of this toxicity study was to assess the toxic potential of the test substance when administered to rats via the diet for a period of 13 weeks. A No Observed Adverse Effect Level (NOAEL) was evaluated.

This study should provide a rational basis for toxicological risk assessment in man. The oral route was selected as it is the route of intended human use.

## 5.4. Guidelines

As required by the Dutch Act on Animal Experimentation (February 1997), the protocol was reviewed and agreed by the Animal Welfare Officer and the Ethical Committee (DEC 14-59). The study procedures described in this report were based on the following guidelines:

- Commission regulation (EC) No 440/2008 Part B: Methods for the Determination of Toxicity and other Health Effects; B.26: "Sub-chronic Oral Toxicity Test: Repeated dose 90-day toxicity study in rodents". Official Journal of the European Union No. L142, May 2008.
- 2. OECD "Guidelines for Testing of Chemicals", Section 4, Health Effects, No. 408, "Repeated Dose 90-day Oral Toxicity Study in Rodents", Paris, September 1998.
- United States Environmental Protection Agency Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-98-199 "Health Effects Test Guidelines" OPPTS 870.3100 "90-Day Oral Toxicity in Rodents", August 1998.
- Japanese Chemical Substances Control Law 1973, Notification of Mar. 31 2011 by MHLW (0331 No.7), METI (H23.03.29 SeiKyoku No. 5) and MOE (No. 110331009).

Final Report - Page 9 -

## 5.5. Storage and retention of records and materials

Records and materials pertaining to the study including protocol, raw data, specimens (except specimens requiring refrigeration or freezing) and the final report are retained in the Charles River Den Bosch archives for a period of at least 5 years after finalization of the report. After this period, the sponsor will be contacted to determine how the records and materials should be handled. Charles River Den Bosch will retain information concerning decisions made.

Those specimens requiring refrigeration or freezing will be retained by Charles River Den Bosch for as long as the quality of the specimens permits evaluation but no longer than three months after finalization of the report.

Charles River Den Bosch will retain a test substance sample until the expiry date, but no longer than 10 years after finalization of the report. After this period the sample will be destroyed.

Final Report - Page 10 -

## 6. MATERIALS AND METHODS

#### 6.1. Test substance

#### 6.1.1. Test substance information 206781/A

Identification Betawell L-Arabinose

Appearance White powder

Batch C32-1

Purity/Composition See Certificate of Analysis
Test substance storage At room temperature
Stable under storage 15 May 2017 (expiry date)

conditions until

From Week 2 onwards, batch C36-1 (expiry date 30 April 2016) was used (registered as test substance 206781/B).

See APPENDIX 3 for Certificate of analysis.

## 6.1.2. Study specific test substance information (Batch A and B)

Purity/composition correction factor

Test substance handling Chemical name (IUPAC), synonym or trade name

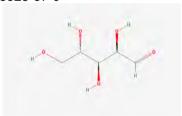
CAS Number
Molecular structure

No correction factor required

No specific handling conditions required

(2R,3S,4S)-2,3,4,5-Tetrahydroxypentanal, arabinose

5328-37-0



 $\begin{array}{ll} \text{Molecular formula} & \quad C_5 H_{10} O_5 \\ \text{Molecular weight} & \quad 150.13 \end{array}$ 

pH 5-7 at concentration of < 20%

## 6.1.3. Diet preparation

Diet Standard powder rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten

GmbH, Soest, Germany).

Method The test substance was mixed directly with some powder feed without the

use of a vehicle (premix) and subsequently mixed with the bulk of the diet. No correction was made for the purity of the test substance.

The control animals received the powdery diet without the test substance.

Frequency of preparation Diets were prepared once weekly.

Storage of preparations Diets were kept at room temperature in the diet storage room in the

animal house.

Final Report - Page 11 -

# 6.2. Chemical analysis of diet preparations

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V. The analysis of the samples was done at the Cosun Food Technology Centre (CFTC). CFTC is a sister company of Cosun Biobased Products B.V. and is specialized in sugar analysis and therefore is well-found with necessary equipment for the analysis of Betawell L-Arabinose in diet.

Analyses were conducted during the treatment phase, according to the method available at Cosun Food Technology Centre (non-GLP). Samples were shipped with no specific conditions required. Samples of diet preparations were analyzed for homogeneity (highest and lowest concentration) and accuracy of preparation (all concentrations, in Weeks 1, 6 and 13). Stability in vehicle over 9 days at room temperature under normal laboratory light conditions was also determined (highest and lowest concentration, in Week 1).

The accuracy of diet preparations was considered acceptable if the mean measured concentrations were 80-120% of the target concentration. Homogeneity was demonstrated if the coefficient of variation was ≤ 10%. Diet preparations were considered stable if the relative difference before and after storage was maximally 10%.

For details see APPENDIX 4.

## 6.3. Test system

Test system Rat: Crl:WI(Han) (outbred, SPF-Quality).

Rationale Recognized by international guidelines as the recommended test system

(e.g. EPA, FDA, OECD and EC).

Source Charles River Deutschland, Sulzfeld, Germany.

Total number of animals 40 males and 40 females (females were nulliparous and non-pregnant).

Age at start of treatment Approximately 6 weeks.

Identification Earmark and tattoo.

Randomization By computer-generated random algorithm according to body weight, with

all animals within ± 20% of the sex mean.

Acclimatization period At least 5 days before the start of treatment under laboratory conditions.

Health inspection Upon receipt of the animals.

#### 6.4. Allocation

| Croun | Dose level 1 | Number of animals |         | Animal numbers |         |
|-------|--------------|-------------------|---------|----------------|---------|
| Group | ppm          | Males             | Females | Males          | Females |
|       |              |                   |         |                |         |
| 1     | 0            | 10                | 10      | 1-10           | 41-50   |
| 2     | 3000         | 10                | 10      | 11-20          | 51-60   |
| 3     | 10,000       | 10                | 10      | 21-30          | 61-70   |
| 4     | 30,000       | 10                | 10      | 31-40          | 71-80   |
|       | ,            |                   |         |                |         |

Dose levels are based on results of a 14-day oral range finding study with Betawell L-Arabinose by dietary administration in the rat (Project 509992). A summary of the results is included in this report (see APPENDIX 6).

Final Report - Page 12 -

## 6.5. Animal husbandry

Room number A 0.16 (A0.23 for motor activity measurements).

Conditions Environmental controls for the animal room were set to maintain 18 to

24°C, a relative humidity of 40 to 70%, at least 10 air changes/hour, and a 12-hour light/12-hour dark cycle. Any variations to these conditions were maintained in the raw data and had no effect on the outcome of the

study.

Accommodation Group housing of 5 animals per sex in Macrolon cages (MIV type, height

18 cm) with sterilized sawdust as bedding material (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and paper as cage-enrichment (Enviro-dri, Wm. Lilico & Son (Wonham Mill Ltd), Surrey, United Kingdom). During locomotor activity monitoring, animals were housed individually in a Hi-temp polycarbonate cage (Ancare corp., USA; dimensions: 48.3 x 26.7 x 20.3 cm) without cage-

enrichment, bedding material, food and water.

Diet Free access to prepared diets. During the acclimatization period, animals

had free access to standard powder diet without the test substance (SM

R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany).

The diet was provided in stainless steel containers, covered by a stainless steel grid to prevent spillage. Food hoppers were shaken on a daily basis to divide any sawdust equally over the diet in order to facilitate food

consumption.

The same diets remained in the food hopper for a maximum of one week. On the day of weighing the remaining food in the food hopper was replaced with new diet. During motor activity measurements, animals did

not have access to food for a maximum of 2 hours.

Water Free access to tap water.

Diet, water, bedding and cage enrichment evaluation for contaminants and/or nutrients was performed according to facility standard procedures. There were no findings that could interfere with the study.

## 6.6. Treatment

Method Oral, by inclusion in the diet.

Dietary Inclusion Levels The amount of test substance incorporated into the diet was kept at a

constant level in terms of ppm, throughout the study period.

The actual test substance intake was estimated based on the body

weight and food consumption values.

Note: In the calculation for concentrations of preparations no correction

was made for the purity of the test substance.

Frequency Ad libitum.

Duration of treatment At least 90 days.

Animals received test diet up to the day prior to necropsy.

Final Report - Page 13 -

- Page 13 of 249 - 000143

## 6.7. Observations

Mortality / Viability

At least twice daily.

Clinical signs

At least once daily from start of treatment onwards, detailed clinical observations were made in all animals. Once prior to start of treatment and at weekly intervals this was also performed outside the home cage in a standard arena (collected under Project 509993 for logistic reasons and reported under Project 509991).

The time of onset, grade and duration of any observed signs were recorded. Signs were graded for severity and the maximum grade was predefined at 3 or 4. Grades were coded as slight (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4). For certain signs, only its presence (grade 1) or absence (grade 0) was scored. In the data tables, the scored grades are reported, as well as the percentage of animals affected in summary tables.

## **Functional Observations**

During Week 12-13 of treatment, the following tests were performed for first 5 animals/sex/group:

- hearing ability, pupillary reflex and static righting reflex (score 0 = normal/present, score 1 = abnormal/absent.
- fore- and hind-limb grip strength was recorded as the mean of three measurements (Series M4-10, Mark-10 Corporation, J.J. Bos, Gouda, The Netherlands).
- locomotor activity (recording period: 1-hour under normal laboratory light conditions, using a computerized monitoring system, Kinder Scientific LLC, Poway, USA). Total movements and ambulations are reported. Ambulations represent movements characterized by a relocation of the entire body position like walking, whereas total movements represent all movements made by the animals, including ambulations but also smaller or more fine movements like grooming, weaving or movements of the head.

Functional observation tests were conducted after observation for clinical signs (incl. arena observation, if applicable) at no specific time point, but within a similar time period after dosing for the respective animals.

Body weights

Weekly.

Food consumption

Weekly. Remaining food was sieved before weighing to withdraw any sawdust/faeces.

Water consumption

Subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected.

Ophthalmoscopic Examination (direct) Following instillation of tropicamide solution (5 mg/mL, Minims® Tropicamide 0.5% w/v, Bausch&Lomb Pharma, Brussel, Belgium) both eyes were examined by means of an ophthalmoscope (Heine Beta 200 or Beta 200S):

at pretest : All animals

at Week 13: Groups 1 and 4 (Main and Recovery group animals)

Since no treatment-related ophthalmologic findings were noted in Week 13, the eyes of the rats of Groups 2 and 3 were not examined.

Final Report - Page 14 -

## 6.8. Clinical laboratory investigations

Blood samples were collected under anaesthesia using isoflurane (Abbott B.V., Hoofddorp, The Netherlands) between 7.00 and 10.30 a.m. at the end of the treatment. Animals were deprived of food overnight (for a maximum of 24 hours), but water was available. Blood samples were drawn from the retro-orbital sinus of all rats/sex/group and collected into tubes (Greiner Bio-One GmbH, Kremsmünster, Austria) prepared with K<sub>3</sub>-EDTA for haematological parameters (0.5 mL), with citrate for clotting tests (0.45 mL) and Li-heparin treated tubes for clinical biochemistry parameters (0.5 mL). An additional blood sample (0.25 mL) was collected into serum tubes for determination of bile acids. The following parameters were determined:

| Parameter   | Abbreviation        | Unit   |
|---|---------------------|--|
| Haematology <sup>a</sup> White blood cells Differential leucocyte count neutrophils, lymphocytes, monocytes,  | WBC                 | 10 <sup>9</sup> /L<br>%WBC   |
| eosinophils, basophils Red blood cells Reticulocytes Red blood cell distribution width Haemoglobin Haematocrit  | RDW                 | 10 <sup>12</sup> /L<br>%RBC<br>%<br>mmol/L<br>L/I                                  |
| Mean corpuscular volume Mean corpuscular haemoglobin Mean corpuscular haemoglobin concentration   | MCV<br>MCH<br>MCHC  | fL<br>fmol<br>mmol/L   |
| Platelets   |                     | 10 <sup>9</sup> /L   |
| Clotting Potential b Prothrombin time Activated Partial thromboplastin time   | PT<br>APTT          | s<br>s   |
| Clinical Biochemistry ° Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Total Protein Albumin Total Bilirubin Urea Creatinine Glucose Cholesterol Sodium Potassium Chloride Calcium Inorganic Phosphate Bile acids | ALAT<br>ASAT<br>ALP | U/L U/L g/L g/L g/L µmol/L mmol/L mmol/L mmol/L mmol/L mmol/L mmol/L mmol/L mmol/L |

<sup>&</sup>lt;sup>a</sup> Instrumentation: ADVIA® 2120i (Siemens Healthcare Diagnostics B.V., Den Haag, The Netherlands).

Final Report - Page 15 -

<sup>&</sup>lt;sup>b</sup> Instrumentation: STA Compact (Diagnostica Stago S.A.S., Asnières, France).

 $<sup>^{\</sup>rm c}$  Instrumentation: Olympus AU400 (Beckman Coulter Nederland B.V., Woerden, The Netherlands).

## 6.9. Pathology

#### 6.9.1. Necropsy

On the scheduled day of necropsy, animals were deeply anaesthetized using isoflurane (Abbott B.V., Hoofddorp, The Netherlands) and subsequently exsanguinated and subjected to a full *post mortem* examination.

Animals were deprived of food overnight (with a maximum of 24 hours) prior to scheduled necropsy.

All animals assigned to the study were necropsied and descriptions of all macroscopic abnormalities recorded. Samples of the following tissues and organs were collected from all animals at necropsy and fixed in 10% buffered formalin (neutral phosphate buffered 4% formaldehyde solution, Klinipath, Duiven, The Netherlands):

Identification marks: not processed Ovaries
Adrenal glands Pancreas

Aorta Peyer's patches [jejunum, ileum] if detectable

Brain [cerebellum, mid-brain, cortex] (7 levels) Pituitary gland
Caecum (Preputial gland)
Cervix Prostate gland
(Clitoral gland) Rectum

Colon Salivary glands - mandibular, sublingual

Duodenum Sciatic nerve

Epididymides \* Seminal vesicles including coagulating gland

Eyes with optic nerve [if detectable] and (Skeletal muscle)

Harderian gland \* Skin

Female mammary gland area Spinal cord -cervical, midthoracic, lumbar

(Femur including joint) Spleen

Heart Sternum with bone marrow

IleumStomachJejunumTestes \*KidneysThymus

Larynx Thyroid including parathyroid [if detectable]

(Lacrimal gland, exorbital)(Tongue)LiverTracheaLung, infused with formalinUrinary bladder

Lymph nodes - mandibular, mesenteric Uterus (Nasopharynx) Vagina

Oesophagus All gross lesions

Tissues/organs mentioned in parentheses were not examined by the pathologist, since no signs of toxicity were noted at macroscopic examination.

Final Report - Page 16 -

<sup>\*</sup> Fixed in modified Davidson's solution, prepared at Charles River Den Bosch using Formaldehyde 37-40%, Ethanol, Acetic acid - glacial (all Merck, Darmstadt, Germany) and Milli-Ro water (Millipore Corporation, Bedford, USA). Tissues were transferred to formalin after fixation for at least 24 hours.

#### 6.9.2. Organ weights

The following organ weights and terminal body weight were recorded from the surviving animals on the scheduled day of necropsy:

Adrenal glands Spleen
Brain Testes
Epididymides Thymus

Heart Uterus (including cervix)

Kidneys Prostate

Liver Seminal vesicles including coagulating glands

Ovaries Thyroid including parathyroid

## 6.9.3. Histotechnology

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded in paraffin wax (Klinipath, Duiven, The Netherlands), cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin (Klinipath, Duiven, The Netherlands).

## 6.9.4. Histopathology

The following slides were examined by a pathologist:

- all tissues collected at the scheduled sacrifice from all Group 1 and 4 animals.
- all gross lesions.

All abnormalities were described and included in the report. An attempt was made to correlate gross observations with microscopic findings.

Histopathology was subjected to a peer review.

#### 6.10. Electronic data capture

Observations/measurements in the study were recorded electronically using the following programmes:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA): Environmental monitoring.
- TOXDATA version 8.0 (Charles River Den Bosch, 's-Hertogenbosch, The Netherlands): Mortality / Clinical signs / Functional Observations (hearing ability, pupillary reflex and static righting reflex) / Body weights / Food consumption / Organ weights.
- Motor Monitor version 08356-14 (Kinder Scientific LLC, Poway, USA): Motor activity measurement
- ADVIA® 2120i Hematology System (Siemens Healthcare Diagnostics B.V., Den Haag, The Netherlands).
- STA Compact® version 107.07 (Diagnostica Stago S.A.S., Asnières, France): Clotting parameters.
- AU400 version 9.1 (Beckman Coulter Nederland B.V., Woerden, The Netherlands): Clinical biochemistry.
- Pathdata version 6.2e2 (Pathology Data Systems, Basel, Switzerland): Histopathology.

Any upgrades were approved by the Study Director (or Principal Scientist/Investigator) in the study files.

Final Report - Page 17 -

#### 6.11. Interpretation

The following statistical methods were used to analyze the data:

If the variables could be assumed to follow a normal distribution, the Dunnett-test (Ref. 1; many-to-one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex.

- The Steel-test (Ref. 2; many-to-one rank test) was applied if the data could not be assumed to follow a normal distribution.
- The Fisher Exact-test (Ref. 3) was applied to frequency data.
- The Kruskal-Wallis nonparametric ANOVA test (Ref. 4) was applied to motor activity data to determine intergroup differences. In case intergroup differences were seen, the Wilcoxon test (Ref. 5) was applied to compare the treated groups to the control group.

All tests were two-sided and in all cases p < 0.05 was accepted as the lowest level of significance. Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables. Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values, means and standard deviations may have been rounded off before printing. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistics values.

#### 6.12. List of deviations

## 6.12.1. List of protocol deviations

- Deviations from the daily mean relative humidity occurred.

  Evaluation: Laboratory historical data do not indicate an effect of the deviations.
- Food hoppers were not shaken on Day 61.
  Evaluation: Since the deviation was on one occasion only and the food hoppers were shaken the day before and after it was considered that this did not affect food consumption.
- Male animals were not fasted on 02 February 2016.
  Evaluation: Necropsy of the males was rescheduled and animals were treated up to the new day of necropsy.
- Urinary bladder of one control female (no. 43) and coagulating glands of one control male (no. 7) were not available for histopathology.
   Evaluation: Sufficient data was available for evaluation.

In the range finding study (Test Facility Study No. 509992), the following deviation from the study plan were observed:

Animals were weighed weekly and on day of necropsy.
Evaluation: Additional information for evaluation of the results.

The study integrity was not adversely affected by the deviations.

#### 6.12.2. List of standard operating procedures deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

Final Report - Page 18 -

#### 7. RESULTS

For further detail on summary data, see APPENDIX 1 and on individual data, see APPENDIX 2.

#### 7.1. Analysis of dose preparations

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V. The analysis of the samples was done at the Cosun Food Technology Centre (CFTC). CFTC is a sister company of Cosun Biobased Products B.V. and is specialized in sugar analysis and therefore is well-found with necessary equipment for the analysis of Betawell L-Arabinose in diet.

#### Accuracy of preparation

The concentrations analysed in the diets of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 80% and 120%).

A minimal response at the retention time of the test item was observed in the chromatograms of the Group 1 diet prepared for use in Week 13. In all other diets of Group 1, no test item was detected.

#### Homogeneity

The diets of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10%).

#### Stability

Diets at the entire range were stable when stored at room temperature for at least 9 days.

For further detail on diet preparation analysis see also APPENDIX 4.

#### 7.2. Observations

#### 7.2.1. Mortality

No mortality occurred during the study period.

#### 7.2.2. Clinical signs

No test substance related clinical signs or abnormalities during weekly arena observations were noted during the observation period.

Any clinical signs noted during the treatment period occurred within the range of background findings to be expected for rats of this age and strain which are housed and treated under the conditions in this study and did not show any apparent dose-related trend. At the incidence observed, these were considered to be unrelated to treatment.

#### 7.2.3. Functional observations

Hearing ability, pupillary reflex and static righting reflex were normal in all examined animals.

Grip strength and motor activity were similar between treated and control groups. All groups showed a similar motor activity habituation profile with a decreasing trend in activity over the duration of the test period.

## 7.2.4. Body weights

A lower body weight gain (achieving a statistically significant difference at some occasions) was observed in female animals at 10000 and 30000 ppm.

Body weights and body weight gain of males remained in the same range as controls over the study period.

Final Report - Page 19 -

#### 7.2.5. Food consumption

Food consumption before or after correction for body weight remained similar to the control level over the study period.

#### 7.2.6. Test article intake

Mean test article intake over the study period was as follows:

| group | Nominal dietary inclusion level [ppm] | Average intake [mg test substance/kg body weight] (range indicated within brackets) |             |      |             |
|-------|---------------------------------------|---|-------------|------|-------------|
|       |                                       | r   | nales       | f    | emales      |
| 2     | 3000                                  | 216   | (180-289)   | 251  | (227-290)   |
| 3     | 10000                                 | 760   | (608-984)   | 872  | (755-997)   |
| 4     | 30000                                 | 2218  | (1859-2833) | 2614 | (2319-3062) |

#### 7.2.7. Ophthalmoscopic examination

The nature and incidence of ophthalmology findings noted during pretest and in Week 13 was similar among the groups, and occurred within the range considered normal for rats of this age and strain. These findings were therefore considered to be unrelated to treatment with the test substance.

## 7.3. Clinical laboratory investigations

## 7.3.1. Haematology

No toxicologically relevant changes were noted in haematological parameters.

Any statistically significant changes in haematology parameters were not considered to be toxicologically relevant as these occurred in the absence of a dose-related trend and/or were very slight in nature (within the range considered normal for rats of this age and strain).

## 7.3.2. Clinical biochemistry

No toxicologically relevant changes were noted in clinical biochemistry parameters.

Clinical biochemistry revealed changes in glucose (slightly lower in high dose males but higher in high dose females) and bile acids (slightly increased in both sexes). Since these changes in glucose occurred in the absence of a dose-related trend and showed different responses in males and females and the changes in bile acids were very slight in nature (within the range considered normal for rats of this age and strain) they were considered not toxicologically relevant.

Any other statistically significant changes in clinical biochemistry parameters were not considered to be toxicologically relevant as these occurred in the absence of a dose-related trend and/or were very slight in nature (within the range considered normal for rats of this age and strain).

#### 7.4. Pathology

## 7.4.1. Macroscopic examination

There were no test item-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

- Page 20 of 249 -

Final Report - Page 20 -

## 7.4.2. Organ weights

There were no test item-related alterations in organ weights.

All organ weight differences observed, including those that reached statistical significance, were considered incidental and unrelated to the administration of the test item.

## 7.4.3. Microscopic examination

There were no test item-related microscopic observations.

All of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There was no test item related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

For further detail on histopathology see also APPENDIX 5.

Final Report - Page 21 -

#### 8. DISCUSSION AND CONCLUSION

Wistar rats were treated with Betawell L-Arabinose for 90 consecutive days by dietary administration at dose levels of 3000, 10000 and 30000 ppm (corresponding to actual test article intake of 216, 760 and 2218 mg/kg respectively for males and 251, 872 and 2614 mg/kg respectively for females).

Dietary analyses, conducted (non-GLP) by the Sponsor and evaluated by Principle Scientist, confirmed that preparations of test substance in diets were prepared accurately and homogenously, and were stable over at least 9 days.

No toxicologically significant changes were noted in any of the parameters investigated in this study (i.e. clinical appearance, functional observations, ophthalmoscopy, food consumption, clinical laboratory investigations, macroscopic examination, organ weights, and microscopic examination).

A lower body weight gain (achieving a statistically significant difference at some occasions) seen in female animals at 10000 and 30000 ppm is considered not toxicologically relevant since a clear dose related trend was absent, the changes were considered slight in nature and no corroborative findings were noted in clinical signs and food consumption.

From the results presented in this report a No Observed Adverse Effect Level (NOAEL) for Betawell L-Arabinose of at least 30000 ppm was established, which corresponded to 2218 mg/kg body weight in males and 2614 mg/kg body weight in females.

Final Report - Page 22 -

## 9. REFERENCES

| Ref. 1 | C.W. Dunnett, A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).                       |
|--------|--|
| Ref. 2 | R.G. Miller, Simultaneous Statistical Inference, Springer Verlag, New York (1981).   |
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| Ref. 4 | Kruskal W.H. and Wallis W.A Use of ranks in one-criterion variance analysis. Journal of the American Statistical Association 47 (260): 583-621, December (1952). |
| Ref. 5 | Wilcoxon, F. Individual comparisons by ranking methods, Biometrics, 1, 80-83 (1945).   |

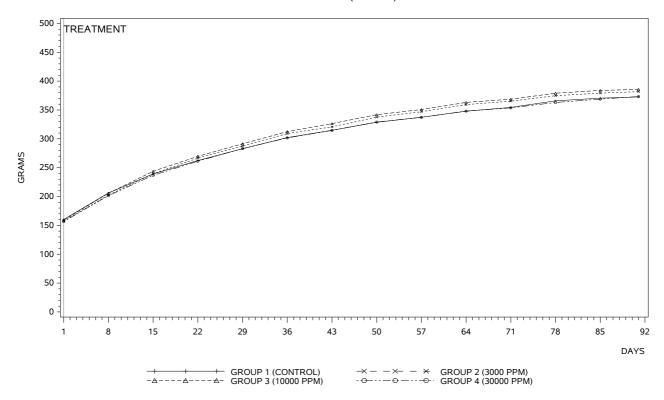
- Page 23 -

## **APPENDIX 1 FIGURES AND SUMMARY TABLES**

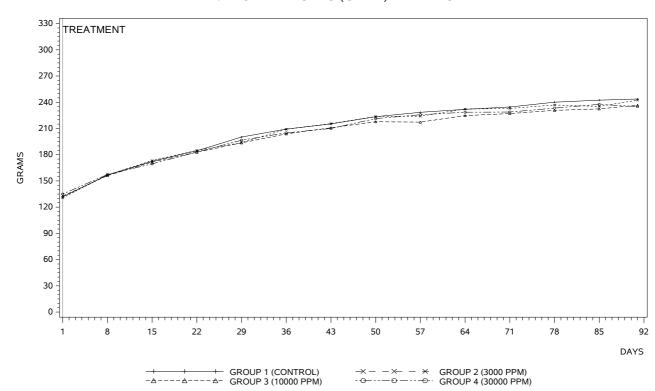
Final Report - Page 1 -

Betawell L-Arabinose Project 509991 APPENDIX 1

## 1.1 BODY WEIGHTS (GRAM) MALES

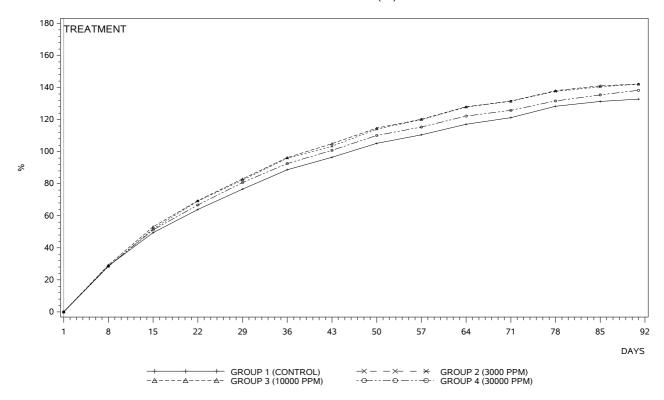


## 1.1 BODY WEIGHTS (GRAM) FEMALES

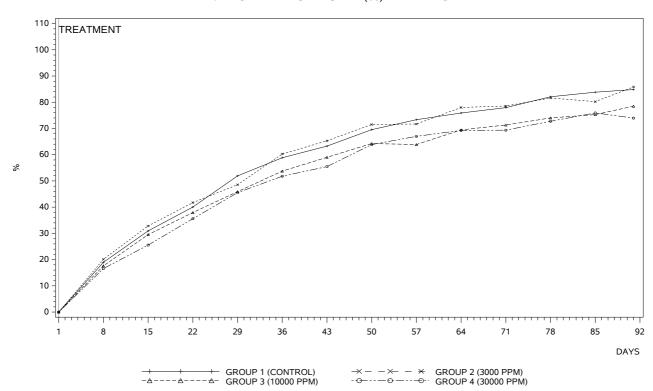


- Page 25 of 249 -

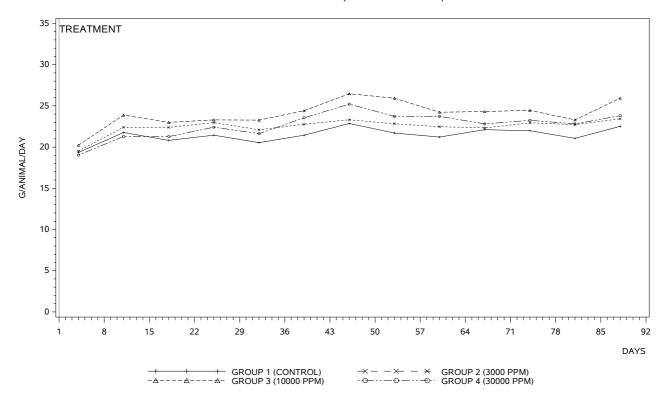
## 1.2 BODY WEIGHT GAIN (%) MALES



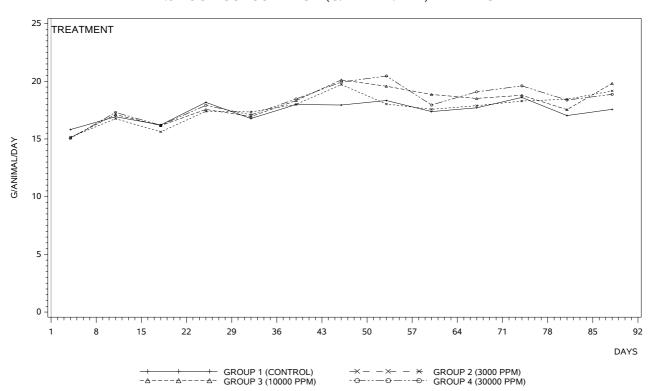
## 1.2 BODY WEIGHT GAIN (%) FEMALES



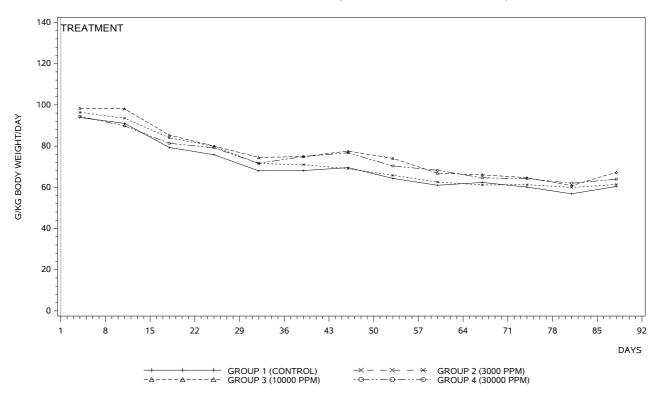
## 1.3 FOOD CONSUMPTION (G/ANIMAL/DAY) MALES



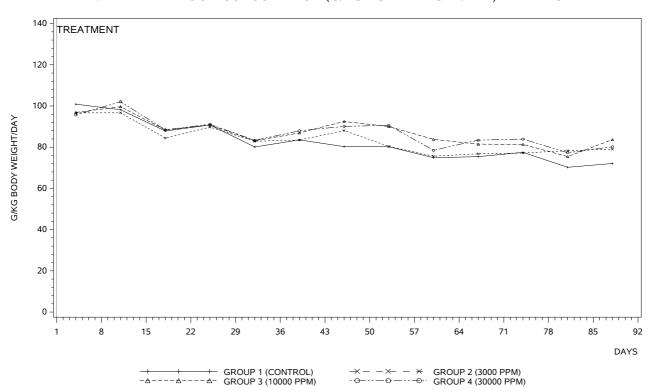
## 1.3 FOOD CONSUMPTION (G/ANIMAL/DAY) FEMALES



## 1.4 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) MALES



## 1.4 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) FEMALES



## APPENDIX 1

#### 1.5 CLINICAL SIGNS SUMMARY **MALES**

|  |            | TDE A TAMEAUT                                 |                           |
|--|------------|---|---------------------------|
| SIGN (MAX. GRADE)                            | WEEK:      | TREATMENT 144                                 | 0                         |
| LOCATION)                                    | DAY:       | 1234567123456712345671234567123456712345      |                           |
| LOCATION)                                    | DAT.       | 1234307 1234307 1234307 1234307 1234307 12343 | 007 1234307 1234307 12343 |
| ROUP 1 (CONTROL)                             |            |   |                           |
| lo clinical signs noted                      |            |   |                           |
| -  |            |   |                           |
| GROUP 2 (3000 PPM)                           |            |   | _                         |
| lo clinical signs noted                      |            |   |                           |
| POUR 2 (40000 PRM)                           |            |   |                           |
| GROUP 3 (10000 PPM)  Io clinical signs noted |            |   |                           |
| io cililicai signis noted                    |            |   |                           |
| ROUP 4 (30000 PPM)                           |            |   |                           |
| lo clinical signs noted                      |            |   |                           |
|  |            |   |                           |
| AALEO  |            |   |                           |
| MALES  |            |   |                           |
|  |            | TREATMENT                                     |                           |
| SIGN (MAX. GRADE)                            | WEEK:      |   |                           |
| LOCATION)                                    | DAY:       | 67123456712345671234567123456712              |                           |
|  |            |   |                           |
| GROUP 1 (CONTROL)                            |            | _   |                           |
| No clinical signs noted                      |            |   |                           |
| DOUD & (COOK DOM)                            |            |   |                           |
| GROUP 2 (3000 PPM)                           |            |   |                           |
| lo clinical signs noted                      |            |   |                           |
| GROUP 3 (10000 PPM)                          |            |   |                           |
| No clinical signs noted                      |            |   |                           |
|  |            | -   |                           |
| GROUP 4 (30000 PPM)                          |            | _   |                           |
| No clinical signs noted                      |            |   |                           |
|  |            |   |                           |
| FEMALES                                      |            |   |                           |
|  |            |   |                           |
|  |            | TREATMENT                                     |                           |
| SIGN (MAX. GRADE)                            | WEEK:      | 1   | 8                         |
| (LOCATION)                                   | DAY:       | 1234567123456712345671234567123456712345      | 5671234567123456712345    |
| CROUR 4 (CONTROL)                            |            |   |                           |
| GROUP 1 (CONTROL) Skin / fur                 |            |   |                           |
| Scabs (3)                                    | G:         |   |                           |
| (Head)                                       | %:         |   |                           |
| Scabs (3)                                    | G:         |   |                           |
| (Back)                                       | %:         |   |                           |
| Scabs (3)                                    | G:         |   |                           |
| (Cervical region)                            | %:         |   |                           |
| Scabs (3)                                    | G:         |   |                           |
| (Shoulder left)                              | %:         |   |                           |
| Scabs (3)                                    | G:         |   |                           |
| (Shoulder right)                             | %:         |   |                           |
| /arious                                      |            |   |                           |
| Pale (3)                                     | G:         |   |                           |
|  | %:         |   |                           |
| NOUD 0 (0000 PRIE)                           |            |   |                           |
| GROUP 2 (3000 PPM)                           |            |   |                           |
| Skin / fur                                   | <b>C</b> . |   |                           |
| Scabs (3)<br>(Back)                          | G:<br>%:   |   |                           |
| (Dack)                                       | /0.        |   |                           |
| GROUP 3 (10000 PPM)                          |            |   |                           |
| lo clinical signs noted                      |            |   |                           |
|  |            | _   |                           |

G: Median value of the highest individual daily grades %: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%) : Observation performed, sign not present

Betawell L-Arabinose Project 509991 APPENDIX 1

#### 1.5 CLINICAL SIGNS SUMMARY **FEMALES**

|                   |        | TREATMENT                                       |                |
|-------------------|--------|---|----------------|
| SIGN (MAX. GRADE) | WEEK.  | 1 4   | Q              |
| ,                 | WLLIN. | 1   | 0              |
| (LOCATION)        | DAY:   | 12345671234567123456712345671234567123456712345 | 67123456712345 |
| <del></del>       |        |   |                |

## GROUP 4 (30000 PPM)

No clinical signs noted

## **FEMALES**

|                          |       | TREATMENT  |  |
|--------------------------|-------|--|--|
| SIGN (MAX. GRADE)        | WEEK: |  |  |
| (LOCATION)               | DAY:  | 6712345671234567123456712  |  |
| GROUP 1 (CONTROL)        |       |  |  |
| Skin / fur               |       |  |  |
| Scabs (3)                | G:    |  |  |
| (Head)                   | %:    |  |  |
| Scabs (3)                | G:    |  |  |
| (Back)                   | %:    |  |  |
| Scabs (3)                | G:    |  |  |
| (Cervical region)        | %:    |  |  |
| Scabs (3)                | G:    |  |  |
| (Shoulder left)          | %:    |  |  |
| Scabs (3)                | G:    |  |  |
| (Shoulder right)         | %:    |  |  |
| Various                  |       |  |  |
| Pale (3)                 | G:    |  |  |
| ,                        | %:    |  |  |
| GROUP 2 (3000 PPM)       |       |  |  |
| Skin / fur               |       |  |  |
| Scabs (3)                | G:    |  |  |
| (Back)                   | %:    | 11111111111111   |  |
| GROUP 3 (10000 PPM)      |       |  |  |
| No clinical signs noted  |       | The state of the s |  |
| GROUP 4 (30000 PPM)      |       |  |  |
| No clinical signs noted  |       |  |  |
| 140 olimbar signo flotod |       |  |  |

G: Median value of the highest individual daily grades %: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%) : Observation performed, sign not present

Betawell L-Arabinose
APPENDIX 1
Project 509991

## 1.6 FUNCTIONAL OBSERVATIONS SUMMARY MALES

|                                    |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| AT WEEK 12<br>HEARING<br>SCORE 0/1 | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0 5                  |
| PUPIL L<br>SCORE 0/1               | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| PUPIL R<br>SCORE 0/1               | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| STATIC R<br>SCORE 0/1              | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| GRIP FORE<br>GRAM                  | MEAN<br>ST.DEV<br>N | 1257<br>200<br>5   | 1420<br>334<br>5    | 1284<br>145<br>5     | 1240<br>147<br>5     |
| GRIP HIND<br>GRAM                  | MEAN<br>ST.DEV<br>N | 806<br>114<br>5    | 948<br>199<br>5     | 834<br>120<br>5      | 774<br>168<br>5      |

#### **FEMALES**

|                                    |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| AT WEEK 12<br>HEARING<br>SCORE 0/1 | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0 5                  |
| PUPIL L<br>SCORE 0/1               | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| PUPIL R<br>SCORE 0/1               | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| STATIC R<br>SCORE 0/1              | MEDIAN<br>N         | 0<br>5             | 0<br>5              | 0<br>5               | 0<br>5               |
| GRIP FORE<br>GRAM                  | MEAN<br>ST.DEV<br>N | 1249<br>200<br>5   | 1166<br>174<br>5    | 1217<br>174<br>5     | 1164<br>86<br>5      |
| GRIP HIND<br>GRAM                  | MEAN<br>ST.DEV<br>N | 647<br>63<br>5     | 640<br>52<br>5      | 613<br>99<br>5       | 627<br>39<br>5       |

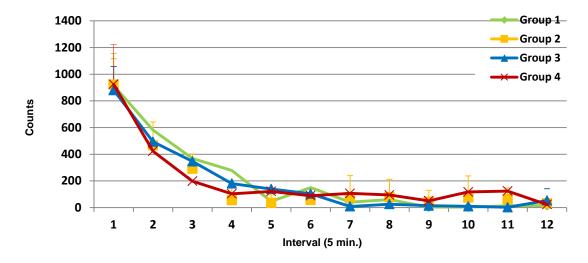
 $<sup>^{*/**}</sup>$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level +/++ Steel-test significant at 5% (+) or 1% (++) level

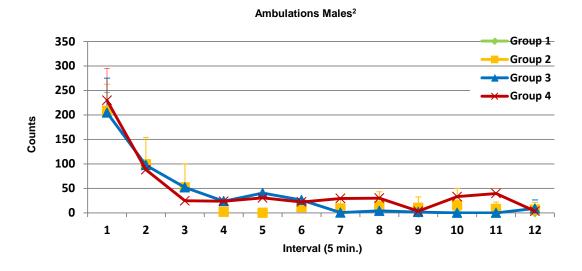
# 1.7 MOTOR ACTIVITY TEST SUMMARY MALES

## AT WEEK 13

|                 |                   | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|-----------------|-------------------|--------------------|---------------------|----------------------|----------------------|
| Total Movements | MEAN <sup>1</sup> | 2481               | 2195                | 2259                 | 2376                 |
|                 | ST.DEV            | 758                | 332                 | 372                  | 1760                 |
|                 | N                 | 5                  | 5                   | 5                    | 5                    |
| Ambulations     | MEAN <sup>1</sup> | 518                | 435                 | 460                  | 558                  |
|                 | ST.DEV            | 140                | 78                  | 170                  | 536                  |
|                 | N                 | 5                  | 5                   | 5                    | 5                    |

#### **Total Movements Males<sup>2</sup>**





<sup>\*/\*\*</sup> Wilcoxon test significant at 5% (\*) or 1% (\*\*) level

<sup>&</sup>lt;sup>1</sup> Group mean of all intervals combined

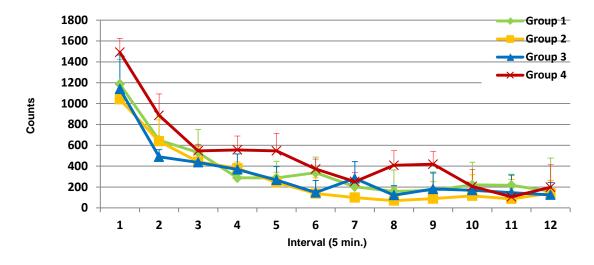
<sup>&</sup>lt;sup>2</sup> Mean counts per interval.

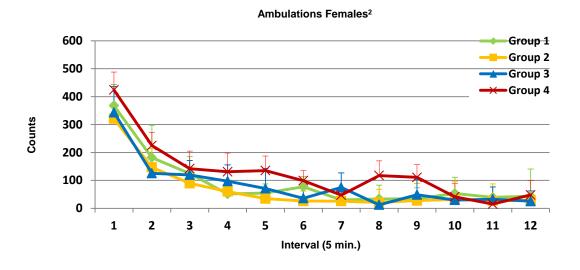
# 1.7 MOTOR ACTIVITY TEST SUMMARY FEMALES

#### AT WEEK 13

|                 |                   | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|-----------------|-------------------|--------------------|---------------------|----------------------|----------------------|
| Total Movements | MEAN <sup>1</sup> | 4405               | 3486                | 3875                 | 5990                 |
|                 | ST.DEV            | 1120               | 1127                | 548                  | 969                  |
|                 | N                 | 5                  | 5                   | 5                    | 5                    |
| Ambulations     | MEAN <sup>1</sup> | 1092               | 841                 | 1018                 | 1537                 |
|                 | ST.DEV            | 267                | 452                 | 292                  | 315                  |
|                 | N                 | 5                  | 5                   | 5                    | 5                    |

## Total Movements Females<sup>2</sup>





<sup>\*/\*\*</sup> Wilcoxon test significant at 5% (\*) or 1% (\*\*) level

<sup>&</sup>lt;sup>1</sup> Group mean of all intervals combined

<sup>&</sup>lt;sup>2</sup> Mean counts per interval.

1.8 BODY WEIGHTS (GRAM) SUMMARY MALES

|                   |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|-------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| REATMENT          |                     |                    |                     |                      |                      |
| OAY 1<br>VEEK 1   | MEAN<br>ST.DEV<br>N | 160<br>10.9<br>10  | 158<br>8.8<br>10    | 159<br>4.0<br>10     | 157<br>9.6<br>10     |
| AY 8<br>/EEK 2    | MEAN<br>ST.DEV<br>N | 206<br>12.8<br>10  | 203<br>15.7<br>10   | 206<br>7.3<br>10     | 202<br>13.5<br>10    |
| AY 15<br>/EEK 3   | MEAN<br>ST.DEV<br>N | 239<br>15.3<br>10  | 240<br>19.9<br>10   | 244<br>13.0<br>10    | 237<br>17.9<br>10    |
| AY 22<br>EEK 4    | MEAN<br>ST.DEV<br>N | 262<br>17.1<br>10  | 267<br>24.1<br>10   | 270<br>19.1<br>10    | 261<br>22.8<br>10    |
| AY 29<br>/EEK 5   | MEAN<br>ST.DEV<br>N | 283<br>22.6<br>10  | 288<br>27.1<br>10   | 291<br>23.5<br>10    | 283<br>27.9<br>10    |
| AY 36<br>/EEK 6   | MEAN<br>ST.DEV<br>N | 302<br>22.1<br>10  | 309<br>28.4<br>10   | 313<br>25.7<br>10    | 302<br>30.9<br>10    |
| AY 43<br>/EEK 7   | MEAN<br>ST.DEV<br>N | 315<br>24.9<br>10  | 321<br>28.7<br>10   | 326<br>30.1<br>10    | 315<br>33.7<br>10    |
| AY 50<br>/EEK 8   | MEAN<br>ST.DEV<br>N | 329<br>25.8<br>10  | 338<br>31.3<br>10   | 342<br>32.9<br>10    | 329<br>36.9<br>10    |
| AY 57<br>/EEK 9   | MEAN<br>ST.DEV<br>N | 337<br>29.6<br>10  | 347<br>32.9<br>10   | 351<br>34.5<br>10    | 337<br>38.1<br>10    |
| AY 64<br>/EEK 10  | MEAN<br>ST.DEV<br>N | 348<br>29.0<br>10  | 359<br>35.4<br>10   | 363<br>36.1<br>10    | 348<br>39.0<br>10    |
| AY 71<br>/EEK 11  | MEAN<br>ST.DEV<br>N | 355<br>29.6<br>10  | 365<br>36.5<br>10   | 369<br>37.8<br>10    | 354<br>42.0<br>10    |
| AY 78<br>/EEK 12  | MEAN<br>ST.DEV<br>N | 366<br>28.9<br>10  | 375<br>36.3<br>10   | 379<br>39.0<br>10    | 363<br>43.0<br>10    |
| AY 85<br>/EEK 13  | MEAN<br>ST.DEV<br>N | 371<br>27.8<br>10  | 379<br>36.6<br>10   | 384<br>38.8<br>10    | 369<br>43.1<br>10    |
| 0AY 91<br>VEEK 13 | MEAN<br>ST.DEV<br>N | 373<br>26.4<br>10  | 382<br>35.1<br>10   | 386<br>39.0<br>10    | 373<br>45.2<br>10    |

25Mar16 08h56

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

## 1.8 BODY WEIGHTS (GRAM) SUMMARY FEMALES

|                              |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAY 1<br>WEEK 1 | MEAN<br>ST.DEV<br>N | 132<br>5.9<br>10   | 131<br>6.2<br>10    | 133<br>6.5<br>10     | 135<br>6.9<br>10     |
| DAY 8<br>WEEK 2              | MEAN<br>ST.DEV<br>N | 157<br>7.4<br>10   | 157<br>6.6<br>10    | 156<br>7.6<br>10     | 157<br>8.8<br>10     |
| DAY 15<br>WEEK 3             | MEAN<br>ST.DEV<br>N | 173<br>9.9<br>10   | 173<br>6.1<br>10    | 172<br>7.4<br>10     | 170<br>10.6<br>10    |
| DAY 22<br>WEEK 4             | MEAN<br>ST.DEV<br>N | 185<br>9.9<br>10   | 185<br>7.3<br>10    | 183<br>9.9<br>10     | 183<br>11.0<br>10    |
| DAY 29<br>WEEK 5             | MEAN<br>ST.DEV<br>N | 200<br>11.8<br>10  | 194<br>8.4<br>10    | 194<br>10.2<br>10    | 197<br>14.2<br>10    |
| DAY 36<br>WEEK 6             | MEAN<br>ST.DEV<br>N | 209<br>12.0<br>10  | 209<br>8.0<br>10    | 204<br>9.8<br>10     | 205<br>13.3<br>10    |
| DAY 43<br>WEEK 7             | MEAN<br>ST.DEV<br>N | 215<br>14.5<br>10  | 216<br>8.4<br>10    | 211<br>12.4<br>10    | 210<br>14.8<br>10    |
| DAY 50<br>WEEK 8             | MEAN<br>ST.DEV<br>N | 224<br>13.9<br>10  | 224<br>7.8<br>10    | 218<br>12.7<br>10    | 221<br>15.9<br>10    |
| DAY 57<br>WEEK 9             | MEAN<br>ST.DEV<br>N | 229<br>15.5<br>10  | 224<br>10.6<br>10   | 217<br>12.6<br>10    | 226<br>18.8<br>10    |
| DAY 64<br>WEEK 10            | MEAN<br>ST.DEV<br>N | 232<br>15.2<br>10  | 232<br>10.1<br>10   | 225<br>12.7<br>10    | 229<br>15.4<br>10    |
| DAY 71<br>WEEK 11            | MEAN<br>ST.DEV<br>N | 235<br>17.0<br>10  | 233<br>8.7<br>10    | 227<br>12.8<br>10    | 229<br>17.5<br>10    |
| DAY 78<br>WEEK 12            | MEAN<br>ST.DEV<br>N | 240<br>17.2<br>10  | 237<br>9.5<br>10    | 231<br>14.6<br>10    | 233<br>18.8<br>10    |
| DAY 85<br>WEEK 13            | MEAN<br>ST.DEV<br>N | 242<br>17.1<br>10  | 235<br>10.8<br>10   | 232<br>12.2<br>10    | 238<br>17.6<br>10    |
| DAY 91<br>WEEK 13            | MEAN<br>ST.DEV<br>N | 244<br>17.9<br>10  | 242<br>10.2<br>10   | 237<br>12.8<br>10    | 235<br>17.2<br>10    |

25Mar16 08h56

 $<sup>^{*/**}</sup>$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

## 1.9 BODY WEIGHT GAIN (%) SUMMARY MALES

|                              |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAY 1<br>WEEK 1 | MEAN<br>ST.DEV<br>N | 0<br>0.0<br>10     | 0<br>0.0<br>10      | 0<br>0.0<br>10       | 0<br>0.0<br>10       |
| DAY 8<br>WEEK 2              | MEAN<br>ST.DEV<br>N | 29<br>2.8<br>10    | 28<br>4.5<br>10     | 29<br>2.5<br>10      | 29<br>3.1<br>10      |
| DAY 15<br>VEEK 3             | MEAN<br>ST.DEV<br>N | 49<br>6.0<br>10    | 52<br>6.9<br>10     | 53<br>5.7<br>10      | 51<br>8.0<br>10      |
| OAY 22<br>VEEK 4             | MEAN<br>ST.DEV<br>N | 64<br>5.9<br>10    | 69<br>12.8<br>10    | 69<br>9.5<br>10      | 67<br>11.5<br>10     |
| OAY 29<br>VEEK 5             | MEAN<br>ST.DEV<br>N | 77<br>8.1<br>10    | 82<br>10.6<br>10    | 83<br>11.8<br>10     | 81<br>14.7<br>10     |
| VAY 36<br>VEEK 6             | MEAN<br>ST.DEV<br>N | 89<br>7.7<br>10    | 96<br>11.4<br>10    | 96<br>13.1<br>10     | 93<br>16.9<br>10     |
| AY 43<br>VEEK 7              | MEAN<br>ST.DEV<br>N | 97<br>8.2<br>10    | 103<br>11.6<br>10   | 105<br>15.8<br>10    | 101<br>18.2<br>10    |
| AY 50<br>/EEK 8              | MEAN<br>ST.DEV<br>N | 105<br>8.0<br>10   | 114<br>12.7<br>10   | 115<br>17.2<br>10    | 110<br>20.5<br>10    |
| VAY 57<br>VEEK 9             | MEAN<br>ST.DEV<br>N | 110<br>8.9<br>10   | 120<br>14.1<br>10   | 120<br>18.3<br>10    | 115<br>21.3<br>10    |
| AY 64<br>/EEK 10             | MEAN<br>ST.DEV<br>N | 117<br>8.5<br>10   | 128<br>15.1<br>10   | 128<br>19.1<br>10    | 122<br>21.3<br>10    |
| AY 71<br>/EEK 11             | MEAN<br>ST.DEV<br>N | 121<br>9.0<br>10   | 132<br>15.9<br>10   | 132<br>20.1<br>10    | 126<br>23.3<br>10    |
| 0AY 78<br>VEEK 12            | MEAN<br>ST.DEV<br>N | 128<br>8.7<br>10   | 138<br>15.7<br>10   | 138<br>20.8<br>10    | 132<br>23.3<br>10    |
| AY 85<br>VEEK 13             | MEAN<br>ST.DEV<br>N | 131<br>9.3<br>10   | 140<br>16.6<br>10   | 141<br>20.8<br>10    | 135<br>23.8<br>10    |
| 0AY 91<br>VEEK 13            | MEAN<br>ST.DEV<br>N | 133<br>9.3<br>10   | 142<br>15.9<br>10   | 142<br>20.9<br>10    | 138<br>25.4<br>10    |

25Mar16 08h56

 $<sup>^{*/**}</sup>$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

## 1.9 BODY WEIGHT GAIN (%) SUMMARY FEMALES

|                              |                     | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------|---------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAY 1<br>WEEK 1 | MEAN<br>ST.DEV<br>N | 0<br>0.0<br>10     | 0<br>0.0<br>10      | 0<br>0.0<br>10       | 0<br>0.0<br>10       |
| DAY 8<br>WEEK 2              | MEAN<br>ST.DEV<br>N | 19<br>4.8<br>10    | 20<br>2.7<br>10     | 18<br>3.9<br>10      | 17<br>1.8<br>10      |
| DAY 15<br>VEEK 3             | MEAN<br>ST.DEV<br>N | 31<br>6.4<br>10    | 33<br>4.5<br>10     | 30<br>5.6<br>10      | 26<br>4.5<br>10      |
| VAY 22<br>VEEK 4             | MEAN<br>ST.DEV<br>N | 40<br>5.7<br>10    | 42<br>6.1<br>10     | 38<br>8.1<br>10      | 36<br>5.4<br>10      |
| AY 29<br>/EEK 5              | MEAN<br>ST.DEV<br>N | 52<br>6.4<br>10    | 49<br>4.1<br>10     | 46<br>6.2<br>10      | 46 *<br>5.2<br>10    |
| AY 36<br>/EEK 6              | MEAN<br>ST.DEV<br>N | 59<br>7.0<br>10    | 60<br>6.1<br>10     | 54<br>7.3<br>10      | 52 *<br>4.3<br>10    |
| AY 43<br>/EEK 7              | MEAN<br>ST.DEV<br>N | 63<br>8.1<br>10    | 65<br>7.8<br>10     | 59<br>8.8<br>10      | 55<br>5.4<br>10      |
| AY 50<br>EEK 8               | MEAN<br>ST.DEV<br>N | 70<br>6.7<br>10    | 72<br>7.4<br>10     | 64<br>10.1<br>10     | 64<br>6.6<br>10      |
| AY 57<br>EEK 9               | MEAN<br>ST.DEV<br>N | 73<br>8.0<br>10    | 72<br>6.3<br>10     | 64 *<br>8.0<br>10    | 67<br>7.2<br>10      |
| AY 64<br>EEK 10              | MEAN<br>ST.DEV<br>N | 76<br>7.5<br>10    | 78<br>8.4<br>10     | 69<br>8.3<br>10      | 69<br>5.5<br>10      |
| AY 71<br>EEK 11              | MEAN<br>ST.DEV<br>N | 78<br>9.0<br>10    | 79<br>8.1<br>10     | 71<br>9.7<br>10      | 69<br>6.6<br>10      |
| AY 78<br>'EEK 12             | MEAN<br>ST.DEV<br>N | 82<br>8.6<br>10    | 82<br>8.7<br>10     | 74<br>10.6<br>10     | 73<br>9.4<br>10      |
| AY 85<br>EEK 13              | MEAN<br>ST.DEV<br>N | 84<br>8.4<br>10    | 80<br>7.2<br>10     | 75<br>8.4<br>10      | 76<br>7.7<br>10      |
| AY 91<br>EEK 13              | MEAN<br>ST.DEV<br>N | 85<br>9.5<br>10    | 86<br>9.2<br>10     | 79<br>9.9<br>10      | 74 *<br>6.4<br>10    |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.10 FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY MALES

|                                    |                            | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|----------------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAYS 1-8<br>WEEKS 1-2 | MEAN<br>ST.DEV<br>N (CAGE) | 19<br>0.1<br>2     | 20<br>0.4<br>2      | 20<br>0.7<br>2       | 19<br>0.5<br>2       |
| DAYS 8-15<br>WEEKS 2-3             | MEAN<br>ST.DEV<br>N (CAGE) | 22<br>0.2<br>2     | 22<br>0.9<br>2      | 24<br>1.1<br>2       | 21<br>2.0<br>2       |
| 0AYS 15-22<br>VEEKS 3-4            | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.7<br>2     | 22<br>0.6<br>2      | 23<br>0.8<br>2       | 21<br>2.0<br>2       |
| AYS 22-29<br>EEKS 4-5              | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.2<br>2     | 23<br>0.3<br>2      | 23<br>0.3<br>2       | 22<br>1.5<br>2       |
| AYS 29-36<br>EEKS 5-6              | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.1<br>2     | 22<br>0.5<br>2      | 23<br>0.4<br>2       | 22<br>1.6<br>2       |
| AYS 36-43<br>EEKS 6-7              | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.6<br>2     | 23<br>0.6<br>2      | 24<br>0.5<br>2       | 24<br>1.0<br>2       |
| AYS 43-50<br>EEKS 7-8              | MEAN<br>ST.DEV<br>N (CAGE) | 23<br>0.4<br>2     | 23<br>1.3<br>2      | 26<br>1.8<br>2       | 25<br>0.0<br>2       |
| AYS 50-57<br>EEKS 8-9              | MEAN<br>ST.DEV<br>N (CAGE) | 22<br>0.2<br>2     | 23<br>0.4<br>2      | 26<br>1.7<br>2       | 24<br>1.4<br>2       |
| YS 57-64<br>EKS 9-10               | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.1<br>2     | 22<br>1.0<br>2      | 24<br>1.1<br>2       | 24<br>0.6<br>2       |
| YS 64-71<br>EKS 10-11              | MEAN<br>ST.DEV<br>N (CAGE) | 22<br>1.7<br>2     | 22<br>0.3<br>2      | 24<br>0.9<br>2       | 23<br>0.6<br>2       |
| YS 71-78<br>EKS 11-12              | MEAN<br>ST.DEV<br>N (CAGE) | 22<br>1.1<br>2     | 23<br>1.0<br>2      | 24<br>1.8<br>2       | 23<br>0.1<br>2       |
| YS 78-85<br>EKS 12-13              | MEAN<br>ST.DEV<br>N (CAGE) | 21<br>0.0<br>2     | 23<br>0.2<br>2      | 23<br>1.5<br>2       | 23<br>0.4<br>2       |
| YS 85-91<br>EEK 13                 | MEAN<br>ST.DEV<br>N (CAGE) | 23<br>0.9<br>2     | 23<br>0.2<br>2      | 26<br>1.2<br>2       | 24<br>0.4<br>2       |
| EAN OF MEANS<br>'ER TREATMENT      | MEAN                       | 21                 | 22                  | 24                   | 23                   |

Betawell L-Arabinose APPENDIX 1

# 1.10 FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY FEMALES

|                                    |                            | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|----------------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAYS 1-8<br>WEEKS 1-2 | MEAN<br>ST.DEV<br>N (CAGE) | 16<br>0.7<br>2     | 15<br>0.1<br>2      | 15<br>0.6<br>2       | 15<br>0.1<br>2       |
| DAYS 8-15<br>WEEKS 2-3             | MEAN<br>ST.DEV<br>N (CAGE) | 17<br>0.1<br>2     | 17<br>0.3<br>2      | 17<br>0.4<br>2       | 17<br>0.5<br>2       |
| DAYS 15-22<br>WEEKS 3-4            | MEAN<br>ST.DEV<br>N (CAGE) | 16<br>0.1<br>2     | 16<br>0.0<br>2      | 16<br>0.5<br>2       | 16<br>0.6<br>2       |
| DAYS 22-29<br>VEEKS 4-5            | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>0.5<br>2     | 17<br>0.4<br>2      | 18<br>0.1<br>2       | 18<br>0.2<br>2       |
| DAYS 29-36<br>VEEKS 5-6            | MEAN<br>ST.DEV<br>N (CAGE) | 17<br>0.5<br>2     | 17<br>1.5<br>2      | 17<br>0.8<br>2       | 17<br>0.4<br>2       |
| 0AYS 36-43<br>VEEKS 6-7            | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>0.5<br>2     | 18<br>0.6<br>2      | 18<br>0.9<br>2       | 18<br>0.1<br>2       |
| 0AYS 43-50<br>VEEKS 7-8            | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>0.6<br>2     | 20<br>1.6<br>2      | 20<br>1.1<br>2       | 20<br>0.7<br>2       |
| 0AYS 50-57<br>VEEKS 8-9            | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>1.3<br>2     | 18<br>1.3<br>2      | 20<br>1.4<br>2       | 20<br>1.0<br>2       |
| 0AYS 57-64<br>VEEKS 9-10           | MEAN<br>ST.DEV<br>N (CAGE) | 17<br>0.9<br>2     | 18<br>0.9<br>2      | 19<br>2.0<br>2       | 18<br>0.3<br>2       |
| AYS 64-71<br>VEEKS 10-11           | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>1.0<br>2     | 18<br>0.3<br>2      | 19<br>1.1<br>2       | 19<br>0.1<br>2       |
| AYS 71-78<br>VEEKS 11-12           | MEAN<br>ST.DEV<br>N (CAGE) | 19<br>1.4<br>2     | 18<br>0.8<br>2      | 19<br>1.6<br>2       | 20<br>1.9<br>2       |
| 0AYS 78-85<br>VEEKS 12-13          | MEAN<br>ST.DEV<br>N (CAGE) | 17<br>0.0<br>2     | 18<br>2.6<br>2      | 18<br>1.0<br>2       | 18<br>0.5<br>2       |
| AYS 85-91<br>VEEK 13               | MEAN<br>ST.DEV<br>N (CAGE) | 18<br>1.5<br>2     | 19<br>0.8<br>2      | 20<br>2.0<br>2       | 19<br>2.1<br>2       |
| MEAN OF MEANS<br>OVER TREATMENT    | MEAN                       | 17                 | 18                  | 18                   | 18                   |

- Page 39 of 249 -

Betawell L-Arabinose APPENDIX 1

## 1.11 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY MALES

|                                    |                            | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|----------------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAYS 1-8<br>WEEKS 1-2 | MEAN<br>ST.DEV<br>N (CAGE) | 94<br>0.9<br>2     | 96<br>2.6<br>2      | 98<br>5.1<br>2       | 94<br>0.8<br>2       |
| DAYS 8-15<br>WEEKS 2-3             | MEAN<br>ST.DEV<br>N (CAGE) | 91<br>0.5<br>2     | 94<br>3.5<br>2      | 98<br>6.6<br>2       | 90<br>5.1<br>2       |
| DAYS 15-22<br>WEEKS 3-4            | MEAN<br>ST.DEV<br>N (CAGE) | 79<br>1.3<br>2     | 84<br>3.1<br>2      | 85<br>4.9<br>2       | 81<br>3.9<br>2       |
| DAYS 22-29<br>NEEKS 4-5            | MEAN<br>ST.DEV<br>N (CAGE) | 76<br>0.8<br>2     | 80<br>1.8<br>2      | 80<br>3.4<br>2       | 79<br>1.2<br>2       |
| DAYS 29-36<br>WEEKS 5-6            | MEAN<br>ST.DEV<br>N (CAGE) | 68<br>0.7<br>2     | 71<br>0.8<br>2      | 75<br>3.3<br>2       | 72<br>1.6<br>2       |
| DAYS 36-43<br>WEEKS 6-7            | MEAN<br>ST.DEV<br>N (CAGE) | 68<br>0.9<br>2     | 71<br>0.7<br>2      | 75<br>4.5<br>2       | 75<br>1.2<br>2       |
| DAYS 43-50<br>NEEKS 7-8            | MEAN<br>ST.DEV<br>N (CAGE) | 70<br>1.8<br>2     | 69<br>2.4<br>2      | 78<br>8.2<br>2       | 77<br>4.5<br>2       |
| DAYS 50-57<br>WEEKS 8-9            | MEAN<br>ST.DEV<br>N (CAGE) | 64<br>0.2<br>2     | 66<br>0.8<br>2      | 74<br>7.6<br>2       | 70<br>0.6<br>2       |
| DAYS 57-64<br>WEEKS 9-10           | MEAN<br>ST.DEV<br>N (CAGE) | 61<br>0.1<br>2     | 63<br>1.0<br>2      | 67<br>5.9<br>2       | 68<br>2.4<br>2       |
| DAYS 64-71<br>VEEKS 10-11          | MEAN<br>ST.DEV<br>N (CAGE) | 62<br>3.9<br>2     | 61<br>0.6<br>2      | 66<br>5.1<br>2       | 65<br>2.7<br>2       |
| DAYS 71-78<br>WEEKS 11-12          | MEAN<br>ST.DEV<br>N (CAGE) | 60<br>2.6<br>2     | 61<br>4.0<br>2      | 65<br>7.5<br>2       | 64<br>3.9<br>2       |
| DAYS 78-85<br>WEEKS 12-13          | MEAN<br>ST.DEV<br>N (CAGE) | 57<br>0.0<br>2     | 60<br>0.4<br>2      | 61<br>6.0<br>2       | 62<br>3.1<br>2       |
| DAYS 85-91<br>VEEK 13              | MEAN<br>ST.DEV<br>N (CAGE) | 60<br>2.8<br>2     | 61<br>1.1<br>2      | 67<br>5.4<br>2       | 64<br>5.5<br>2       |
| MEAN OF MEANS<br>OVER TREATMENT    | MEAN                       | 70                 | 72                  | 76                   | 74                   |

## 1.11 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY FEMALES

|                                 |                            | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|---------------------------------|----------------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT                       |                            |                    |                     |                      |                      |
| DAYS 1-8<br>WEEKS 1-2           | MEAN<br>ST.DEV<br>N (CAGE) | 101<br>1.1<br>2    | 97<br>0.1<br>2      | 97<br>2.9<br>2       | 96<br>1.6<br>2       |
| DAYS 8-15<br>WEEKS 2-3          | MEAN<br>ST.DEV<br>N (CAGE) | 98<br>3.1<br>2     | 97<br>1.7<br>2      | 100<br>0.9<br>2      | 102<br>2.0<br>2      |
| DAYS 15-22<br>WEEKS 3-4         | MEAN<br>ST.DEV<br>N (CAGE) | 88<br>0.3<br>2     | 84<br>1.0<br>2      | 88<br>2.4<br>2       | 88<br>1.2<br>2       |
| DAYS 22-29<br>WEEKS 4-5         | MEAN<br>ST.DEV<br>N (CAGE) | 91<br>2.8<br>2     | 90<br>2.0<br>2      | 91<br>2.0<br>2       | 91<br>2.0<br>2       |
| DAYS 29-36<br>WEEKS 5-6         | MEAN<br>ST.DEV<br>N (CAGE) | 80<br>1.0<br>2     | 83<br>6.4<br>2      | 83<br>1.5<br>2       | 83<br>0.1<br>2       |
| DAYS 36-43<br>WEEKS 6-7         | MEAN<br>ST.DEV<br>N (CAGE) | 84<br>1.9<br>2     | 83<br>1.1<br>2      | 87<br>0.8<br>2       | 88<br>0.8<br>2       |
| DAYS 43-50<br>WEEKS 7-8         | MEAN<br>ST.DEV<br>N (CAGE) | 80<br>2.3<br>2     | 88<br>5.4<br>2      | 93<br>8.0<br>2       | 90<br>5.1<br>2       |
| DAYS 50-57<br>WEEKS 8-9         | MEAN<br>ST.DEV<br>N (CAGE) | 80<br>6.2<br>2     | 80<br>4.1<br>2      | 90<br>3.6<br>2       | 91<br>1.6<br>2       |
| DAYS 57-64<br>WEEKS 9-10        | MEAN<br>ST.DEV<br>N (CAGE) | 75<br>3.3<br>2     | 76<br>3.4<br>2      | 84<br>5.3<br>2       | 78<br>0.5<br>2       |
| DAYS 64-71<br>WEEKS 10-11       | MEAN<br>ST.DEV<br>N (CAGE) | 75<br>3.8<br>2     | 77<br>0.0<br>2      | 81<br>1.8<br>2       | 83<br>1.3<br>2       |
| DAYS 71-78<br>WEEKS 11-12       | MEAN<br>ST.DEV<br>N (CAGE) | 77<br>6.6<br>2     | 77<br>2.6<br>2      | 81<br>4.5<br>2       | 84<br>6.1<br>2       |
| DAYS 78-85<br>WEEKS 12-13       | MEAN<br>ST.DEV<br>N (CAGE) | 70<br>0.4<br>2     | 78<br>9.7<br>2      | 75<br>2.5<br>2       | 77<br>1.1<br>2       |
| DAYS 85-91<br>WEEK 13           | MEAN<br>ST.DEV<br>N (CAGE) | 72<br>6.2<br>2     | 79<br>1.9<br>2      | 84<br>5.7<br>2       | 80<br>6.9<br>2       |
| MEAN OF MEANS<br>OVER TREATMENT | MEAN                       | 82                 | 84                  | 87                   | 87                   |

Betawell L-Arabinose APPENDIX 1

## 1.12 TEST ARTICLE INTAKE (MG SUBSTANCE/KG BODY WEIGHT/DAY) SUMMARY MALES

|                                    |                            | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------------|----------------------------|--------------------|---------------------|----------------------|----------------------|
| TREATMENT<br>DAYS 1-8<br>WEEKS 1-2 | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 289<br>7.8<br>2     | 984<br>50.9<br>2     | 2833<br>24.5<br>2    |
| DAYS 8-15<br>WEEKS 2-3             | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 281<br>10.5<br>2    | 981<br>66.3<br>2     | 2694<br>153.0<br>2   |
| DAYS 15-22<br>WEEKS 3-4            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 252<br>9.4<br>2     | 853<br>49.2<br>2     | 2440<br>118.1<br>2   |
| DAYS 22-29<br>WEEKS 4-5            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 240<br>5.5<br>2     | 800<br>33.7<br>2     | 2374<br>36.5<br>2    |
| DAYS 29-36<br>WEEKS 5-6            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 214<br>2.4<br>2     | 745<br>32.8<br>2     | 2150<br>47.9<br>2    |
| DAYS 36-43<br>WEEKS 6-7            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 213<br>2.1<br>2     | 749<br>44.6<br>2     | 2247<br>35.1<br>2    |
| DAYS 43-50<br>WEEKS 7-8            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 207<br>7.3<br>2     | 776<br>81.8<br>2     | 2302<br>135.4<br>2   |
| DAYS 50-57<br>WEEKS 8-9            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 197<br>2.3<br>2     | 741<br>76.2<br>2     | 2111<br>18.6<br>2    |
| DAYS 57-64<br>WEEKS 9-10           | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 188<br>2.9<br>2     | 668<br>59.0<br>2     | 2047<br>73.3<br>2    |
| DAYS 64-71<br>WEEKS 10-11          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 183<br>1.8<br>2     | 660<br>50.7<br>2     | 1938<br>82.5<br>2    |
| DAYS 71-78<br>WEEKS 11-12          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 184<br>11.9<br>2    | 647<br>75.1<br>2     | 1925<br>117.3<br>2   |
| DAYS 78-85<br>WEEKS 12-13          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 180<br>1.1<br>2     | 608<br>59.7<br>2     | 1859<br>92.4<br>2    |
| DAYS 85-91<br>WEEK 13              | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2      | 184<br>3.4<br>2     | 673<br>53.5<br>2     | 1919<br>166.2<br>2   |
| MEAN OF MEANS<br>OVER TREATMENT    | MEAN                       | 0                  | 216                 | 760                  | 2218                 |

- Page 42 of 249 -

# 1.12 TEST ARTICLE INTAKE (MG SUBSTANCE/KG BODY WEIGHT/DAY) SUMMARY FEMALES

|                                    |                            | GROUP 1       | GROUP 2          | GROUP 3          | GROUP 4            |
|------------------------------------|----------------------------|---------------|------------------|------------------|--------------------|
|                                    |                            | CONTROL       | 3000 PPM         | 10000 PPM        | 30000 PPM          |
| TREATMENT<br>DAYS 1-8<br>WEEKS 1-2 | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 290<br>0.4<br>2  | 969<br>29.1<br>2 | 2870<br>48.9<br>2  |
| DAYS 8-15<br>WEEKS 2-3             | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 290<br>5.2<br>2  | 997<br>8.9<br>2  | 3062<br>61.3<br>2  |
| DAYS 15-22<br>WEEKS 3-4            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 253<br>3.0<br>2  | 884<br>23.5<br>2 | 2653<br>34.5<br>2  |
| DAYS 22-29<br>WEEKS 4-5            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 269<br>6.1<br>2  | 907<br>19.9<br>2 | 2735<br>59.7<br>2  |
| DAYS 29-36<br>WEEKS 5-6            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 249<br>19.3<br>2 | 831<br>15.1<br>2 | 2500<br>3.0<br>2   |
| DAYS 36-43<br>WEEKS 6-7            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 250<br>3.3<br>2  | 869<br>8.1<br>2  | 2639<br>23.3<br>2  |
| DAYS 43-50<br>WEEKS 7-8            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 264<br>16.3<br>2 | 925<br>80.2<br>2 | 2703<br>152.9<br>2 |
| DAYS 50-57<br>WEEKS 8-9            | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 241<br>12.2<br>2 | 900<br>35.7<br>2 | 2718<br>47.4<br>2  |
| DAYS 57-64<br>WEEKS 9-10           | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 227<br>10.3<br>2 | 838<br>52.8<br>2 | 2355<br>15.3<br>2  |
| DAYS 64-71<br>WEEKS 10-11          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 230<br>0.1<br>2  | 815<br>18.1<br>2 | 2503<br>38.9<br>2  |
| DAYS 71-78<br>WEEKS 11-12          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 232<br>7.9<br>2  | 814<br>44.7<br>2 | 2518<br>181.6<br>2 |
| DAYS 78-85<br>WEEKS 12-13          | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 235<br>29.2<br>2 | 755<br>25.2<br>2 | 2319<br>33.2<br>2  |
| DAYS 85-91<br>WEEK 13              | MEAN<br>ST.DEV<br>N (CAGE) | 0<br>0.0<br>2 | 237<br>5.8<br>2  | 837<br>56.7<br>2 | 2406<br>206.9<br>2 |
| MEAN OF MEANS<br>OVER TREATMENT    | MEAN                       | 0             | 251              | 872              | 2614               |

- Page 43 of 249 -

Betawell L-Arabinose
APPENDIX 1

Project 509991

## 1.13 OPHTHALMOSCOPIC EXAMINATIONS SUMMARY MALES

|                              | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------------------|--------------------|---------------------|----------------------|----------------------|
| PRE-TEST                     |                    |                     |                      |                      |
| No Findings                  | 10/10              | 10/10               | 8/10                 | 9/10                 |
| Focal Corneal Edema          | 0/10               | 0/10                | 2/10                 | 0/10                 |
| Multifocal Corneal Opacities | 0/10               | 0/10                | 1/10                 | 1/10                 |
| AT WEEK 13                   |                    |                     |                      |                      |
| No Findings                  | 5/10               |                     |                      | 6/10                 |
| Focal Corneal Opacity        | 5/10               |                     |                      | 4/10                 |

## **FEMALES**

|  | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|--|--------------------|---------------------|----------------------|----------------------|
| PRE-TEST                                 | ,                  |                     |                      |                      |
| No Findings                              | 10/10              | 9/10                | 9/10                 | 9/10                 |
| Corneal Opacity                          | 0/10               | 1/10                | 0/10                 | 0/10                 |
| Corneal Opacity With Vascularization     | 0/10               | 0/10                | 1/10                 | 0/10                 |
| Pinpoint Corneal Opacities               | 0/10               | 0/10                | 0/10                 | 1/10                 |
| Underlying Structures Cannot Be Examined | 0/10               | 0/10                | 1/10                 | 0/10                 |
| AT WEEK 13                               |                    |                     |                      |                      |
| No Findings                              | 6/10               |                     |                      | 7/10                 |
| Focal Corneal Edema                      | 1/10               |                     |                      | 1/10                 |
| Focal Corneal Opacity                    | 4/10               |                     |                      | 3/10                 |

Betawell L-Arabinose APPENDIX 1

#### 1.14 HAEMATOLOGY SUMMARY **MALES**

|                     |                | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM   | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |  |
|---------------------|----------------|--------------------|-----------------------|----------------------|----------------------|--|
| END OF TREATMENT    |                | ,                  | ,                     |                      |                      |  |
| NBC                 | MEAN           | 7.9                | 7.0                   | 7.7                  | 7.2                  |  |
| 10E9/L              | ST.DEV         | 1.4                | 1.1                   | 0.8                  | 1.5                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| Neutrophils         | MEAN           | 16.8               | 15.6                  | 16.3                 | 16.6                 |  |
| %WBC                | ST.DEV         | 6.3                | 2.7                   | 4.6                  | 3.0                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| _ymphocytes         | MEAN           | 80.3               | 81.0                  | 80.0                 | 80.0                 |  |
| %WBC                | ST.DEV         | 6.2                | 2.6                   | 5.6                  | 3.1                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| Monocytes           | MEAN           | 1.9                | 1.9                   | 1.9                  | 1.9                  |  |
| %WBC                | ST.DEV         | 0.6                | 0.5                   | 0.9                  | 0.5                  |  |
| 20                  | N              | 10                 | 10                    | 9                    | 10                   |  |
|                     |                |                    |                       |                      |                      |  |
| Eosinophils<br>%WBC | MEAN<br>ST.DEV | 1.0<br>0.3         | 1.5 +<br>0.4          | 1.8<br>1.0           | 1.5 ++<br>0.2        |  |
| OVVDC               | N SI.DEV       | 0.3<br>10          | 0. <del>4</del><br>10 | 9                    | 0.2<br>10            |  |
|                     |                | . •                | . •                   | · ·                  |                      |  |
| Basophils           | MEAN           | 0.1                | 0.1                   | 0.1                  | 0.1                  |  |
| %WBC                | ST.DEV         | 0.1                | 0.1                   | 0.1                  | 0.0                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| Red blood cells     | MEAN           | 9.42               | 9.06                  | 9.20                 | 9.50                 |  |
| 10E12/L             | ST.DEV         | 0.54               | 0.37                  | 0.34                 | 0.46                 |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| Reticulocytes       | MEAN           | 2.2                | 2.1                   | 2.2                  | 2.1                  |  |
| %RBC                | ST.DEV         | 0.3                | 0.2                   | 0.2                  | 0.2                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
|                     | NAT A NI       | 40.0               | 40.7                  | 40.0                 | 40.0                 |  |
| RDW<br>%            | MEAN<br>ST.DEV | 12.3<br>0.6        | 12.7<br>0.6           | 12.0<br>0.4          | 12.3<br>0.6          |  |
| 10                  | N N            | 10                 | 10                    | 9                    | 10                   |  |
|                     |                |                    |                       |                      |                      |  |
| -laemoglobin        | MEAN           | 9.9                | 9.6                   | 9.6                  | 9.9                  |  |
| nmol/L              | ST.DEV<br>N    | 0.5<br>10          | 0.2<br>10             | 0.2<br>9             | 0.4<br>10            |  |
|                     | 14             | 10                 | 10                    | J                    | 10                   |  |
| -laematocrit        | MEAN           | 0.485              | 0.462 *               | 0.471                | 0.484                |  |
| _/L                 | ST.DEV         | 0.030              | 0.014                 | 0.012                | 0.023                |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| MCV                 | MEAN           | 51.6               | 51.0                  | 51.1                 | 51.0                 |  |
| L                   | ST.DEV         | 1.0                | 1.2                   | 1.1                  | 0.7                  |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| MCH                 | MEAN           | 1.06               | 1.07                  | 1.04                 | 1.04                 |  |
| mol                 | ST.DEV         | 0.02               | 0.04                  | 0.03                 | 0.01                 |  |
|                     | N              | 10                 | 10                    | 9                    | 10                   |  |
| 40110               | N4= ^ . ·      | 00.47              | 00.00.                | 00.04                | 00.00                |  |
| MCHC<br>mmol/L      | MEAN<br>ST.DEV | 20.47<br>0.29      | 20.88 *<br>0.46       | 20.34<br>0.32        | 20.39<br>0.22        |  |
| IIIIOI/L            | N N            | 10                 | 10                    | 0.32<br>9            | 10                   |  |
|                     | ••             |                    |                       |                      |                      |  |
| Platelets           | MEAN           | 776                | 736<br>74             | 733<br>107           | 770<br>69            |  |
| 10E9/L              | ST.DEV         | 65                 |                       |                      |                      |  |

<sup>+/++</sup> Steel-test significant at 5% (+) or 1% (++) level  $^{*}$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Project 509991 Betawell L-Arabinose APPENDIX 1

#### 1.14 HAEMATOLOGY SUMMARY **MALES**

|                  |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------|--------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT |        |                    |                     |                      |                      |
| PT               | MEAN   | 17.0               | 17.2                | 16.9                 | 17.1                 |
| S                | ST.DEV | 0.5                | 0.6                 | 1.1                  | 0.9                  |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| APTT             | MEAN   | 16.4               | 18.7                | 17.6                 | 17.7                 |
| S                | ST.DEV | 2.2                | 2.5                 | 2.9                  | 2.9                  |
|                  | N      | 10                 | 10                  | 10                   | 10                   |

<sup>+/++</sup> Steel-test significant at 5% (+) or 1% (++) level  $^{*/**}$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

#### 1.14 HAEMATOLOGY SUMMARY **FEMALES**

|                            |                     | GROUP 1<br>CONTROL   | GROUP 2<br>3000 PPM    | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|----------------------------|---------------------|----------------------|------------------------|----------------------|----------------------|
| END OF TREATMENT           |                     |                      |                        |                      |                      |
| WBC<br>10E9/L              | MEAN<br>ST.DEV<br>N | 5.3<br>2.0<br>8      | 4.3<br>1.3<br>10       | 4.3<br>0.8<br>8      | 4.5<br>1.2<br>10     |
| Neutrophils<br>%WBC        | MEAN<br>ST.DEV<br>N | 22.1<br>21.2<br>10   | 18.6<br>13.3<br>10     | 18.5<br>7.3<br>8     | 12.0<br>3.4<br>10    |
| Lymphocytes<br>%WBC        | MEAN<br>ST.DEV<br>N | 74.1<br>22.0<br>10   | 76.9<br>15.3<br>10     | 77.5<br>8.0<br>8     | 84.3<br>3.3<br>10    |
| Monocytes<br>%WBC          | MEAN<br>ST.DEV<br>N | 1.9<br>0.5<br>10     | 2.2<br>1.6<br>10       | 2.1<br>0.6<br>8      | 1.8<br>0.9<br>10     |
| Eosinophils<br>%WBC        | MEAN<br>ST.DEV<br>N | 1.9<br>1.2<br>10     | 2.3<br>1.3<br>10       | 1.8<br>1.0<br>8      | 1.8<br>0.5<br>10     |
| Basophils<br>%WBC          | MEAN<br>ST.DEV<br>N | 0.1<br>0.1<br>10     | 0.1<br>0.1<br>10       | 0.1<br>0.1<br>8      | 0.0<br>0.1<br>10     |
| Red blood cells<br>10E12/L | MEAN<br>ST.DEV<br>N | 8.38<br>0.32<br>10   | 8.09<br>0.32<br>10     | 8.29<br>0.26<br>8    | 8.35<br>0.32<br>10   |
| Reticulocytes<br>%RBC      | MEAN<br>ST.DEV<br>N | 2.6<br>0.5<br>10     | 2.7<br>0.3<br>10       | 2.5<br>0.1<br>8      | 2.3<br>0.3<br>10     |
| RDW<br>%                   | MEAN<br>ST.DEV<br>N | 11.5<br>1.2<br>10    | 11.3<br>0.5<br>10      | 10.9<br>0.2<br>8     | 10.7 *<br>0.4<br>10  |
| Haemoglobin<br>mmol/L      | MEAN<br>ST.DEV<br>N | 9.4<br>0.3<br>10     | 8.9 **<br>0.2<br>10    | 9.1 *<br>0.3<br>8    | 9.2<br>0.2<br>10     |
| Haematocrit<br>L/L         | MEAN<br>ST.DEV<br>N | 0.449<br>0.014<br>10 | 0.431 *<br>0.013<br>10 | 0.445<br>0.016<br>8  | 0.446<br>0.013<br>10 |
| MCV<br>fL                  | MEAN<br>ST.DEV<br>N | 53.6<br>0.9<br>10    | 53.2<br>1.2<br>10      | 53.8<br>2.1<br>8     | 53.4<br>1.1<br>10    |
| MCH<br>fmol                | MEAN<br>ST.DEV<br>N | 1.12<br>0.04<br>10   | 1.10<br>0.05<br>10     | 1.09<br>0.05<br>8    | 1.10<br>0.03<br>10   |
| MCHC<br>mmol/L             | MEAN<br>ST.DEV<br>N | 20.86<br>0.49<br>10  | 20.68<br>0.50<br>10    | 20.32 *<br>0.19<br>8 | 20.57<br>0.33<br>10  |
| Platelets<br>10E9/L        | MEAN<br>ST.DEV<br>N | 695<br>86<br>10      | 787<br>107<br>10       | 858 **<br>89<br>8    | 730<br>93<br>10      |

<sup>+/++</sup> Steel-test significant at 5% (+) or 1% (++) level  $^{*}$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Project 509991 Betawell L-Arabinose APPENDIX 1

## 1.14 HAEMATOLOGY SUMMARY **FEMALES**

|                  |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------|--------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT |        |                    |                     |                      |                      |
| PT               | MEAN   | 16.3               | 16.4                | 17.5 **              | 16.4                 |
| S                | ST.DEV | 0.4                | 0.7                 | 0.6                  | 0.5                  |
|                  | N      | 10                 | 10                  | 8                    | 10                   |
| APTT             | MEAN   | 16.8               | 17.5                | 18.0                 | 17.8                 |
| s                | ST.DEV | 1.4                | 2.3                 | 2.2                  | 2.4                  |
|                  | N      | 10                 | 10                  | 8                    | 10                   |

<sup>+/++</sup> Steel-test significant at 5% (+) or 1% (++) level  $^{*/**}$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

#### 1.15 CLINICAL BIOCHEMISTRY SUMMARY **MALES**

|                   |                | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|-------------------|----------------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT  |                | ,                  |                     |                      |                      |
| ALAT              | MEAN           | 42.8               | 44.3                | 47.8                 | 43.9                 |
| U/L               | ST.DEV         | 8.8                | 6.3                 | 10.9                 | 5.2                  |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| ASAT              | MEAN           | 76.9               | 75.9                | 76.7                 | 83.4                 |
| U/L               | ST.DEV         | 7.8                | 5.3                 | 10.5                 | 17.4                 |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| ALP               | MEAN           | 157                | 174                 | 176                  | 191                  |
| U/L               | ST.DEV         | 89                 | 59                  | 60                   | 76                   |
| <b>.</b>          | N              | 10                 | 10                  | 10                   | 10                   |
| Total protoin     | MEAN           | 64.4               | 62.4                | 64.5                 | 65.0                 |
| Total protein     | MEAN<br>ST.DEV | 64.4<br>1.7        | 63.4<br>2.1         | 1.4                  | 0.9                  |
| g/L               | N N            | 1.7                | 10                  | 10                   | 10                   |
|                   |                |                    |                     |                      |                      |
| Albumin           | MEAN           | 32.4               | 31.6                | 32.0                 | 32.2                 |
| g/L               | ST.DEV<br>N    | 0.9<br>10          | 0.7<br>10           | 0.8<br>10            | 0.9<br>10            |
|                   | 14             | 10                 | 10                  | 10                   | 10                   |
| Total bilirubin   | MEAN           | 2.0                | 1.8 *               | 1.8                  | 2.1                  |
| umol/L            | ST.DEV         | 0.2                | 0.3                 | 0.2                  | 0.2                  |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| Urea              | MEAN           | 6.7                | 6.6                 | 8.1                  | 6.9                  |
| mmol/L            | ST.DEV         | 1.9                | 1.5                 | 1.8                  | 1.1                  |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| Creatinine        | MEAN           | 38.8               | 38.5                | 38.3                 | 39.3                 |
| umol/L            | ST.DEV         | 1.7                | 1.4                 | 2.3                  | 2.1                  |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| Glucose           | MEAN           | 11.58              | 11.02               | 11.13                | 10.26 *              |
| mmol/L            | ST.DEV         | 1.36               | 0.71                | 1.13                 | 1.19                 |
| IIIIIO//L         | N N            | 10                 | 10                  | 10                   | 10                   |
| Ob -1t1           | NATANI         | 0.00               | 2.00                | 2.24                 | 0.44                 |
| Cholesterol       | MEAN<br>ST.DEV | 2.06<br>0.19       | 2.08<br>0.19        | 2.21<br>0.30         | 2.14<br>0.37         |
| mmol/L            | N N            | 10                 | 10                  | 10                   | 10                   |
|                   |                |                    |                     |                      |                      |
| Bile Acids        | MEAN           | 15.8               | 14.6                | 16.3                 | 18.9                 |
| umol/L            | ST.DEV<br>N    | 9.2<br>10          | 6.3<br>10           | 7.4<br>10            | 8.2<br>10            |
|                   | IN             | 10                 | 10                  | 10                   | 10                   |
| Sodium            | MEAN           | 142.2              | 142.4               | 142.2                | 142.0                |
| mmol/L            | ST.DEV         | 1.5                | 1.9                 | 1.5                  | 2.1                  |
|                   | N              | 10                 | 10                  | 10                   | 10                   |
| Potassium         | MEAN           | 4.04               | 3.98                | 4.29                 | 4.11                 |
| mmol/L            | ST.DEV         | 0.15               | 0.22                | 0.27                 | 0.31                 |
| <b></b>           | N              | 10                 | 10                  | 10                   | 10                   |
| Chloride          | MEAN           | 104                | 104                 | 104                  | 104                  |
| mmol/L            | ST.DEV         | 1                  | 2                   | 1                    | 2                    |
|                   | N              | 10                 | _<br>10             | 10                   | 10                   |
| Coloium           | MEAN           | 2.61               | 2.55                | 2.63                 | 2.61                 |
| Calcium<br>mmol/L | MEAN<br>ST.DEV | 2.61<br>0.04       | 2.55<br>0.08        | 2.63<br>0.05         | 0.04                 |
| 111101/L          | N N            | 10                 | 10                  | 10                   | 10                   |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose
APPENDIX 1
Project 509991

## 1.15 CLINICAL BIOCHEMISTRY SUMMARY MALES

|                      |                | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|----------------------|----------------|--------------------|---------------------|----------------------|----------------------|
| ND OF TREATMENT      | MEAN           | 1.56               | 1 45                | 1.46                 | 1 10                 |
| Inorg.Phos<br>mmol/L | MEAN<br>ST.DEV | 1.56<br>0.18       | 1.45<br>0.12        | 1.46<br>0.13         | 1.48<br>0.21         |
|                      | N              | 10                 | 10                  | 10                   | 10                   |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose APPENDIX 1

# 1.15 CLINICAL BIOCHEMISTRY SUMMARY FEMALES

|                |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|----------------|--------|--------------------|---------------------|----------------------|----------------------|
| D OF TREATMENT |        |                    |                     | ,                    |                      |
| AT             | MEAN   | 39.1               | 37.8                | 42.4                 | 43.1                 |
| =              | ST.DEV | 9.3                | 13.5                | 10.7                 | 6.0                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| AT             | MEAN   | 73.3               | 76.6                | 72.6                 | 71.7                 |
| =              | ST.DEV | 8.1                | 21.4                | 8.9                  | 10.0                 |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| Р              | MEAN   | 69                 | 77                  | 81                   | 79                   |
| -              | ST.DEV | 17                 | 34                  | 32                   | 45                   |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| tal protein    | MEAN   | 67.9               | 66.5                | 69.9                 | 68.6                 |
| •              | ST.DEV | 3.9                | 2.7                 | 3.4                  | 3.9                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| oumin          | MEAN   | 35.8               | 35.3                | 37.4                 | 36.2                 |
|                | ST.DEV | 2.1                | 1.5                 | 2.2                  | 2.5                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| al bilirubin   | MEAN   | 2.5                | 2.3                 | 2.2                  | 2.7                  |
| ol/L           | ST.DEV | 0.3                | 0.4                 | 0.3                  | 0.7                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| a              | MEAN   | 6.9                | 7.0                 | 6.7                  | 6.5                  |
| ol/L           | ST.DEV | 1.4                | 1.3                 | 1.3                  | 1.3                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| atinine        | MEAN   | 41.1               | 44.5 **             | 43.9 *               | 40.7                 |
| ol/L           | ST.DEV | 2.7                | 2.8                 | 1.4                  | 2.3                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| cose           | MEAN   | 8.40               | 9.30                | 8.90                 | 9.96 *               |
| ol/L           | ST.DEV | 1.50               | 1.46                | 1.24                 | 1.23                 |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| olesterol      | MEAN   | 1.90               | 1.63                | 1.85                 | 1.83                 |
| nol/L          | ST.DEV | 0.25               | 0.26                | 0.37                 | 0.25                 |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| e Acids        | MEAN   | 13.8               | 16.8                | 17.4                 | 23.6 *               |
| ol/L           | ST.DEV | 3.4                | 9.6                 | 5.7                  | 12.4                 |
|                | N      | 9                  | 10                  | 10                   | 10                   |
| dium           | MEAN   | 141.6              | 142.0               | 142.8 **             | 141.7                |
| nol/L          | ST.DEV | 1.1                | 1.0                 | 0.6                  | 0.6                  |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| assium         | MEAN   | 3.75               | 3.76                | 3.60                 | 3.70                 |
| ol/L           | ST.DEV | 0.14               | 0.29                | 0.23                 | 0.25                 |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| loride         | MEAN   | 105                | 106 *               | 106                  | 104                  |
| nol/L          | ST.DEV | 1                  | 1                   | 1                    | 1                    |
|                | N      | 10                 | 10                  | 10                   | 10                   |
| cium           | MEAN   | 2.67               | 2.60                | 2.66                 | 2.67                 |
| ol/L           | ST.DEV | 0.06               | 0.09                | 0.06                 | 0.07                 |
|                | N      | 10                 | 10                  | 10                   | 10                   |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.15 CLINICAL BIOCHEMISTRY SUMMARY FEMALES

|                  |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------|--------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT |        |                    |                     |                      |                      |
| Inorg.Phos       | MEAN   | 1.27               | 1.14                | 0.97 *               | 1.28                 |
| mmol/L           | ST.DEV | 0.28               | 0.20                | 0.20                 | 0.29                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.16 MACROSCOPIC FINDINGS SUMMARY MALES

|                           | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|---------------------------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT          |                    |                     |                      |                      |
| Animals examined          | 10                 | 10                  | 10                   | 10                   |
| Animals without findings  | 10                 | 7                   | 10                   | 7                    |
| Animals affected          | 0                  | 3                   | 0                    | 3                    |
| Testes                    |                    |                     |                      |                      |
| Reduced in size           | 0                  | 0                   | 0                    | 1                    |
| Epididymides              |                    |                     |                      |                      |
| Reduced in size           | 0                  | 0                   | 0                    | 1                    |
| Preputial glands          |                    |                     |                      |                      |
| Focus/foci                | 0                  | 1                   | 0                    | 0                    |
| Thyroid gland             |                    |                     |                      |                      |
| Reduced in size           | 0                  | 1                   | 0                    | 0                    |
| Thymus                    | •                  | •                   |                      |                      |
| Focus/foci                | 0                  | 0                   | 0                    | 1                    |
| Mandibular lymph n        | ^                  | 4                   | 0                    | 0                    |
| Discolouration            | 0                  | 1                   | 0                    | 0                    |
| Bone Sternum: malaligned. | 0                  | 0                   | 0                    | 1                    |

### **FEMALES**

|                          | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|--------------------------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT         |                    |                     |                      |                      |
| Animals examined         | 10                 | 10                  | 10                   | 10                   |
| Animals without findings | 3                  | 2                   | 5                    | 6                    |
| Animals affected         | 7                  | 8                   | 5                    | 4                    |
| Stomach                  |                    |                     |                      |                      |
| Focus/foci               | 0                  | 1                   | 0                    | 0                    |
| Jterus (                 |                    |                     |                      |                      |
| Contains fluid           | 5                  | 7                   | 5                    | 4                    |
| Spleen                   |                    |                     |                      |                      |
| Nodule(s)                | 1                  | 0                   | 0                    | 0                    |
| hymus                    |                    |                     |                      |                      |
| Focus/foci               | 1                  | 1                   | 0                    | 0                    |
| xillary lymph node       |                    |                     |                      |                      |
| Enlarged                 | 1                  | 0                   | 0                    | 0                    |
| Discolouration           | 1                  | 0                   | 0                    | 0                    |
| /landibular lymph n      |                    |                     |                      |                      |
| Discolouration           | 1                  | 0                   | 0                    | 0                    |
| Skin                     |                    |                     |                      |                      |
| Scab formation           | 1                  | 1                   | 0                    | 0                    |

1.17 ORGAN WEIGHTS (GRAM) SUMMARY MALES

|                  |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------|--------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT |        |                    |                     |                      |                      |
| BODY W.          | MEAN   | 358                | 362                 | 370                  | 361                  |
| RAM)             | ST.DEV | 25                 | 38                  | 33                   | 39                   |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| AIN              | MEAN   | 2.00               | 2.01                | 2.00                 | 1.97                 |
| AM)              | ST.DEV | 0.08               | 0.08                | 0.07                 | 0.07                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| RT               | MEAN   | 0.896              | 0.921               | 0.949                | 0.913                |
| M)               | ST.DEV | 0.085              | 0.089               | 0.128                | 0.097                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| R                | MEAN   | 8.36               | 8.71                | 9.21                 | 8.39                 |
| AM)              | ST.DEV | 1.02               | 1.03                | 0.96                 | 0.99                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| ROIDS            | MEAN   | 0.017              | 0.015               | 0.015                | 0.014                |
| AM)              | ST.DEV | 0.005              | 0.005               | 0.003                | 0.004                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| MUS              | MEAN   | 0.317              | 0.276               | 0.283                | 0.278                |
| M)               | ST.DEV | 0.042              | 0.084               | 0.026                | 0.057                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| EYS              | MEAN   | 2.19               | 2.37                | 2.39                 | 2.21                 |
| AM)              | ST.DEV | 0.23               | 0.35                | 0.25                 | 0.30                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| ENALS            | MEAN   | 0.047              | 0.053               | 0.047                | 0.044                |
| AM)              | ST.DEV | 0.009              | 0.010               | 0.006                | 0.006                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| EEN              | MEAN   | 0.497              | 0.551               | 0.530                | 0.526                |
| AM)              | ST.DEV | 0.089              | 0.056               | 0.070                | 0.086                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| TES              | MEAN   | 3.54               | 3.47                | 3.65                 | 3.44                 |
| AM)              | ST.DEV | 0.14               | 0.21                | 0.25                 | 0.60                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| OSTATE GLAND     | MEAN   | 0.985              | 0.895               | 0.813                | 0.932                |
| AM)              | ST.DEV | 0.168              | 0.214               | 0.149                | 0.180                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| DIDYMIDES        | MEAN   | 1.187              | 1.158               | 1.229                | 1.140                |
| AM)              | ST.DEV | 0.075              | 0.095               | 0.092                | 0.184                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| MINAL VESICLES   | MEAN   | 1.386              | 1.402               | 1.511                | 1.588                |
| RAM)             | ST.DEV | 0.319              | 0.257               | 0.215                | 0.205                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |

25Mar16 08h56

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.17 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY MALES

|                      |                     | GROUP 1<br>CONTROL   | GROUP 2<br>3000 PPM  | GROUP 3<br>10000 PPM   | GROUP 4<br>30000 PPM |
|----------------------|---------------------|----------------------|----------------------|------------------------|----------------------|
| END OF TREATMENT     |                     |                      | ,                    |                        |                      |
| BODY W.<br>(GRAM)    | MEAN<br>ST.DEV<br>N | 358<br>25<br>10      | 362<br>38<br>10      | 370<br>33<br>10        | 361<br>39<br>10      |
| BRAIN<br>(%)         | MEAN<br>ST.DEV<br>N | 0.56<br>0.04<br>10   | 0.56<br>0.05<br>10   | 0.54<br>0.04<br>10     | 0.55<br>0.05<br>10   |
| HEART<br>(%)         | MEAN<br>ST.DEV<br>N | 0.250<br>0.009<br>10 | 0.255<br>0.013<br>10 | 0.256<br>0.020<br>10   | 0.253<br>0.014<br>10 |
| LIVER (%)            | MEAN<br>ST.DEV<br>N | 2.33<br>0.19<br>10   | 2.40<br>0.11<br>10   | 2.49<br>0.15<br>10     | 2.33<br>0.15<br>10   |
| THYROIDS (%)         | MEAN<br>ST.DEV<br>N | 0.005<br>0.001<br>10 | 0.004<br>0.001<br>10 | 0.004<br>0.001<br>10   | 0.004<br>0.001<br>10 |
| THYMUS<br>(%)        | MEAN<br>ST.DEV<br>N | 0.089<br>0.010<br>10 | 0.076<br>0.022<br>10 | 0.077<br>0.010<br>10   | 0.077<br>0.013<br>10 |
| KIDNEYS<br>(%)       | MEAN<br>ST.DEV<br>N | 0.61<br>0.04<br>10   | 0.65<br>0.04<br>10   | 0.64<br>0.03<br>10     | 0.61<br>0.04<br>10   |
| ADRENALS<br>(%)      | MEAN<br>ST.DEV<br>N | 0.013<br>0.002<br>10 | 0.015<br>0.003<br>10 | 0.013<br>0.002<br>10   | 0.012<br>0.001<br>10 |
| SPLEEN<br>(%)        | MEAN<br>ST.DEV<br>N | 0.138<br>0.019<br>10 | 0.153<br>0.016<br>10 | 0.143<br>0.013<br>10   | 0.145<br>0.016<br>10 |
| TESTES<br>(%)        | MEAN<br>ST.DEV<br>N | 0.99<br>0.10<br>10   | 0.96<br>0.08<br>10   | 0.99<br>0.07<br>10     | 0.95<br>0.15<br>10   |
| PROSTATE GLAND (%)   | MEAN<br>ST.DEV<br>N | 0.276<br>0.046<br>10 | 0.249<br>0.060<br>10 | 0.221 *<br>0.044<br>10 | 0.257<br>0.037<br>10 |
| EPIDIDYMIDES (%)     | MEAN<br>ST.DEV<br>N | 0.333<br>0.029<br>10 | 0.321<br>0.028<br>10 | 0.333<br>0.016<br>10   | 0.316<br>0.045<br>10 |
| SEMINAL VESICLES (%) | MEAN<br>ST.DEV<br>N | 0.387<br>0.084<br>10 | 0.386<br>0.055<br>10 | 0.411<br>0.066<br>10   | 0.442<br>0.053<br>10 |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.17 ORGAN WEIGHTS (GRAM) SUMMARY FEMALES

|                    |                     | GROUP 1<br>CONTROL   | GROUP 2<br>3000 PPM  | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|--------------------|---------------------|----------------------|----------------------|----------------------|----------------------|
| END OF TREATMENT   |                     |                      | ,                    | ,                    |                      |
| BODY W.<br>(GRAM)  | MEAN<br>ST.DEV<br>N | 233<br>16<br>10      | 229<br>11<br>10      | 223<br>12<br>10      | 228<br>18<br>10      |
| BRAIN<br>(GRAM)    | MEAN<br>ST.DEV<br>N | 1.91<br>0.08<br>10   | 1.92<br>0.06<br>10   | 1.89<br>0.06<br>10   | 1.87<br>0.09<br>10   |
| HEART<br>(GRAM)    | MEAN<br>ST.DEV<br>N | 0.694<br>0.052<br>10 | 0.695<br>0.056<br>10 | 0.664<br>0.025<br>10 | 0.713<br>0.060<br>10 |
| LIVER<br>(GRAM)    | MEAN<br>ST.DEV<br>N | 5.85<br>0.47<br>10   | 6.17<br>0.52<br>10   | 5.94<br>0.56<br>10   | 6.36<br>0.69<br>10   |
| THYROIDS<br>(GRAM) | MEAN<br>ST.DEV<br>N | 0.015<br>0.004<br>10 | 0.014<br>0.003<br>10 | 0.012<br>0.002<br>10 | 0.015<br>0.003<br>10 |
| THYMUS<br>(GRAM)   | MEAN<br>ST.DEV<br>N | 0.301<br>0.072<br>10 | 0.298<br>0.040<br>10 | 0.282<br>0.044<br>10 | 0.294<br>0.046<br>10 |
| KIDNEYS<br>(GRAM)  | MEAN<br>ST.DEV<br>N | 1.63<br>0.15<br>10   | 1.65<br>0.13<br>10   | 1.58<br>0.09<br>10   | 1.59<br>0.17<br>10   |
| ADRENALS<br>(GRAM) | MEAN<br>ST.DEV<br>N | 0.067<br>0.007<br>10 | 0.071<br>0.007<br>10 | 0.062<br>0.006<br>10 | 0.064<br>0.012<br>10 |
| SPLEEN<br>(GRAM)   | MEAN<br>ST.DEV<br>N | 0.429<br>0.075<br>10 | 0.447<br>0.049<br>10 | 0.419<br>0.041<br>10 | 0.467<br>0.062<br>10 |
| OVARIES<br>(GRAM)  | MEAN<br>ST.DEV<br>N | 0.135<br>0.021<br>10 | 0.152<br>0.014<br>10 | 0.139<br>0.018<br>10 | 0.143<br>0.018<br>10 |
| UTERUS<br>(GRAM)   | MEAN<br>ST.DEV<br>N | 0.730<br>0.263<br>10 | 0.976<br>0.317<br>10 | 0.753<br>0.290<br>10 | 0.711<br>0.438<br>10 |

<sup>\*/\*\*</sup> Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

# 1.17 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY FEMALES

|                  |        | GROUP 1<br>CONTROL | GROUP 2<br>3000 PPM | GROUP 3<br>10000 PPM | GROUP 4<br>30000 PPM |
|------------------|--------|--------------------|---------------------|----------------------|----------------------|
| END OF TREATMENT |        |                    | ,                   | ,                    |                      |
| BODY W.          | MEAN   | 233                | 229                 | 223                  | 228                  |
| (GRAM)           | ST.DEV | 16                 | 11                  | 12                   | 18                   |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| BRAIN            | MEAN   | 0.82               | 0.84                | 0.85                 | 0.82                 |
| %)               | ST.DEV | 0.04               | 0.05                | 0.06                 | 0.06                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| HEART            | MEAN   | 0.298              | 0.303               | 0.298                | 0.314                |
| %)               | ST.DEV | 0.015              | 0.015               | 0.014                | 0.021                |
| •                | N      | 10                 | 10                  | 10                   | 10                   |
| _IVER            | MEAN   | 2.52               | 2.69                | 2.66                 | 2.79 *               |
| %)               | ST.DEV | 0.20               | 0.20                | 0.27                 | 0.23                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| THYROIDS         | MEAN   | 0.007              | 0.006               | 0.006                | 0.006                |
| %)               | ST.DEV | 0.001              | 0.001               | 0.001                | 0.001                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| THYMUS           | MEAN   | 0.131              | 0.130               | 0.126                | 0.130                |
| %)               | ST.DEV | 0.035              | 0.019               | 0.017                | 0.025                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| KIDNEYS          | MEAN   | 0.70               | 0.72                | 0.71                 | 0.70                 |
| %)               | ST.DEV | 0.04               | 0.04                | 0.03                 | 0.04                 |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| ADRENALS         | MEAN   | 0.029              | 0.031               | 0.028                | 0.028                |
| %)               | ST.DEV | 0.002              | 0.003               | 0.004                | 0.005                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| SPLEEN           | MEAN   | 0.184              | 0.196               | 0.188                | 0.205                |
| %)               | ST.DEV | 0.030              | 0.022               | 0.021                | 0.027                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| OVARIES          | MEAN   | 0.058              | 0.066 *             | 0.062                | 0.063                |
| %)               | ST.DEV | 0.007              | 0.006               | 0.008                | 0.008                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |
| JTERUS           | MEAN   | 0.316              | 0.427               | 0.340                | 0.318                |
| %)               | ST.DEV | 0.121              | 0.137               | 0.142                | 0.208                |
|                  | N      | 10                 | 10                  | 10                   | 10                   |

 $<sup>^{*/**}</sup>$  Dunnett-test based on pooled variance significant at 5% (\*) or 1% (\*\*) level

Betawell L-Arabinose Project 509991

### **APPENDIX 2 INDIVIDUAL DATA TABLES**

Final Report - Page 1 -

- Page 58 of 249 -

### 2.1 MORTALITY DATA MALES

| ANIMAL  | SCHEDULED<br>SACRIFICE  | TREATMENT<br>FROM  | то   |
|---|---|--|--|
| GROUP 1 1 2 3 4 5 6 7 8 9 10  | 1 (CONTROL)<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16   | 04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15 | 03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16 |
| GROUP 2<br>11<br>12<br>13<br>14<br>15<br>16<br>17<br>18<br>19<br>20 | 2 (3000 PPM)<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16  | 04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15 | 03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16 |
| 21<br>22<br>23<br>24<br>25<br>26<br>27<br>28<br>29<br>30            | 3 (10000 PPM)<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16 | 04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15 | 03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16            |
| GROUP 4<br>31<br>32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40 | 4 (30000 PPM)<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>05FEB16<br>05FEB16<br>05FEB16<br>05FEB16            | 04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15 | 03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16            |
| FEMALE  | s   |  |  |
| ANIMAL  | SCHEDULED<br>SACRIFICE  | TREATMENT<br>FROM  | то   |
| GROUP 1 41 42 43 44 45 46 47  | 04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16<br>04FEB16  | 04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15<br>04NOV15                                  | 03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16<br>03FEB16                                  |

# 2.1 MORTALITY DATA FEMALES

| ANIMAL   | SCHEDULED<br>SACRIFICE | TREATMENT<br>FROM  | то                 |  |
|----------|------------------------|--------------------|--------------------|--|
| GROUP    | 1 (CONTROL)            |                    |                    |  |
| 48       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 49       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 50       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| GROUP    | 2 (3000 PPM)           |                    |                    |  |
| 51       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 52       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 53       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 54       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 55       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 56       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 57       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 58       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 59       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 60       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| GROUP    | 3 (10000 PPM)          |                    |                    |  |
| 61       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 62       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 63       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 64       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 65       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 66       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 67<br>69 | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 68<br>69 | 04FEB16<br>04FEB16     | 04NOV15<br>04NOV15 | 03FEB16<br>03FEB16 |  |
| 69<br>70 | 04FEB16<br>04FEB16     | 04NOV15<br>04NOV15 | 03FEB16            |  |
| 10       | 071 LD 10              | OTINO VIO          | 001 LD 10          |  |
|          | 4 (30000 PPM)          |                    |                    |  |
| 71       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 72       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 73       | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 74<br>75 | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 75<br>76 | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 76<br>77 | 04FEB16<br>04FEB16     | 04NOV15<br>04NOV15 | 03FEB16<br>03FEB16 |  |
| 77<br>78 | 04FEB16<br>04FEB16     | 04NOV15<br>04NOV15 | 03FEB16            |  |
| 78<br>79 | 04FEB16<br>04FEB16     | 04NOV15<br>04NOV15 | 03FEB16            |  |
| 79<br>80 | 04FEB16                | 04NOV15            | 03FEB16            |  |
| 00       | OTI LD 10              | UTINO VIJ          |                    |  |

### 2.2 CLINICAL SIGNS **MALES**

| -                                    |               | TREATMENT  |
|--------------------------------------|---------------|--|
| SIGN (MAX. GRADE)<br>(LOCATION)      | WEEK:<br>DAY: | 188<br>123456712345671234567123456712345671234567123456712 |
| GROUP 1 (CONTROL)<br>ANIMAL 1        |               |  |
| No clinical signs noted ANIMAL 2     |               |  |
| No clinical signs noted  ANIMAL 3    |               |  |
| No clinical signs noted  ANIMAL 4    |               |  |
| No clinical signs noted  ANIMAL 5    |               |  |
| No clinical signs noted  ANIMAL 6    |               |  |
| No clinical signs noted  ANIMAL 7    |               |  |
| No clinical signs noted ANIMAL 8     |               |  |
| No clinical signs noted ANIMAL 9     |               |  |
| No clinical signs noted  ANIMAL 10   |               |  |
| No clinical signs noted              |               |  |
| GROUP 2 (3000 PPM)<br>ANIMAL 11      |               |  |
| No clinical signs noted              |               |  |
| ANIMAL 12 No clinical signs noted    |               |  |
| ANIMAL 13 No clinical signs noted    |               |  |
| ANIMAL 14 No clinical signs noted    |               |  |
| ANIMAL 15 No clinical signs noted    |               |  |
| No clinical signs noted              |               |  |
| ANIMAL 17 No clinical signs noted    |               |  |
| ANIMAL 18 No clinical signs noted    |               |  |
| ANIMAL 19 No clinical signs noted    |               |  |
| ANIMAL 20<br>No clinical signs noted |               |  |
| GROUP 3 (10000 PPM)<br>ANIMAL 21     |               |  |
| No clinical signs noted  ANIMAL 22   |               |  |
| No clinical signs noted ANIMAL 23    |               |  |
| No clinical signs noted ANIMAL 24    |               |  |
| No clinical signs noted              |               |  |
| ANIMAL 25 No clinical signs noted    |               |  |
| ANIMAL 26 No clinical signs noted    |               |  |
| ANIMAL 27 No clinical signs noted    |               |  |
| ANIMAL 28 No clinical signs noted    |               |  |

G: Highest daily grades
.: Observation performed, sign not present

Betawell L-Arabinose Project 509991 APPENDIX 2

#### 2.2 CLINICAL SIGNS **MALES**

|                                    |       | TREATMENT  |
|------------------------------------|-------|--|
| SIGN (MAX. GRADE)                  | WEEK: | 1 4  |
| (LOCATION)                         | DAY:  | 123456712345671234567123456712345671234567123456712345671234 |
| CDOUD & (40000 DDIN)               |       |  |
| GROUP 3 (10000 PPM)                |       |  |
| ANIMAL 29                          |       |  |
| No clinical signs noted  ANIMAL 30 |       |  |
|                                    |       |  |
| No clinical signs noted            |       |  |
| GROUP 4 (30000 PPM)                |       |  |
| ANIMAL 31                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 32                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 33                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 34                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 35                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 36                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 37                          |       |  |
| No clinical signs noted            |       |  |
| ANIMAL 38                          |       |  |
| No clinical signs noted            |       |  |

### **MALES**

ANIMAL 1

ANIMAL 2

**ANIMAL 39** 

No clinical signs noted ANIMAL 40

No clinical signs noted

|                   |       | TREATMENT                 |
|-------------------|-------|---------------------------|
| SIGN (MAX. GRADE) | WEEK: |                           |
| (LOCATION)        | DAY:  | 6712345671234567123456712 |

#### No clinical signs noted ANIMAL 3 No clinical signs noted ANIMAL 4 No clinical signs noted ANIMAL 5

**GROUP 1 (CONTROL)** 

No clinical signs noted

No clinical signs noted

**ANIMAL 6** No clinical signs noted

ANIMAL 7 No clinical signs noted

**ANIMAL 8** 

No clinical signs noted

ANIMAL 9

No clinical signs noted

**ANIMAL 10** 

No clinical signs noted

## **GROUP 2 (3000 PPM)**

ANIMAL 11

No clinical signs noted

G: Highest daily grades

.: Observation performed, sign not present

Betawell L-Arabinose Project 509991 APPENDIX 2

#### 2.2 CLINICAL SIGNS **MALES**

TREATMENT SIGN (MAX. GRADE) WEEK: (LOCATION) 67123456712345671234567123456712

### GROUP 2 (3000 PPM)

**ANIMAL 12** 

No clinical signs noted

**ANIMAL 13** 

No clinical signs noted

**ANIMAL 14** 

No clinical signs noted

ANIMAL 15

No clinical signs noted

**ANIMAL 16** 

No clinical signs noted

**ANIMAL 17** 

No clinical signs noted

**ANIMAL 18** 

No clinical signs noted

ANIMAL 19

No clinical signs noted

**ANIMAL 20** 

No clinical signs noted

#### **GROUP 3 (10000 PPM)**

ANIMAL 21

No clinical signs noted

**ANIMAL 22** 

No clinical signs noted

**ANIMAL 23** 

No clinical signs noted

**ANIMAL 24** 

No clinical signs noted ANIMAL 25

No clinical signs noted

ANIMAL 26

No clinical signs noted **ANIMAL 27** 

No clinical signs noted

**ANIMAL 28** 

No clinical signs noted

ANIMAL 29

No clinical signs noted

**ANIMAL 30** 

No clinical signs noted

#### GROUP 4 (30000 PPM)

ANIMAL 31

No clinical signs noted

ANIMAL 32

No clinical signs noted

**ANIMAL 33** No clinical signs noted

**ANIMAL 34** 

No clinical signs noted ANIMAL 35

No clinical signs noted

**ANIMAL 36** 

No clinical signs noted

**ANIMAL 37** No clinical signs noted

**ANIMAL 38** 

No clinical signs noted

**ANIMAL 39** 

No clinical signs noted

G: Highest daily grades

.: Observation performed, sign not present

### 2.2 CLINICAL SIGNS MALES

|                         |       | TREATMENT                 |  |
|-------------------------|-------|---------------------------|--|
| SIGN (MAX. GRADE)       | WEEK: |                           |  |
| (LOCATION)              | DAY:  | 6712345671234567123456712 |  |
|                         |       |                           |  |
| GROUP 4 (30000 PPM)     |       |                           |  |
| ANIMAL 40               |       |                           |  |
| No clinical signs noted |       |                           |  |

#### **FEMALES**

| SIGN (MAX, GRADE)  |                                       |      | TREATMENT  |
|--|---------------------------------------|------|--|
| GROUP 1 (CONTROL) ANIMAL 41 Skin / fur Scabs (3)   |                                       |      |  |
| ANIMAL 41 Scabs (3)  | (LOCATION)                            | DAY: | 123456/123456/1234567123456712345671234567123456712345 |
| ANIMAL 41 Scabs (3)  | GROUP 1 (CONTROL)                     |      |  |
| Skin / fur Scabs (3)   |                                       |      |  |
| Scabs (3)  |                                       |      |  |
| (Head) Scabs (3)   |                                       | G:   |  |
| Scabs (3)  | ( )                                   |      |  |
| (Back) Scabs (3)   | ` ,                                   | G:   |  |
| Scabs (3)  |                                       |      |  |
| Scabs (3) G: (Shoulder left) Scabs (3) G: (Shoulder right) Various Pale (3) G: (Animal L 42 No clinical signs noted ANIMAL 43 No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  | , ,                                   | G:   |  |
| Scabs (3) G: (Shoulder left) Scabs (3) G: (Shoulder right) Various Pale (3) G: (Animal L 42 No clinical signs noted ANIMAL 43 No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| Scabs (3)  | · · · · · · · · · · · · · · · · · · · | G:   |  |
| (Shoulder right) Various Pale (3) G: ANIMAL 42 No clinical signs noted ANIMAL 43 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   | (Shoulder left)                       |      |  |
| Various Pale (3) Pale (4) Pale | Scabs (3)                             | G:   |  |
| Pale (3)  ANIMAL 42  No clinical signs noted ANIMAL 43  No clinical signs noted ANIMAL 44  No clinical signs noted ANIMAL 45  No clinical signs noted ANIMAL 45  No clinical signs noted ANIMAL 46  No clinical signs noted ANIMAL 47  No clinical signs noted ANIMAL 47  No clinical signs noted ANIMAL 48  No clinical signs noted ANIMAL 49  No clinical signs noted ANIMAL 50  No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 50  No clinical signs noted  GROUP 2 (3000 PPM) ANIMAL 51  No clinical signs noted ANIMAL 52  Skin / fur Scabs (3)  (Back)  ANIMAL 53  No clinical signs noted ANIMAL 53  No clinical signs noted ANIMAL 55  No clinical signs noted ANIMAL 56   | (Shoulder right)                      |      |  |
| ANIMAL 42 No clinical signs noted ANIMAL 43 No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 57 No clinical signs noted ANIMAL 58 No clinical signs noted ANIMAL 59 No clinical signs noted ANIMAL 56  | Various                               |      |  |
| No clinical signs noted ANIMAL 43 No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  | Pale (3)                              | G:   |  |
| ANIMAL 43 No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted SROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56   | ANIMAL 42                             |      |  |
| No clinical signs noted ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56   | No clinical signs noted               |      |  |
| ANIMAL 44 No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 57 No clinical signs noted ANIMAL 58 No clinical signs noted ANIMAL 59 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 56  | ANIMAL 43                             |      |  |
| No clinical signs noted ANIMAL 45 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56   | No clinical signs noted               |      |  |
| ANIMAL 45 No clinical signs noted ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted  GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56  | ANIMAL 44                             |      |  |
| No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  ANIMAL 56  ANIMAL 56  | No clinical signs noted               |      |  |
| ANIMAL 46 No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 57 No clinical signs noted ANIMAL 58 No clinical signs noted ANIMAL 56 No clinical signs noted ANIMAL 56   |                                       |      |  |
| No clinical signs noted ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| ANIMAL 47 No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| No clinical signs noted ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| ANIMAL 48 No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55   |                                       |      |  |
| No clinical signs noted ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| ANIMAL 49 No clinical signs noted ANIMAL 50 No clinical signs noted  GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| No clinical signs noted  ANIMAL 50  No clinical signs noted  GROUP 2 (3000 PPM)  ANIMAL 51  No clinical signs noted  ANIMAL 52  Skin / fur  Scabs (3)  (Back)  ANIMAL 53  No clinical signs noted  ANIMAL 54  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 56   |                                       |      |  |
| ANIMAL 50 No clinical signs noted  GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) G: (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| No clinical signs noted  GROUP 2 (3000 PPM)  ANIMAL 51  No clinical signs noted  ANIMAL 52  Skin / fur  Scabs (3)  (Back)  ANIMAL 53  No clinical signs noted  ANIMAL 54  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 56   |                                       |      |  |
| GROUP 2 (3000 PPM) ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56   |                                       |      |  |
| ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  | No clinical signs noted               |      |  |
| ANIMAL 51 No clinical signs noted ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  | GPOUR 2 (3000 PPM)                    |      |  |
| No clinical signs noted  ANIMAL 52 Skin / fur Scabs (3) (Back)  ANIMAL 53 No clinical signs noted  ANIMAL 54 No clinical signs noted  ANIMAL 55 No clinical signs noted  ANIMAL 55 No clinical signs noted  ANIMAL 55 No clinical signs noted  ANIMAL 56   |                                       |      |  |
| ANIMAL 52 Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55  |                                       |      |  |
| Skin / fur Scabs (3) (Back) ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| Scabs (3) G: (Back)  ANIMAL 53 No clinical signs noted  ANIMAL 54 No clinical signs noted  ANIMAL 55 No clinical signs noted  ANIMAL 55 No clinical signs noted  ANIMAL 56   |                                       |      |  |
| (Back)  ANIMAL 53  No clinical signs noted  ANIMAL 54  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 56  |                                       | G·   |  |
| ANIMAL 53 No clinical signs noted ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  | . ,                                   |      |  |
| No clinical signs noted  ANIMAL 54  No clinical signs noted  ANIMAL 55  No clinical signs noted  ANIMAL 56   |                                       |      |  |
| ANIMAL 54 No clinical signs noted ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| ANIMAL 55 No clinical signs noted ANIMAL 56  |                                       |      |  |
| ANIMAL 56  |                                       |      |  |
|  | No clinical signs noted               |      |  |
| No clinical signs noted  | ANIMAL 56                             |      |  |
| No cililical signs noted   | No clinical signs noted               |      |  |

G: Highest daily grades
.: Observation performed, sign not present

### 2.2 CLINICAL SIGNS **FEMALES**

|  |       | TREATMENT   |
|--|-------|---|
| SIGN (MAX. GRADE)  | WEEK: | 188   |
| (LOCATION)   | DAY:  | 1234567123456712345671234567123456712345671234567123456712345 |
| GROUP 2 (3000 PPM)   |       |   |
| ANIMAL 57  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 58  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 59  |       |   |
| No clinical signs noted  ANIMAL 60   |       |   |
| No clinical signs noted  |       |   |
| , and the second |       |   |
| GROUP 3 (10000 PPM)  |       |   |
| ANIMAL 61  |       |   |
| No clinical signs noted  ANIMAL 62   |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 63  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 64  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 65 No clinical signs noted  |       |   |
| ANIMAL 66  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 67  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 68  |       |   |
| No clinical signs noted  ANIMAL 69   |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 70  |       |   |
| No clinical signs noted  |       |   |
| GROUP 4 (30000 PPM)  |       |   |
| ANIMAL 71  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 72  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 73  |       |   |
| No clinical signs noted  ANIMAL 74   |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 75  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 76  |       |   |
| No clinical signs noted  ANIMAL 77   |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 78  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 79  |       |   |
| No clinical signs noted  |       |   |
| ANIMAL 80 No clinical signs noted  |       |   |
| INO CITIICAL SIGNS HOLEG   |       |   |

G: Highest daily grades
.: Observation performed, sign not present

### 2.2 CLINICAL SIGNS **FEMALES**

| FEMALES                                |                 |                           |
|--|-----------------|---------------------------|
| CICN (MAY CDADE)                       | \\/ <b>\</b> \\ | TREATMENT1212             |
| SIGN (MAX. GRADE)<br>(LOCATION)        | WEEK:<br>DAY:   | 6712345671234567123456712 |
| GROUP 1 (CONTROL) ANIMAL 41 Skin / fur |                 |                           |
| Scabs (3)                              | G:              | 11111111111111111         |
| (Head)<br>Scabs (3)                    | G:              |                           |
| (Back)                                 |                 |                           |
| Scabs (3)<br>(Cervical region)         | G:              |                           |
| Scabs (3)                              | G:              | 1111111222222222222       |
| (Shoulder left)<br>Scabs (3)           | G:              |                           |
| (Shoulder right)                       |                 |                           |
| Various<br>Pale (3)                    | G:              |                           |
| ANIMAL 42 No clinical signs noted      |                 |                           |
| ANIMAL 43                              |                 |                           |
| No clinical signs noted  ANIMAL 44     |                 |                           |
| No clinical signs noted                |                 |                           |
| ANIMAL 45 No clinical signs noted      |                 |                           |
| ANIMAL 46 No clinical signs noted      |                 |                           |
| ANIMAL 47                              |                 |                           |
| No clinical signs noted  ANIMAL 48     |                 |                           |
| No clinical signs noted                |                 |                           |
| ANIMAL 49 No clinical signs noted      |                 |                           |
| ANIMAL 50                              |                 |                           |
| No clinical signs noted                |                 |                           |
| GROUP 2 (3000 PPM)<br>ANIMAL 51        |                 |                           |
| No clinical signs noted                |                 |                           |
| ANIMAL 52<br>Skin / fur                |                 |                           |
| Scabs (3)                              | G:              |                           |
| (Back) ANIMAL 53                       |                 |                           |
| No clinical signs noted                |                 |                           |
| ANIMAL 54 No clinical signs noted      |                 |                           |
| ANIMAL 55 No clinical signs noted      |                 |                           |
| ANIMAL 56                              |                 |                           |
| No clinical signs noted  ANIMAL 57     |                 |                           |
| No clinical signs noted                |                 |                           |
| ANIMAL 58 No clinical signs noted      |                 |                           |
| ANIMAL 59  No clinical signs noted     |                 |                           |
| ANIMAL 60                              |                 |                           |
| No clinical signs noted                |                 |                           |
| GROUP 3 (10000 PPM)                    |                 |                           |
| ANIMAL 61 No clinical signs noted      |                 |                           |
| Ŭ                                      |                 | -                         |

G: Highest daily grades
.: Observation performed, sign not present

Betawell L-Arabinose Project 509991 APPENDIX 2

#### 2.2 CLINICAL SIGNS **FEMALES**

TREATMENT SIGN (MAX. GRADE) WEEK: (LOCATION) 67123456712345671234567123456712

### **GROUP 3 (10000 PPM)**

ANIMAL 62

No clinical signs noted

**ANIMAL 63** 

No clinical signs noted

**ANIMAL 64** 

No clinical signs noted

ANIMAL 65 No clinical signs noted

**ANIMAL 66** 

No clinical signs noted

**ANIMAL 67** 

No clinical signs noted

**ANIMAL 68** 

No clinical signs noted

**ANIMAL 69** No clinical signs noted

**ANIMAL 70** 

No clinical signs noted

### **GROUP 4 (30000 PPM)**

ANIMAL 71

No clinical signs noted

ANIMAL 72

No clinical signs noted

**ANIMAL 73** 

No clinical signs noted

**ANIMAL 74** 

No clinical signs noted

**ANIMAL 75** 

No clinical signs noted

ANIMAL 76 No clinical signs noted

**ANIMAL 77** 

No clinical signs noted

**ANIMAL 78** 

No clinical signs noted

ANIMAL 79

No clinical signs noted **ANIMAL 80** 

No clinical signs noted

G: Highest daily grades

.: Observation performed, sign not present

# 2.3 FUNCTIONAL OBSERVATIONS MALES

| ΑT | W | ΈE | Κ | 12 |
|----|---|----|---|----|
|----|---|----|---|----|

| ANIMAL      | HEARING<br>SCORE 0/1 | PUPIL L<br>SCORE 0/1 | PUPIL R<br>SCORE 0/1 | STATIC R<br>SCORE 0/1 | GRIP FORE<br>GRAM | GRIP HIND<br>GRAM |
|-------------|----------------------|----------------------|----------------------|-----------------------|-------------------|-------------------|
| GROUP 1 (Co | ONTROL)              |                      |                      |                       |                   |                   |
| 1           | 0                    | 0                    | 0                    | 0                     | 1062              | 721               |
| 2           | 0                    | 0                    | 0                    | 0                     | 1061              | 780               |
| 3           | 0                    | 0                    | 0                    | 0                     | 1483              | 981               |
| 4           | 0                    | 0                    | 0                    | 0                     | 1436              | 699               |
| 5           | 0                    | 0                    | 0                    | 0                     | 1244              | 849               |
| GROUP 2 (30 | 000 PPM)             |                      |                      |                       |                   |                   |
| 11          | 0 ′                  | 0                    | 0                    | 0                     | 1384              | 847               |
| 12          | 0                    | 0                    | 0                    | 0                     | 1271              | 831               |
| 13          | 0                    | 0                    | 0                    | 0                     | 1997              | 1178              |
| 14          | 0                    | 0                    | 0                    | 0                     | 1309              | 741               |
| 15          | 0                    | 0                    | 0                    | 0                     | 1141              | 1145              |
| GROUP 3 (10 | 0000 PPM)            |                      |                      |                       |                   |                   |
| 21          | 0                    | 0                    | 0                    | 0                     | 1235              | 799               |
| 22          | 0                    | 0                    | 0                    | 0                     | 1351              | 693               |
| 23          | 0                    | 0                    | 0                    | 0                     | 1497              | 839               |
| 24          | 0                    | 0                    | 0                    | 0                     | 1119              | 815               |
| 25          | 0                    | 0                    | 0                    | 0                     | 1220              | 1025              |
| GROUP 4 (30 | 0000 PPM)            |                      |                      |                       |                   |                   |
| 31          | 0                    | 0                    | 0                    | 0                     | 1199              | 971               |
| 32          | 0                    | 0                    | 0                    | 0                     | 1487              | 917               |
| 33          | 0                    | 0                    | 0                    | 0                     | 1112              | 611               |
| 34          | 0                    | 0                    | 0                    | 0                     | 1245              | 609               |
| 35          | 0                    | 0                    | 0                    | 0                     | 1157              | 763               |
|             |                      |                      |                      |                       |                   |                   |

### **FEMALES**

| ANIMAL      | HEARING<br>SCORE 0/1 | PUPIL L<br>SCORE 0/1 | PUPIL R<br>SCORE 0/1 | STATIC R<br>SCORE 0/1 | GRIP FORE<br>GRAM | GRIP HIND<br>GRAM |
|-------------|----------------------|----------------------|----------------------|-----------------------|-------------------|-------------------|
| GROUP 1 (C  | ONTROL)              |                      |                      |                       |                   |                   |
| 41          | 0                    | 0                    | 0                    | 0                     | 1559              | 667               |
| 42          | 0                    | 0                    | 0                    | 0                     | 1303              | 707               |
| 43          | 0                    | 0                    | 0                    | 0                     | 1173              | 612               |
| 44          | 0                    | 0                    | 0                    | 0                     | 1192              | 555               |
| 45          | 0                    | 0                    | 0                    | 0                     | 1020              | 694               |
| GROUP 2 (30 | 000 PPM)             |                      |                      |                       |                   |                   |
| 51          | 0                    | 0                    | 0                    | 0                     | 1033              | 597               |
| 52          | 0                    | 0                    | 0                    | 0                     | 941               | 727               |
| 53          | 0                    | 0                    | 0                    | 0                     | 1223              | 604               |
| 54          | 0                    | 0                    | 0                    | 0                     | 1268              | 627               |
| 55          | 0                    | 0                    | 0                    | 0                     | 1363              | 645               |
| GROUP 3 (10 | 0000 PPM)            |                      |                      |                       |                   |                   |
| 61          | 0                    | 0                    | 0                    | 0                     | 1357              | 657               |
| 62          | 0                    | 0                    | 0                    | 0                     | 1278              | 497               |
| 63          | 0                    | 0                    | 0                    | 0                     | 1343              | 682               |
| 64          | 0                    | 0                    | 0                    | 0                     | 934               | 712               |
| 65          | 0                    | 0                    | 0                    | 0                     | 1171              | 517               |
| GROUP 4 (30 | •                    |                      |                      |                       |                   |                   |
| 71          | 0                    | 0                    | 0                    | 0                     | 1200              | 691               |
| 72          | 0                    | 0                    | 0                    | 0                     | 1199              | 628               |
| 73          | 0                    | 0                    | 0                    | 0                     | 1087              | 614               |
| 74          | 0                    | 0                    | 0                    | 0                     | 1270              | 611               |

# 2.3 FUNCTIONAL OBSERVATIONS FEMALES

| ANIMAL                | HEARING              | PUPIL L   | PUPIL R   | STATIC R  | GRIP FORE | GRIP HIND |
|-----------------------|----------------------|-----------|-----------|-----------|-----------|-----------|
|                       | SCORE 0/1            | SCORE 0/1 | SCORE 0/1 | SCORE 0/1 | GRAM      | GRAM      |
| <b>GROUP 4 (30</b> 75 | <b>000 PPM)</b><br>0 | 0         | 0         | 0         | 1063      | 589       |

# 2.4 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS MALES

|             | Interval (5 min.) |     |     |     |     |     |     |     |     |     |     |     |       |
|-------------|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| ANIMAL      | 1                 | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | Total |
| GROUP 1 (Co | ONTROL            | .)  |     |     |     |     |     |     |     |     |     |     |       |
| 1           | 724               | 639 | 311 | 343 | 43  | 281 | 1   | 6   | 6   | 2   | 16  | 61  | 2433  |
| 2           | 800               | 475 | 362 | 28  | 20  | 14  | 6   | 29  | 0   | 0   | 15  | 8   | 1757  |
| 3           | 1030              | 571 | 307 | 150 | 86  | 2   | 11  | 96  | 4   | 12  | 0   | 0   | 2269  |
| 4           | 1209              | 675 | 558 | 465 | 66  | 377 | 189 | 163 | 7   | 6   | 36  | 10  | 3761  |
| 5           | 815               | 542 | 303 | 409 | 22  | 78  | 0   | 9   | 4   | 0   | 3   | 1   | 2186  |
| GROUP 2 (30 | 00 PPM            | )   |     |     |     |     |     |     |     |     |     |     |       |
| 11          | 631               | 381 | 395 | 243 | 17  | 6   | 14  | 50  | 0   | 0   | 2   | 1   | 1740  |
| 12          | 946               | 321 | 309 | 3   | 1   | 0   | 0   | 21  | 14  | 366 | 167 | 1   | 2149  |
| 13          | 1235              | 704 | 393 | 3   | 15  | 129 | 1   | 1   | 2   | 0   | 0   | 112 | 2595  |
| 14          | 767               | 321 | 144 | 29  | 144 | 146 | 369 | 316 | 2   | 10  | 141 | 37  | 2426  |
| 15          | 1030              | 602 | 217 | 0   | 0   | 4   | 0   | 0   | 197 | 0   | 3   | 11  | 2064  |
| GROUP 3 (10 | 000 PPN           | VI) |     |     |     |     |     |     |     |     |     |     |       |
| 21          | 1164              | 498 | 351 | 157 | 35  | 98  | 2   | 17  | 3   | 24  | 0   | 0   | 2349  |
| 22          | 790               | 467 | 382 | 249 | 427 | 239 | 10  | 6   | 63  | 20  | 5   | 33  | 2691  |
| 23          | 944               | 626 | 368 | 205 | 229 | 14  | 24  | 30  | 1   | 0   | 4   | 14  | 2459  |
| 24          | 777               | 388 | 288 | 152 | 5   | 166 | 3   | 76  | 3   | 1   | 1   | 209 | 2069  |
| 25          | 726               | 490 | 345 | 140 | 2   | 0   | 7   | 0   | 2   | 2   | 2   | 12  | 1728  |
| GROUP 4 (30 | 000 PPN           | VI) |     |     |     |     |     |     |     |     |     |     |       |
| 31          | 981               | 525 | 110 | 39  | 7   | 6   | 1   | 0   | 10  | 0   | 11  | 1   | 1691  |
| 32          | 1193              | 397 | 59  | 7   | 12  | 12  | 39  | 5   | 24  | 2   | 16  | 32  | 1798  |
| 33          | 737               | 306 | 180 | 0   | 32  | 37  | 10  | 5   | 14  | 8   | 7   | 0   | 1336  |
| 34          | 512               | 287 | 160 | 77  | 145 | 151 | 17  | 0   | 0   | 114 | 15  | 67  | 1545  |
| 35          | 1197              | 598 | 482 | 395 | 411 | 241 | 467 | 462 | 206 | 464 | 571 | 16  | 5510  |

# 2.4 MOTOR ACTIVITY TEST - AMBULATIONS MALES

|           | Interv   | Interval (5 min.) |     |    |     |    |     |     |    |     |     |    |       |  |
|-----------|----------|-------------------|-----|----|-----|----|-----|-----|----|-----|-----|----|-------|--|
| ANIMAL    | 1        | 2                 | 3   | 4  | 5   | 6  | 7   | 8   | 9  | 10  | 11  | 12 | Total |  |
| GROUP 1 ( | CONTRO   | L)                |     |    |     |    |     |     |    |     |     |    |       |  |
| 1         | 189      | 191               | 44  | 98 | 9   | 50 | 0   | 0   | 0  | 0   | 2   | 5  | 588   |  |
| 2         | 200      | 147               | 63  | 0  | 1   | 0  | 0   | 0   | 0  | 0   | 0   | 0  | 411   |  |
| 3         | 204      | 90                | 70  | 16 | 24  | 0  | 0   | 12  | 0  | 0   | 0   | 0  | 416   |  |
| 4         | 273      | 100               | 94  | 76 | 4   | 76 | 69  | 29  | 0  | 0   | 11  | 0  | 732   |  |
| 5         | 177      | 117               | 54  | 72 | 1   | 23 | 0   | 0   | 0  | 0   | 0   | 0  | 444   |  |
| GROUP 2 ( | 3000 PPM | l)                |     |    |     |    |     |     |    |     |     |    |       |  |
| 11        | 223      | 105               | 116 | 10 | 0   | 0  | 0   | 1   | 0  | 0   | 0   | 0  | 455   |  |
| 12        | 186      | 51                | 67  | 0  | 0   | 0  | 0   | 2   | 1  | 77  | 6   | 0  | 390   |  |
| 13        | 245      | 139               | 69  | 0  | 0   | 35 | 0   | 0   | 0  | 0   | 0   | 33 | 521   |  |
| 14        | 125      | 36                | 0   | 0  | 0   | 22 | 44  | 66  | 0  | 0   | 33  | 0  | 326   |  |
| 15        | 262      | 164               | 8   | 0  | 0   | 0  | 0   | 0   | 50 | 0   | 0   | 0  | 484   |  |
| GROUP 3 ( | 10000 PP | M)                |     |    |     |    |     |     |    |     |     |    |       |  |
| 21        | 310      | 105               | 49  | 29 | 0   | 0  | 0   | 0   | 0  | 0   | 0   | 0  | 493   |  |
| 22        | 190      | 108               | 89  | 66 | 153 | 81 | 0   | 0   | 7  | 0   | 0   | 5  | 699   |  |
| 23        | 202      | 113               | 39  | 11 | 49  | 0  | 2   | 2   | 1  | 0   | 0   | 0  | 419   |  |
| 24        | 209      | 86                | 61  | 0  | 0   | 50 | 0   | 18  | 0  | 0   | 0   | 40 | 464   |  |
| 25        | 113      | 75                | 22  | 13 | 0   | 0  | 0   | 0   | 0  | 0   | 0   | 0  | 223   |  |
| GROUP 4 ( | 30000 PP | M)                |     |    |     |    |     |     |    |     |     |    |       |  |
| 31        | 220      | ,<br>114          | 0   | 3  | 0   | 0  | 0   | 0   | 0  | 0   | 0   | 0  | 337   |  |
| 32        | 275      | 72                | 1   | 0  | 0   | 0  | 0   | 0   | 0  | 0   | 0   | 0  | 348   |  |
| 33        | 172      | 30                | 25  | 0  | 0   | 4  | 0   | 0   | 0  | 1   | 0   | 0  | 232   |  |
| 34        | 166      | 56                | 18  | 22 | 37  | 42 | 1   | 0   | 0  | 0   | 1   | 17 | 360   |  |
| 35        | 316      | 168               | 79  | 93 | 116 | 65 | 146 | 150 | 17 | 165 | 197 | 0  | 1512  |  |

# 2.4 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS FEMALES

| Interv             | Interval (5 min.) |     |     |     |     |     |                     |     |     |     |     |       |  |
|--------------------|-------------------|-----|-----|-----|-----|-----|---------------------|-----|-----|-----|-----|-------|--|
| ANIMAL 1           | 2                 | 3   | 4   | 5   | 6   | 7   | 8                   | 9   | 10  | 11  | 12  | Total |  |
| GROUP 1 (CONTROL   | GROUP 1 (CONTROL) |     |     |     |     |     |                     |     |     |     |     |       |  |
| 41 891             | <b>-,</b><br>353  | 472 | 326 | 358 | 538 | 137 | 2                   | 387 | 477 | 201 | 41  | 4183  |  |
| 42 1489            | 838               | 880 | 390 | 399 | 417 | 245 | <del>-</del><br>471 | 132 | 154 | 169 | 727 | 6311  |  |
| 43 1360            | 627               | 520 | 253 | 327 | 332 | 326 | 43                  | 0   | 9   | 369 | 11  | 4177  |  |
| 44 1110            | 930               | 517 | 291 | 345 | 151 | 133 | 9                   | 3   | 422 | 83  | 19  | 4013  |  |
| 45 1081            | 497               | 263 | 181 | 5   | 251 | 175 | 267                 | 317 | 43  | 260 | 0   | 3340  |  |
| GROUP 2 (3000 PPM  |                   |     |     |     |     |     |                     |     |     |     |     |       |  |
| 51 1127            | <b>,</b><br>649   | 646 | 415 | 293 | 2   | 0   | 6                   | 15  | 66  | 2   | 21  | 3242  |  |
| 52 904             | 310               | 289 | 461 | 315 | 317 | 165 | 11                  | 31  | 1   | 10  | 298 | 3112  |  |
| 53 1225            | 641               | 532 | 377 | 338 | 279 | 272 | 322                 | 381 | 475 | 419 | 208 | 5469  |  |
| 54 1000            | 732               | 324 | 308 | 137 | 0   | 4   | 3                   | 0   | 33  | 1   | 160 | 2702  |  |
| 55 949             | 864               | 420 | 339 | 141 | 92  | 53  | 6                   | 16  | 5   | 2   | 18  | 2905  |  |
| GROUP 3 (10000 PPI | M)                |     |     |     |     |     |                     |     |     |     |     |       |  |
| 61 1031            | 397               | 355 | 146 | 356 | 65  | 437 | 257                 | 102 | 211 | 296 | 129 | 3782  |  |
| 62 1414            | 559               | 370 | 419 | 96  | 59  | 255 | 2                   | 140 | 54  | 5   | 171 | 3544  |  |
| 63 1057            | 437               | 452 | 288 | 297 | 70  | 17  | 144                 | 8   | 212 | 357 | 10  | 3349  |  |
| 64 692             | 517               | 508 | 499 | 408 | 306 | 337 | 112                 | 408 | 119 | 4   | 19  | 3929  |  |
| 65 1503            | 536               | 498 | 488 | 183 | 237 | 365 | 94                  | 248 | 251 | 71  | 298 | 4772  |  |
| GROUP 4 (30000 PPI | VI)               |     |     |     |     |     |                     |     |     |     |     |       |  |
| 71 1666            | 1251              | 619 | 613 | 784 | 279 | 312 | 469                 | 412 | 397 | 166 | 530 | 7498  |  |
| 72 1319            | 834               | 568 | 461 | 323 | 307 | 205 | 587                 | 457 | 15  | 1   | 270 | 5347  |  |
| 73 1580            | 766               | 551 | 513 | 479 | 354 | 161 | 387                 | 587 | 95  | 52  | 160 | 5685  |  |
| 74 1427            | 795               | 443 | 435 | 558 | 521 | 209 | 204                 | 238 | 178 | 55  | 7   | 5070  |  |
| 75 1468            | 787               | 554 | 759 | 589 | 403 | 373 | 392                 | 400 | 346 | 256 | 24  | 6351  |  |

# 2.4 MOTOR ACTIVITY TEST - AMBULATIONS FEMALES

| ANIMAL    | Interv   | Interval (5 min.) |     |     |     |     |     |     |     |     |     |     |       |  |
|-----------|----------|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|--|
| ANIWAL    | 1        | 2                 | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | Total |  |
| GROUP 1 ( | CONTRO   | L)                |     |     |     |     |     |     |     |     |     |     |       |  |
| 41        | 235      | 23                | 106 | 60  | 72  | 134 | 7   | 0   | 73  | 109 | 2   | 0   | 821   |  |
| 42        | 422      | 200               | 217 | 79  | 52  | 74  | 55  | 112 | 19  | 37  | 41  | 218 | 1526  |  |
| 43        | 397      | 144               | 93  | 60  | 73  | 69  | 88  | 3   | 0   | 0   | 81  | 0   | 1008  |  |
| 44        | 399      | 343               | 149 | 12  | 78  | 31  | 0   | 0   | 0   | 120 | 2   | 0   | 1134  |  |
| 45        | 387      | 199               | 58  | 45  | 0   | 77  | 1   | 54  | 80  | 0   | 71  | 0   | 972   |  |
| GROUP 2 ( | 3000 PPN | 1)                |     |     |     |     |     |     |     |     |     |     |       |  |
| 51        | 326      | 118               | 183 | 71  | 3   | 0   | 0   | 0   | 0   | 9   | 0   | 0   | 710   |  |
| 52        | 271      | 44                | 42  | 85  | 50  | 49  | 19  | 0   | 1   | 0   | 0   | 42  | 603   |  |
| 53        | 405      | 192               | 118 | 49  | 118 | 78  | 108 | 105 | 138 | 146 | 135 | 52  | 1644  |  |
| 54        | 274      | 168               | 46  | 42  | 1   | 0   | 0   | 0   | 0   | 4   | 0   | 50  | 585   |  |
| 55        | 329      | 212               | 60  | 54  | 1   | 4   | 2   | 0   | 0   | 0   | 0   | 1   | 663   |  |
| GROUP 3 ( | 10000 PP | M)                |     |     |     |     |     |     |     |     |     |     |       |  |
| 61        | 305      | 76                | 63  | 28  | 110 | 8   | 100 | 39  | 13  | 57  | 67  | 0   | 866   |  |
| 62        | 335      | 138               | 109 | 128 | 4   | 24  | 58  | 0   | 34  | 1   | 0   | 44  | 875   |  |
| 63        | 295      | 116               | 128 | 55  | 33  | 2   | 0   | 1   | 0   | 1   | 92  | 1   | 724   |  |
| 64        | 278      | 199               | 201 | 175 | 178 | 98  | 141 | 6   | 138 | 35  | 0   | 0   | 1449  |  |
| 65        | 505      | 99                | 98  | 100 | 31  | 49  | 75  | 17  | 59  | 55  | 5   | 82  | 1175  |  |
| GROUP 4 ( | 30000 PP | M)                |     |     |     |     |     |     |     |     |     |     |       |  |
| 71        | 396      | 299               | 79  | 81  | 208 | 50  | 53  | 121 | 88  | 107 | 8   | 123 | 1613  |  |
| 72        | 406      | 238               | 114 | 128 | 68  | 73  | 22  | 162 | 111 | 0   | 0   | 68  | 1390  |  |
| 73        | 431      | 199               | 173 | 106 | 115 | 127 | 52  | 140 | 186 | 18  | 2   | 49  | 1598  |  |
| 74        | 358      | 176               | 107 | 93  | 125 | 132 | 23  | 28  | 65  | 7   | 0   | 0   | 1114  |  |
| 75        | 529      | 213               | 237 | 247 | 160 | 114 | 87  | 137 | 105 | 74  | 66  | 0   | 1969  |  |

# 2.5 BODY WEIGHTS (GRAM) MALES

|                         | TRE        | ATME       | ENT        |            |            |            |            |            |            |            |            |            |            |            |  |  |  |
|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|--|--|--|
| DAYS<br>WEEKS<br>ANIMAL | 1<br>1     | 8 2        | 15<br>3    | 22<br>4    | 29<br>5    | 36<br>6    | 43<br>7    | 50<br>8    | 57<br>9    | 64<br>10   | 71<br>11   | 78<br>12   | 85<br>13   | 91<br>13   |  |  |  |
| GROUP 1 (C              | CONTRO     | OL)        |            |            |            |            |            |            |            | ,          |            |            |            |            |  |  |  |
| 1                       |            | 183        | 218        | 234        | 253        | 273        | 282        | 295        | 293        | 300        | 302        | 313        | 323        | 329        |  |  |  |
| 2                       | 169        | 219        | 258        | 284        | 313        | 333        | 353        | 373        | 386        | 399        | 404        | 416        | 421        | 423        |  |  |  |
| 3                       | 173        | 221        | 255        | 279        | 301        | 320        | 335        | 347        | 361        | 372        | 378        | 389        | 394        | 394        |  |  |  |
| 4                       | 146        | 186        | 209        | 233        | 240        | 260        | 269        |            | 292        | 311        | 317        | 334        | 341        | 348        |  |  |  |
| 5                       | 159        | 210        | 242        | 268        | 286        | 307        | 317        | 331        | 342        | 351        | 353        | 368        | 377        | 376        |  |  |  |
| 6                       | 166        | 207        | 236        | 257        | 274        | 293        | 306        | 320        | 328        | 338        | 346        | 359        | 361        | 366        |  |  |  |
| 7                       | 152        | 202        | 242        | 262        |            | 299        | 310        | 317        | 322        | 334        | 344        | 351        | 353        | 352        |  |  |  |
| 8                       | 171        | 217        | 247        | 272        | 303        | 319        | 334        | 350        | 358        | 366        | 371        | 380        | 383<br>370 | 384<br>370 |  |  |  |
| 9                       | 166        | 208        | 239        | 264        | 282        | 306        | 319        | 334        | 344        | 354        | 361        | 370        |            | 385        |  |  |  |
| 10                      | 159        | 208        | 246        | 271        | 295        | 312        | 323        | 334        | 348        | 354        | 369        | 378        | 382        | 363        |  |  |  |
| GROUP 2 (3              |            | •          |            |            |            |            |            |            | •          | 00-        | 00-        | 00         | 050        | 050        |  |  |  |
| 11                      |            | 196        |            | 254        | 273        | 288        | 299        | 314        | 322        |            | 337        | 348        | 352        | 352        |  |  |  |
| 12                      | 161        |            | 255        | 291        | 320        | 344        | 362        | 384        | 400        | 413        | 423        | 432        | 439        | 438        |  |  |  |
| 13                      | 171        | 220        | 262        | 296        | 320        | 343        | 358        | 377        | 391        | 409        | 414        | 426        | 426        | 425        |  |  |  |
| 14                      | 140        | 171        | 199        | 222        | 234        | 257        | 273        |            | 297        | 304        | 308        | 319        | 322<br>378 | 325<br>380 |  |  |  |
| 15                      | 163        | 216        | 248        | 280        | 300        | 324        | 331        | 351        | 359        | 372        | 375<br>384 | 379<br>394 | 404        | 408        |  |  |  |
| 16                      | 153        |            | 250        | 281        | 303        | 327        | 336        | 353<br>301 | 362<br>310 | 377<br>318 | 324        | 334        | 339        | 347        |  |  |  |
| 17                      | 150        | 182        | 213        | 276        | 257<br>284 | 276<br>305 | 287<br>313 | 327        |            | 350        | 358        | 367        | 374        | 375        |  |  |  |
| 18                      | 154        | 201        | 240<br>246 | 263<br>269 | 289        |            | 321        | 340        | 342        | 354        | 362        | 372        | 376        | 381        |  |  |  |
| 19<br>20                | 164<br>163 | 208<br>212 |            |            |            | 318        |            | 343        |            | 361        | 368        | 377        |            | 387        |  |  |  |
|                         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |  |  |  |
| GROUP 3 (1              |            |            | 000        | 040        | 050        | 075        | 207        | 207        | 204        | 247        | 224        | 222        | 227        | 341        |  |  |  |
| 21                      |            |            | 228        |            | 259        | 275        | 287        | 297        | 304        |            | 321        | 333        | 337<br>432 | 437        |  |  |  |
| 22                      | 162        |            | 256        | 288        | 317        | 342        | 363        | 379<br>350 | 390<br>361 | 404<br>376 | 414<br>375 | 425<br>390 | 385        | 381        |  |  |  |
| 23                      | 158        | 208        | 242        | 269<br>261 | 293<br>279 | 316<br>297 | 331<br>310 | 323        | 331        | 339        | 343        | 351        | 356        | 357        |  |  |  |
| 24<br>25                | 161<br>166 | 204<br>221 | 238        | 309        | 339        | 361        | 384        | 406        | 415        | 433        | 443        | 455        | 457        | 459        |  |  |  |
| 26                      | 166<br>155 | 199        | 242        | 278        | 299        | 323        | 339        | 354        | 365        | 371        | 380        | 389        | 398        | 402        |  |  |  |
| 27                      | 161        | 211        | 252        |            | 300        | 323        | 335        | 351        | 363        | 376        | 381        | 394        | 403        | 403        |  |  |  |
| 28                      | 156        | 204        | 232        | 259        | 274        | 292        | 303        |            | 317        | 330        | 338        | 344        | 354        | 357        |  |  |  |
| 29                      | 162        | 207        | 236        | 255        | 276        | 298        | 303        |            | 326        | 335        | 340        | 348        | 350        | 352        |  |  |  |
| 30                      |            | 196        |            |            |            |            |            |            |            |            |            | 362        | 367        | 368        |  |  |  |
| CPOUR 4 /2              | 0000 0     | DM)        |            |            |            |            |            |            |            |            |            |            |            |            |  |  |  |
| <b>GROUP 4 (3</b> 31    |            | 199        | 224        | 239        | 254        | 272        | 284        | 294        | 302        | 313        | 319        | 330        | 336        | 335        |  |  |  |
| 32                      |            |            | 244        | 268        | 291        | 313        | 323        | 338        | 344        | 357        | 354        | 369        | 370        | 375        |  |  |  |
| 33                      | 156        | 204        | 243        | 272        | 296        | 315        | 326        | 341        | 345        | 354        | 363        | 371        | 378        | 383        |  |  |  |
| 34                      | 163        | 202        | 231        | 253        | 275        | 285        | 300        |            | 319        | 333        | 335        | 347        | 348        | 354        |  |  |  |
| 35                      | 140        | 176        | 210        | 230        | 249        | 269        | 274        |            | 298        | 307        | 310        | 312        | 323        | 326        |  |  |  |
| 36                      | 165        | 213        | 252        | 282        | 308        | 327        | 339        | 350        | 359        | 375        | 380        | 386        | 395        | 397        |  |  |  |
| 37                      | 139        | 179        | 211        | 234        | 252        | 268        | 280        | 291        | 299        | 308        | 311        | 319        | 324        | 330        |  |  |  |
| 38                      | 157        | 210        | 264        | 299        | 333        | 359        | 378        | 402        | 412        | 421        | 433        | 442        | 450        | 459        |  |  |  |
| 39                      | 159        | 207        | 237        | 255        | 269        | 282        | 295        | 305        | 315        | 320        | 326        | 335        | 341        | 342        |  |  |  |
| 40                      | 162        | 212        | 252        | 280        | 304        | 326        | 347        | 365        | 380        | 393        | 406        | 419        | 423        | 432        |  |  |  |
|                         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |  |  |  |

# 2.5 BODY WEIGHTS (GRAM) FEMALES

|                         | TRE    | ATME   | ENT     |         |         |         |         |         |         |          |          |             |          |          |  |  |  |
|-------------------------|--------|--------|---------|---------|---------|---------|---------|---------|---------|----------|----------|-------------|----------|----------|--|--|--|
| DAYS<br>WEEKS<br>ANIMAL | 1<br>1 | 8<br>2 | 15<br>3 | 22<br>4 | 29<br>5 | 36<br>6 | 43<br>7 | 50<br>8 | 57<br>9 | 64<br>10 | 71<br>11 | 78<br>12    | 85<br>13 | 91<br>13 |  |  |  |
| GROUP 1 (C              | ONTRO  | DL)    |         |         |         |         |         |         |         |          |          |             |          |          |  |  |  |
| 41                      | 136    | 159    | 167     | 182     | 199     | 207     | 209     | 229     | 233     | 236      | 233      | 249         | 246      | 239      |  |  |  |
| 42                      | 137    | 166    | 179     | 183     | 204     | 217     | 222     | 223     | 229     | 235      | 237      | 235         | 246      | 248      |  |  |  |
| 43                      | 135    | 161    | 180     | 190     | 199     | 211     | 218     | 226     | 225     | 236      | 242      | 245         | 245      | 253      |  |  |  |
| 44                      | 124    | 156    | 173     | 181     | 199     | 210     | 213     | 217     | 227     | 228      | 229      | 225         | 234      | 233      |  |  |  |
| 45                      | 131    | 159    | 179     | 190     | 197     | 215     | 220     | 225     | 222     | 230      | 237      | 239         | 234      | 243      |  |  |  |
| 46                      | 130    | 154    | 166     | 185     | 204     | 209     | 213     | 228     | 232     | 234      | 233      | 246         | 249      | 245      |  |  |  |
| 47                      | 138    | 155    | 181     | 197     | 212     | 214     | 235     | 247     | 252     | 247      | 259      | 268         | 267      | 270      |  |  |  |
| 48                      | 129    | 142    | 153     | 167     | 183     | 189     | 189     | 201     |         | 207      |          | 213         | 216      | 211      |  |  |  |
| 49                      | 137    | 166    | 184     | 198     | 222     | 230     | 235     | 236     | 252     | 257      | 258      | 260         | 267      | 268      |  |  |  |
| 50                      | 121    | 149    | 163     | 172     | 183     | 191     | 198     | 203     | 205     | 209      | 214      | 221         | 220      | 227      |  |  |  |
|                         |        |        |         |         |         |         |         |         |         |          |          |             |          |          |  |  |  |
| GROUP 2 (3              |        | •      | 400     | 40=     | 001     | 000     | 000     | 000     | 004     | 250      | 247      | 040         | 242      | 252      |  |  |  |
| 51                      |        | 170    |         |         | 204     |         |         |         | 234     |          |          |             | 243      | 252      |  |  |  |
| 52                      | 134    |        | 176     | 193     | 208     |         |         |         | 235     |          | 237      |             | 250      | 250      |  |  |  |
| 53                      | 119    | 145    | 163     | 173     | 181     |         |         |         | 208     |          |          |             | 217      | 226      |  |  |  |
| 54                      | 133    | 158    | 175     | 186     |         | 201     |         |         | 211     |          |          |             | 220      | 227      |  |  |  |
| 55                      | 124    | 150    | 168     | 184     | 186     |         |         |         | 214     |          |          | 234         | 230      | 240      |  |  |  |
| 56                      | 135    | 160    | 174     | 188     | 194     |         |         |         | 226     |          |          | 238         | 239      | 245      |  |  |  |
| 57                      | 135    | 158    | 171     | 175     | 195     |         |         |         | 235     |          |          | 237         | 245      | 247      |  |  |  |
| 58                      | 125    | 157    | 177     | 188     | 191     |         |         |         | 229     |          |          | 249         | 240      | 257      |  |  |  |
| 59                      | 128    | 153    | 170     |         |         |         |         |         | 217     |          |          |             |          | 237      |  |  |  |
| 60                      | 135    | 159    | 173     | 183     | 201     | 212     | 219     | 225     | 232     | 231      | 232      | 234         | 239      | 243      |  |  |  |
| GROUP 3 (1              | 0000 P | PM)    |         |         |         |         |         |         |         |          |          |             |          |          |  |  |  |
| 61                      |        | 157    | 164     | 169     | 181     | 188     | 190     | 194     | 199     | 206      | 205      | 206         | 217      | 215      |  |  |  |
| 62                      | 125    | 146    | 159     | 173     | 187     | 195     | 195     | 211     | 212     | 216      | 214      | 219         | 228      | 220      |  |  |  |
| 63                      | 135    | 168    | 182     | 194     | 201     |         |         |         | 218     |          |          | 241         | 235      | 243      |  |  |  |
| 64                      | 134    | 150    | 180     | 194     |         |         |         |         | 229     |          |          |             |          | 247      |  |  |  |
| 65                      | 124    | 152    | 166     | 181     |         |         |         |         | 205     |          |          |             | 221      | 232      |  |  |  |
| 66                      | 134    | 157    | 172     | 185     |         |         |         |         | 215     |          |          |             | 229      | 243      |  |  |  |
| 67                      | 126    | 153    | 173     | 187     | 190     |         |         |         | 218     |          |          | 239         | 237      | 245      |  |  |  |
| 68                      | 141    | 164    | 175     | 182     |         |         |         |         | 228     |          |          | 237         | 244      | 247      |  |  |  |
| 69                      | 129    | 148    | 168     |         |         |         |         |         | 208     |          |          |             |          | 224      |  |  |  |
| 70                      |        | 165    | 178     |         |         |         |         |         | 241     |          |          |             |          | 250      |  |  |  |
| ODOUR 4 (C              | 0000   | D14'   |         |         |         |         |         |         |         |          |          |             |          |          |  |  |  |
| <b>GROUP 4 (3</b> 71    | 137    | ,      | 178     | 175     | 107     | 20⊿     | 200     | 212     | 221     | 223      | 224      | 215         | 224      | 230      |  |  |  |
| 71<br>72                | 128    | 152    | 168     | 181     | 194     |         |         |         | 209     |          |          |             | 222      | 226      |  |  |  |
| 73                      | 138    | 161    | 168     | 196     |         |         |         |         | 242     |          |          | 257         | 259      | 247      |  |  |  |
|                         |        |        |         | 196     | 210     |         |         |         | 258     |          |          | 255         | 255      | 257      |  |  |  |
| 74<br>75                | 145    | 168    | 179     |         |         |         |         |         | 224     |          |          | 236         | 240      | 235      |  |  |  |
| 75<br>76                | 133    | 150    | 160     | 182     | 194     | 199     | 194     |         | 204     |          |          | 207         | 216      | 218      |  |  |  |
| 76<br>77                | 130    | 152    | 158     | 166     | 176     |         |         | 225     | 204     | 223      | 222      | 230         | 235      | 226      |  |  |  |
| 77<br>70                | 138    | 161    | 171     | 185     | 200     | 204     |         |         | 245     |          |          | 253         | 264      | 262      |  |  |  |
| 78<br>70                | 144    | 170    | 184     | 191     | 218     |         |         |         |         |          |          |             |          |          |  |  |  |
| 79                      | 134    | 158    | 178     | 191     |         |         |         |         |         |          |          |             | 243      |          |  |  |  |
| 80                      | 123    | 141    | 151     | 107     | 1/4     | 182     | 103     | 190     | ∠00     | 200      | 200      | <b>4</b> 11 | 218      | 201      |  |  |  |
|                         |        |        |         |         |         |         |         |         |         |          |          |             |          |          |  |  |  |

# 2.6 BODY WEIGHT GAIN (%) MALES

|                         | TRI     | EATME    | ENT      |          |          |           |            |            |            |            |            |            |            |            |  |  |
|-------------------------|---------|----------|----------|----------|----------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|--|--|
| DAYS<br>WEEKS<br>ANIMAL | 1       | 8<br>2   | 15<br>3  | 22<br>4  | 29<br>5  | 36<br>6   | 43<br>7    | 50<br>8    | 57<br>9    | 64<br>10   | 71<br>11   | 78<br>12   | 85<br>13   | 91<br>13   |  |  |
| GROUP 1 (0              | CONTR   | OL)      |          |          |          |           |            |            |            |            |            |            |            |            |  |  |
| 1                       | 0       | 30       | 55       | 66       | 79       | 94        | 100        | 109        | 108        | 113        | 114        | 122        | 129        | 133        |  |  |
| 2                       | 0       | 30       | 53       | 68       | 85       | 97        | 109        | 121<br>101 | 128        | 136<br>115 | 139<br>118 | 146<br>125 | 149<br>128 | 150<br>128 |  |  |
| 3                       | 0       | 28       | 47       | 61       | 74<br>64 | 85<br>78  | 94<br>84   | 96         | 109<br>100 | 113        | 117        | 129        | 134        | 138        |  |  |
| 4                       | 0<br>0  | 27<br>32 | 43<br>52 | 60<br>69 | 64<br>80 | 93        | 99         | 108        | 115        | 121        | 122        | 131        | 137        | 136        |  |  |
| 5<br>6                  | 0       | 25       | 42       | 55       | 65       | 93<br>77  | 84         | 93         | 98         | 104        | 108        | 116        | 117        | 120        |  |  |
| 7                       | 0       | 33       | 59       | 72       | 86       | 97        | 104        | 109        | 112        | 120        | 126        | 131        | 132        | 132        |  |  |
| 8                       | 0       | 27       | 44       | 59       | 77       | 87        | 95         | 105        | 109        | 114        | 117        | 122        | 124        | 125        |  |  |
| 9                       | 0       | 25       | 44       | 59       | 70       | 84        | 92         | 101        | 107        | 113        | 117        | 123        | 123        | 123        |  |  |
| 10                      | Ö       | 31       | 55       | 70       | 86       | 96        | 103        | 110        | 119        | 123        | 132        | 138        | 140        | 142        |  |  |
| 10                      | Ü       | 0.       | 00       | , 0      | 00       |           |            |            |            |            |            |            |            |            |  |  |
| GROUP 2 (3              |         | ,        | 40       | 00       | 7.4      | 00        | 00         | 100        | 105        | 113        | 115        | 122        | 124        | 124        |  |  |
| 11                      | 0       | 25       | 46<br>50 | 62       | 74       | 83<br>114 | 90<br>125  | 100<br>139 | 105<br>148 | 157        | 115<br>163 | 168        | 173        | 172        |  |  |
| 12                      | 0       | 33       | 58       | 81<br>73 | 99<br>87 | 101       | 125<br>109 | 120        | 129        | 139        | 142        | 149        | 149        | 149        |  |  |
| 13<br>14                | 0<br>0  | 29<br>22 | 53<br>42 | 73<br>59 | 67       | 84        | 95         | 104        | 112        | 117        | 120        | 128        | 130        | 132        |  |  |
| 15                      | 0       | 33       | 42<br>52 | 72       | 84       | 99        | 103        | 115        | 120        | 128        | 130        | 133        | 132        | 133        |  |  |
| 16                      | 0       | 34       | 63       | 84       | 98       | 114       | 120        | 131        | 137        | 146        | 151        | 158        | 164        | 167        |  |  |
| 17                      | 0       | 21       | 42       | 84       | 71       | 84        | 91         | 101        | 107        | 112        | 116        | 123        | 126        | 131        |  |  |
| 18                      | Ö       | 31       | 56       | 71       | 84       | 98        | 103        | 112        | 119        | 127        | 132        | 138        | 143        | 144        |  |  |
| 19                      | ő       | 27       | 50       | 64       | 76       | 88        | 96         | 107        | 109        | 116        | 121        | 127        | 129        | 132        |  |  |
| 20                      | 0       | 30       | 55       | 43       | 82       | 95        | 101        | 110        | 115        | 121        | 126        | 131        | 134        | 137        |  |  |
| GROUP 3 (1              | 10000 🖪 | DM\      |          |          |          |           |            |            |            |            |            |            |            |            |  |  |
| 21                      | 0       | 29       | 49       | 59       | 69       | 80        | 88         | 94         | 99         | 107        | 110        | 118        | 120        | 123        |  |  |
| 22                      | 0       | 29       | 58       | 78       | 96       | 111       | 124        | 134        | 141        | 149        | 156        | 162        | 167        | 170        |  |  |
| 23                      | 0       | 32       | 53       | 70       | 85       | 100       | 109        | 122        | 128        | 138        | 137        | 147        | 144        | 141        |  |  |
| 24                      | ő       | 27       | 48       | 62       | 73       | 84        | 93         | 101        | 106        | 111        | 113        | 118        | 121        | 122        |  |  |
| 25                      | Ō       | 33       | 64       | 86       | 104      | 117       | 131        | 145        | 150        | 161        | 167        | 174        | 175        | 177        |  |  |
| 26                      | 0       | 28       | 56       | 79       | 93       | 108       | 119        | 128        | 135        | 139        | 145        | 151        | 157        | 159        |  |  |
| 27                      | 0       | 31       | 57       | 73       | 86       | 101       | 108        | 118        | 125        | 134        | 137        | 145        | 150        | 150        |  |  |
| 28                      | 0       | 31       | 53       | 66       | 76       | 87        | 94         | 101        | 103        | 112        | 117        | 121        | 127        | 129        |  |  |
| 29                      | 0       | 28       | 46       | 57       | 70       | 84        | 87         | 98         | 101        | 107        | 110        | 115        | 116        | 117        |  |  |
| 30                      | 0       | 25       | 48       | 64       | 77       | 90        | 97         | 108        | 113        | 123        | 124        | 131        | 134        | 134        |  |  |
| GROUP 4 (3              | 30000 P | PM)      |          |          |          |           |            |            |            |            |            |            |            |            |  |  |
| 31                      | 0       | 24       | 40       | 49       | 59       | 70        | 78         | 84         | 89         | 96         | 99         | 106        | 110        | 109        |  |  |
| 32                      | 0       | 28       | 47       | 61       | 75       | 89        | 95         | 104        | 107        | 115        | 113        | 122        | 123        | 126        |  |  |
| 33                      | 0       | 31       | 56       | 74       | 90       | 102       | 109        | 119        | 121        | 127        | 133        | 138        | 142        | 146        |  |  |
| 34                      | 0       | 24       | 42       | 55       | 69       | 75        | 84         | 93         | 96         | 104        | 106        | 113        | 113        | 117        |  |  |
| 35                      | 0       | 26       | 50       | 64       | 78       | 92        | 96         | 107        | 113        | 119        | 121        | 123        | 131        | 133        |  |  |
| 36                      | 0       | 29       | 53       | 71       | 87       | 98        | 105        | 112        | 118        | 127        | 130        | 134<br>129 | 139<br>133 | 141<br>137 |  |  |
| 37                      | 0       | 29       | 52       | 68       | 81       | 93        | 101        | 109        | 115        | 122        | 124<br>176 | 182        | 133        | 192        |  |  |
| 38                      | 0       | 34       | 68<br>40 | 90       | 112      | 129<br>77 | 141<br>86  | 156<br>92  | 162<br>98  | 168<br>101 | 105        | 111        | 114        | 115        |  |  |
| 39                      | 0<br>0  | 30       | 49<br>56 | 60<br>73 | 69<br>88 | 101       | 114        | 125        | 135        | 143        | 151        | 159        | 161        | 167        |  |  |
| 40                      | U       | 31       | 56       | 73       | 00       | 101       | 114        | 120        | 100        | 173        | 131        | 100        | 101        | 101        |  |  |

# 2.6 BODY WEIGHT GAIN (%) FEMALES

|                         | TRE     | EATME | ENT     |         |         |         |          |          |          |          |           |          |          |          |
|-------------------------|---------|-------|---------|---------|---------|---------|----------|----------|----------|----------|-----------|----------|----------|----------|
| DAYS<br>WEEKS<br>ANIMAL | 1       | 8 2   | 15<br>3 | 22<br>4 | 29<br>5 | 36<br>6 | 43<br>7  | 50<br>8  | 57<br>9  | 64<br>10 | 71<br>11  | 78<br>12 | 85<br>13 | 91<br>13 |
| GROUP 1 (0              | CONTR   | OL)   |         |         |         |         |          |          |          |          |           |          |          |          |
| 41                      | 0       | 17    | 23      | 34      | 46      | 52      | 54       | 68       | 71       | 74       | 71        | 83       | 81       | 76       |
| 42                      | 0       | 21    | 31      | 34      | 49      | 58      | 62       | 63       | 67       | 72       | 73        | 72       | 80       | 81       |
| 43                      | 0       | 19    | 33      | 41      | 47      | 56      | 61       | 67       | 67       | 75       | 79        | 81       | 81       | 87       |
| 44                      | 0       | 26    | 40      | 46      | 60      | 69      | 72       | 75       | 83       | 84       | 85        | 81       | 89       | 88       |
| 45                      | 0       | 21    | 37      | 45      | 50      | 64      | 68       | 72       | 69       | 76       | 81        | 82       | 79       | 85       |
| 46                      | 0       | 18    | 28      | 42      | 57      | 61      | 64       | 75       | 78       | 80       | 79        | 89       | 92       | 88       |
| 47                      | Ö       | 12    | 31      | 43      | 54      | 55      | 70       | 79       | 83       | 79       | 88        | 94       | 93       | 96       |
| 48                      | Ö       | 10    | 19      | 29      | 42      | 47      | 47       | 56       | 61       | 60       | 58        | 65       | 67       | 64       |
| 49                      | 0       | 21    | 34      | 45      | 62      | 68      | 72       | 72       | 84       | 88       | 88        | 90       | 95       | 96       |
| 50                      | 0       | 23    | 35      | 42      | 51      | 58      | 64       | 68       | 69       | 73       | 77        | 83       | 82       | 88       |
| 50                      | U       | 23    | 55      | 74      | J 1     | 50      | J-1      | 50       | 50       | . 0      |           |          | J_       |          |
| GROUP 2 (3              | 3000 PF |       |         |         |         |         |          |          |          |          |           |          |          |          |
| 51                      | 0       | 23    | 35      | 43      | 48      | 61      | 66       | 69       | 70       | 81       | 79        | 80       | 76       | 83       |
| 52                      | 0       | 18    | 31      | 44      | 55      | 62      | 63       | 72       | 75       | 80       | 77        | 84       | 87       | 87       |
| 53                      | 0       | 22    | 37      | 45      | 52      | 65      | 72       | 77       | 75       | 84       | 85        | 86       | 82       | 90       |
| 54                      | Ö       | 19    | 32      | 40      | 43      | 51      | 53       | 61       | 59       | 65       | 65        | 69       | 65       | 71       |
| 55                      | Ö       | 21    | 35      | 48      | 50      | 64      | 68       | 74       | 73       | 82       | 84        | 89       | 85       | 94       |
| 56                      | Ö       | 19    | 29      | 39      | 44      | 54      | 61       | 66       | 67       | 71       | 74        | 76       | 77       | 81       |
| 57                      | 0       | 17    | 27      | 30      | 44      | 56      | 59       | 67       | 74       | 73       | 74        | 76       | 81       | 83       |
| 58                      | 0       | 26    | 42      | 50      | 53      | 73      | 82       | 87       | 83       | 94       | 94        | 99       | 92       | 106      |
| 59                      | 0       | 20    | 33      | 42      | 48      | 60      | 67       | 75       | 70       | 79       | 81        | 84       | 79       | 85       |
| 60                      | 0       | 18    | 28      | 36      | 49      | 57      | 62       | 67       | 72       | 71       | 72        | 73       | 77       | 80       |
| GPOUR 2 /               | 10000 0 | DM/   |         |         |         |         |          |          |          |          |           |          |          |          |
| GROUP 3 (1              |         |       | 20      | 23      | 32      | 37      | 39       | 42       | 45       | 50       | 50        | 50       | 58       | 57       |
| 61                      | 0       | 15    | 20      |         |         |         |          | 42<br>69 | 70       | 73       | 71        | 75       | 82       | 76       |
| 62                      | 0       | 17    | 27      | 38      | 50      | 56      | 56       |          | 70<br>61 |          | 7 1<br>74 | 79       | o∠<br>74 | 80       |
| 63                      | 0       | 24    | 35      | 44      | 49      | 59      | 62       | 64       |          | 72<br>67 |           |          |          |          |
| 64                      | 0       | 12    | 34      | 45      | 51      | 51      | 63       | 71       | 71       | 67       | 75        | 81       | 81       | 84       |
| 65                      | 0       | 23    | 34      | 46      | 51      | 59      | 63       | 69       | 65       | 71       | 76        | 78       | 78       | 87       |
| 66                      | 0       | 17    | 28      | 38      | 42      | 55      | 61       | 65       | 60       | 70       | 73        | 77       | 71       | 81       |
| 67                      | 0       | 21    | 37      | 48      | 51      | 64      | 74       | 80       | 73       | 83       | 89        | 90       | 88       | 94       |
| 68                      | 0       | 16    | 24      | 29      | 43      | 49      | 57       | 58       | 62       | 68       | 69        | 68       | 73       | 75       |
| 69                      | 0       | 15    | 30      | 31      | 42      | 53      | 57       | 59       | 61       | 66       | 67        | 66       | 68       | 74       |
| 70                      | 0       | 16    | 25      | 37      | 50      | 55      | 58       | 66       | 70       | 74       | 70        | 77       | 78       | 76       |
| GROUP 4 (3              | 30000 P | PM)   |         |         |         |         |          |          |          |          |           |          |          |          |
| 71                      | 0       | 18    | 30      | 28      | 44      | 49      | 53       | 55       | 61       | 63       | 64        | 57       | 64       | 68       |
| 72                      | 0       | 19    | 31      | 41      | 52      | 57      | 61       | 66       | 63       | 70       | 73        | 75       | 73       | 77       |
| 73                      | 0       | 17    | 22      | 42      | 52      | 59      | 57       | 71       | 75       | 78       | 74        | 86       | 88       | 79       |
| 73<br>74                | 0       | 16    | 23      | 35      | 46      | 51      | 55       | 68       | 78       | 70       | 72        | 76       | 76       | 77       |
|                         | 0       |       | 20      | 37      | 46      | 50      | 52       | 64       | 68       | 71       | 69        | 77       | 80       | 77       |
| 75<br>76                |         | 13    |         |         |         |         | 52<br>49 |          | 57       | 63       | 62        | 59       | 66       | 68       |
| 76                      | 0       | 17    | 22      | 28      | 35      | 48      |          | 53       |          |          | 62<br>61  | 59<br>67 | 70       | 64       |
| 77                      | 0       | 17    | 24      | 34      | 45      | 48      | 53       | 63       | 60       | 62       |           |          |          |          |
| 78                      | 0       | 18    | 28      | 33      | 51      | 57      | 62       | 63       | 70       | 74       | 78<br>70  | 76       | 83       | 82       |
| 79                      | 0       | 18    | 33      | 43      | 43      | 51      | 64       | 74       | 74       | 75       | 78        | 83       | 81       | 81       |
| 80                      | 0       | 15    | 23      | 36      | 41      | 48      | 49       | 61       | 63       | 67       | 63        | 72       | 77       | 68       |

Betawell L-Arabinose APPENDIX 2

# 2.7 FOOD CONSUMPTION (G/ANIMAL/DAY) MALES

|                                | TREAT                         | MENT          |              |              |              |              |              |              |               |                |                |                |             |
|--------------------------------|-------------------------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|----------------|----------------|----------------|-------------|
| DAYS<br>WEEKS<br>CAGE          | 1-8<br>1-2                    | 8-15<br>2-3   | 15-22<br>3-4 | 22-29<br>4-5 | 29-36<br>5-6 | 36-43<br>6-7 | 43-50<br>7-8 | 50-57<br>8-9 | 57-64<br>9-10 | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13 | 85-91<br>13 |
| GROUP 1 (CC                    |                               |               |              |              |              |              |              |              |               |                |                |                |             |
| 1<br>2                         | 19<br>19                      | 22<br>22      | 20<br>21     | 21<br>22     | 20<br>21     | 21<br>22     | 23<br>23     | 22<br>22     | 21<br>21      | 21<br>23       | 21<br>23       | 21<br>21       | 22<br>23    |
| GROUP 2 (30                    | 00 PPM)                       |               |              |              |              |              |              |              |               |                |                |                |             |
| 3<br>4                         | 19<br>20                      | 22<br>23      | 22<br>23     | 23<br>23     | 22<br>22     | 23<br>22     | 24<br>22     | 23<br>23     | 23<br>22      | 23<br>22       | 22<br>24       | 23<br>23       | 23<br>24    |
| GROUP 3 (10                    | 000 PPM                       |               |              |              |              |              |              |              |               |                |                |                |             |
| 5<br>6                         | 20<br>21                      | 23<br>25      | 22<br>24     | 23<br>24     | 23<br>24     | 24<br>25     | 25<br>28     | 25<br>27     | 23<br>25      | 24<br>25       | 23<br>26       | 22<br>24       | 25<br>27    |
| GROUP 4 (30                    | 000 PPM                       | )             |              |              |              |              |              |              |               |                |                |                |             |
| 7                              | 19<br>19                      | 20<br>23      | 20<br>23     | 21<br>23     | 21<br>23     | 23<br>24     | 25<br>25     | 23<br>25     | 23<br>24      | 22<br>23       | 23<br>23       | 23<br>23       | 24<br>24    |
| FEMALES                        | TREAT                         | MENT          |              |              |              |              |              |              |               |                |                |                |             |
| DAYS<br>WEEKS<br>CAGE          | 1-8<br>1-2                    | 8-15<br>2-3   | 15-22<br>3-4 | 22-29<br>4-5 | 29-36<br>5-6 | 36-43<br>6-7 | 43-50<br>7-8 | 50-57<br>8-9 | 57-64<br>9-10 | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13 | 85-91<br>13 |
| GROUP 1 (CO                    |                               |               |              |              |              |              |              |              |               |                |                |                |             |
| 9<br>10                        | 16<br>15                      | 17<br>17      | 16<br>16     | 19<br>18     | 17<br>16     | 18<br>18     | 18<br>18     | 19<br>17     | 18<br>17      | 18<br>17       | 20<br>18       | 17<br>17       | 19<br>17    |
| <b>GROUP 2 (30</b>             | <b>00 PPM)</b><br>15          | 17            | 16           | 17           | 16           | 18           | 19           | 17           | 17            | 18             | 18             | 17             | 19          |
| 12                             | 15                            | 17            | 16           | 18           | 18           | 18           | 21           | 19           | 18            | 18             | 19             | 20             | 20          |
| <b>GROUP 3 (10</b><br>13<br>14 | 0 <b>00 PPM</b> )<br>15<br>16 | )<br>17<br>17 | 16<br>17     | 18<br>17     | 16<br>18     | 18<br>19     | 21<br>19     | 19<br>21     | 17<br>20      | 18<br>19       | 18<br>20       | 17<br>18       | 18<br>21    |
| <b>GROUP 4 (30</b><br>15<br>16 | 000 PPM)<br>15<br>15          | )<br>18<br>17 | 17<br>16     | 18<br>18     | 17<br>17     | 19<br>18     | 19<br>20     | 21<br>20     | 18<br>18      | 19<br>19       | 21<br>18       | 19<br>18       | 20<br>17    |

Betawell L-Arabinose APPENDIX 2

# 2.8 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) MALES

|                       | TREAT         | MENT          |              |              |              |              |              |              |               |                |                |                |             |
|-----------------------|---------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|----------------|----------------|----------------|-------------|
| DAYS<br>WEEKS<br>CAGE | 1-8<br>1-2    | 8-15<br>2-3   | 15-22<br>3-4 | 22-29<br>4-5 | 29-36<br>5-6 | 36-43<br>6-7 | 43-50<br>7-8 | 50-57<br>8-9 | 57-64<br>9-10 | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13 | 85-91<br>13 |
| GROUP 1 (C            | ONTROL)<br>94 | 91            | 78           | 76           | 69           | 67           | 71           | 64           | 61            | 60             | 58             | 57             | 58          |
| 2                     | 93            | 91            | 80           | 75<br>75     | 67           | 69           | 68           | 64           | 61            | 65             | 62             | 57<br>57       | 62          |
| GROUP 2 (3            | ,             |               |              |              |              |              |              |              |               |                |                |                |             |
| 3<br>4                | 95<br>98      | 91<br>96      | 82<br>86     | 79<br>81     | 72<br>71     | 71<br>70     | 71<br>67     | 65<br>66     | 63<br>62      | 61<br>62       | 58<br>64       | 60<br>60       | 61<br>62    |
| GROUP 3 (1            | 0000 PPM      | )             |              |              |              |              |              |              |               |                |                |                |             |
| 5                     | 95<br>102     | 93<br>103     | 82<br>89     | 78<br>82     | 72<br>77     | 72<br>78     | 72<br>83     | 69<br>79     | 63<br>71      | 62<br>70       | 59<br>70       | 57<br>65       | 64<br>71    |
| GROUP 4 (3            |               |               |              |              |              | . •          |              | . •          |               | . •            | . •            | 20             | • •         |
| 7<br>8                | 94<br>95      | ,<br>86<br>93 | 79<br>84     | 78<br>80     | 71<br>73     | 76<br>74     | 80<br>74     | 71<br>70     | 70<br>67      | 67<br>63       | 67<br>61       | 64<br>60       | 68<br>60    |
| 0                     | 90            | 93            | 04           | 00           | 13           | 74           | 74           | 70           | 07            | 03             | 01             | 00             | 00          |
| FEMALES               |               |               |              |              |              |              |              |              |               |                |                |                |             |
|                       | TREAT         | MENT          |              |              |              |              |              |              |               |                |                |                |             |
| DAYS<br>WEEKS<br>CAGE | 1-8<br>1-2    | 8-15<br>2-3   | 15-22<br>3-4 | 22-29<br>4-5 | 29-36<br>5-6 | 36-43<br>6-7 | 43-50<br>7-8 | 50-57<br>8-9 | 57-64<br>9-10 | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13 | 85-91<br>13 |
| GROUP 1 (C            | ONTROL)       |               |              |              |              |              | ,            |              |               |                |                |                |             |
| 9                     | 102<br>100    | 96<br>100     | 88<br>88     | 93<br>89     | 81<br>79     | 85<br>82     | 82<br>79     | 85<br>76     | 77<br>73      | 78<br>73       | 82<br>73       | 71<br>70       | 76<br>68    |
| GROUP 2 (3            |               |               |              |              |              |              |              |              |               |                |                |                |             |
| 11<br>12              | 97<br>97      | 98<br>95      | 84<br>85     | 88<br>91     | 78<br>87     | 83<br>84     | 84<br>92     | 78<br>83     | 73<br>78      | 77<br>77       | 75<br>79       | 71<br>85       | 78<br>80    |
| GROUP 3 (1            | 0000 PPM      | )             |              |              |              |              |              |              |               |                |                |                |             |
| 13<br>14              | 95<br>99      | 99<br>100     | 87<br>90     | 92<br>89     | 82<br>84     | 86<br>88     | 98<br>87     | 87<br>93     | 80<br>88      | 80<br>83       | 78<br>85       | 74<br>77       | 80<br>88    |
| GROUP 4 (3            |               |               |              |              |              |              |              |              |               |                |                |                |             |
| 15<br>16              | 95            | 104           | 89           | 90           | 83<br>83     | 87           | 87           | 92           | 78<br>70      | 83             | 88             | 78<br>77       | 85<br>75    |
| ıσ                    | 97            | 101           | 88           | 93           | გვ           | 89           | 94           | 89           | 79            | 84             | 80             | 11             | 75          |

# 2.9 TEST ARTICLE INTAKE (MG SUBSTANCE/KG BODY WEIGHT/DAY) MALES

|  | TREAT   | MENT                       |               |               |               |               |               |               |                |                |                |                 |               |
|--|---|----------------------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|----------------|----------------|-----------------|---------------|
| DAYS<br>WEEKS<br>CAGE                              | 1-8<br>1-2  | 8-15<br>2-3                | 15-22<br>3-4  | 22-29<br>4-5  | 29-36<br>5-6  | 36-43<br>6-7  | 43-50<br>7-8  | 50-57<br>8-9  | 57-64<br>9-10  | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13  | 85-91<br>13   |
| <b>GROUP 1 (CC</b> 1 2                             | ONTROL)   | 0 0                        | 0 0           | 0 0           | 0 0           | 0 0           | 0             | 0             | 0 0            | 0 0            | 0 0            | 0 0             | 0 0           |
| <b>GROUP 2 (30</b> ) 3 4                           | <b>00 PPM)</b><br>284<br>295  | 273<br>288                 | 245<br>259    | 236<br>244    | 216<br>213    | 214<br>211    | 212<br>202    | 196<br>199    | 190<br>186     | 182<br>185     | 175<br>192     | 179<br>181      | 182<br>187    |
| <b>GROUP 3 (10</b> )<br>5<br>6                     | 948<br>1020   | 934<br>1028                | 819<br>888    | 776<br>824    | 722<br>768    | 717<br>780    | 718<br>834    | 687<br>795    | 627<br>710     | 625<br>696     | 594<br>700     | 566<br>650      | 635<br>711    |
| <b>GROUP 4 (30</b> )<br>7<br>8                     | 000 PPM<br>2815<br>2850   | 2586<br>2802               | 2357<br>2524  | 2349<br>2400  | 2116<br>2184  | 2272<br>2223  | 2398<br>2207  | 2124<br>2098  | 2099<br>1995   | 1996<br>1880   | 2008<br>1842   | 1924<br>1794    | 2036<br>1801  |
|  |   |                            |               |               |               |               |               |               |                |                |                |                 |               |
| FEMALES  | TDEAT   | N 4 5 N 1 7                |               |               |               |               |               |               |                |                |                |                 |               |
| DAYS<br>WEEKS                                      | TREAT<br>1-8<br>1-2   | MENT<br>8-15<br>2-3        | 15-22<br>3-4  | 22-29<br>4-5  | 29-36<br>5-6  | 36-43<br>6-7  | 43-50<br>7-8  | 50-57<br>8-9  | 57-64<br>9-10  | 64-71<br>10-11 | 71-78<br>11-12 | 78-85<br>12-13  | 85-91<br>13   |
| DAYS WEEKS CAGE GROUP 1 (CC                        | 1-8<br>1-2  | 8-15<br>2-3                |               |               |               |               |               |               |                |                |                |                 |               |
| DAYS WEEKS CAGE  GROUP 1 (CC 9 10  GROUP 2 (30) 11 | 1-8<br>1-2<br><b>DNTROL)</b><br>0<br>0                                | 8-15<br>2-3                | 0             | 0             | 5-6           | 6-7           | 7-8           | 8-9           | 9-10           | 0              | 11-12          | 0               | 0             |
| DAYS   | 1-8<br>1-2<br>DNTROL)<br>0<br>0<br>0<br>0<br>0<br>0PPM)<br>290<br>290 | 8-15<br>2-3<br>0<br>0<br>0 | 0<br>0<br>251 | 0<br>0<br>265 | 5-6<br>0<br>0 | 0<br>0<br>248 | 7-8<br>0<br>0 | 8-9<br>0<br>0 | 9-10<br>0<br>0 | 0<br>0<br>230  | 0<br>0<br>226  | 12-13<br>0<br>0 | 0<br>0<br>233 |

# 2.10 OPHTHALMOSCOPIC EXAMINATIONS MALES

### PRE-TEST

| ANIMAL              | EYES  | OBSERVATION                  |
|---------------------|-------|------------------------------|
| GROUP 1 (CONTROL)   |       |                              |
| 1 ` ´               | Both  | No Findings                  |
| 2                   | Both  | No Findings                  |
| 3                   | Both  | No Findings                  |
| 4                   | Both  | No Findings                  |
| 5                   | Both  | No Findings                  |
| 6                   | Both  | No Findings                  |
| 7                   | Both  | No Findings                  |
| 8                   | Both  | No Findings                  |
| 9                   | Both  | No Findings                  |
| 10                  | Both  | No Findings                  |
| GROUP 2 (3000 PPM)  |       |                              |
| 11                  | Both  | No Findings                  |
| 12                  | Both  | No Findings                  |
| 13                  | Both  | No Findings                  |
| 14                  | Both  | No Findings                  |
| 15                  | Both  | No Findings                  |
| 16                  | Both  | No Findings                  |
| 17                  | Both  | No Findings                  |
| 18                  | Both  | No Findings                  |
| 19                  | Both  | No Findings                  |
| 20                  | Both  | No Findings                  |
| GROUP 3 (10000 PPM) |       |                              |
| 21                  | Both  | No Findings                  |
| 22                  | Both  | No Findings                  |
| 23                  | Both  | No Findings                  |
| 24                  | Both  | No Findings                  |
| 25                  | Both  | No Findings                  |
| 26                  | Both  | No Findings                  |
| 27                  | Both  | No Findings                  |
| 28                  | Both  | Focal Corneal Edema          |
| 29                  | Both  | No Findings                  |
| 30                  | Left  | Focal Corneal Edema          |
| 30                  | Both  | Multifocal Corneal Opacities |
| GROUP 4 (30000 PPM) |       |                              |
| 31                  | Both  | No Findings                  |
| 32                  | Both  | No Findings                  |
| 33                  | Both  | No Findings                  |
| 34                  | Both  | No Findings                  |
| 35                  | Both  | No Findings                  |
| 36                  | Both  | No Findings                  |
| 37                  | Both  | No Findings                  |
| 38                  | Both  | No Findings                  |
| 39                  | Right | Multifocal Corneal Opacities |
| 40                  | Both  | No Findings                  |
| MALES               |       |                              |
| AT WEEK 13          |       |                              |
| ANIMAL              | EYES  | OBSERVATION                  |

| ANIMAL                       | EYES   | OBSERVATION   |
|------------------------------|--|---|
| GROUP 1 (CONTROL)  1 2 3 4 5 | Right<br>Both<br>Both<br>Left<br>Right<br>Both | Focal Corneal Opacity No Findings No Findings Focal Corneal Opacity Focal Corneal Opacity No Findings |

# 2.10 OPHTHALMOSCOPIC EXAMINATIONS MALES

| AT | W | ΈE | Κ | 13 |
|----|---|----|---|----|
|----|---|----|---|----|

| ANIMAL              | EYES  | OBSERVATION                              |
|---------------------|-------|--|
| GROUP 1 (CONTROL)   |       |  |
|                     | Both  | No Findings                              |
| 7                   |       | No Findings                              |
| 8                   | Right | Focal Corneal Opacity                    |
| 9                   | Right | Focal Corneal Opacity                    |
| 10                  | Both  | No Findings                              |
| GROUP 4 (30000 PPM) | Diale | Freed Command Constitu                   |
| 31                  | Right | Focal Corneal Opacity                    |
| 32                  | Both  | No Findings                              |
| 33                  | Both  | No Findings                              |
| 34                  | Both  | No Findings                              |
| 35                  | Left  | Focal Corneal Opacity                    |
| 36                  | Both  | No Findings                              |
| 37                  | Left  | Focal Corneal Opacity                    |
| 38                  | Both  | No Findings                              |
| 39                  | Both  | No Findings                              |
| 40                  | Right | Focal Corneal Opacity                    |
| FEMALES             |       |  |
| PRE-TEST            |       |  |
| ANIMAL              | EYES  | OBSERVATION                              |
| GROUP 1 (CONTROL)   |       |  |
| 41                  | Both  | No Findings                              |
| 42                  | Both  | No Findings                              |
| 43                  | Both  | No Findings                              |
| 44                  | Both  | No Findings                              |
| 45                  |       |  |
|                     | Both  | No Findings                              |
| 46                  | Both  | No Findings                              |
| 47                  | Both  | No Findings                              |
| 48                  | Both  | No Findings                              |
| 49                  | Both  | No Findings                              |
| 50                  | Both  | No Findings                              |
| GROUP 2 (3000 PPM)  |       |  |
| 51                  | Both  | No Findings                              |
| 52                  | Left  | Corneal Opacity                          |
| 53                  | Both  | No Findings                              |
| 54                  | Both  | No Findings                              |
| 55                  | Both  | No Findings                              |
| 56                  | Both  | No Findings                              |
| 57                  | Both  | No Findings                              |
| 58                  | Both  | No Findings                              |
| 59                  | Both  | No Findings                              |
| 60                  | Both  | No Findings                              |
| GROUP 3 (10000 PPM) |       |  |
| 61                  | Both  | No Findings                              |
| 62                  | Both  | No Findings                              |
| 63                  | Both  | No Findings                              |
| 64                  | Both  | No Findings No Findings                  |
| 65                  | Both  | No Findings<br>No Findings               |
|                     |       |  |
| 66                  | Both  | No Findings                              |
| 67                  | Both  | No Findings                              |
| 68                  | Both  | No Findings                              |
| 69                  | Left  | Corneal Opacity With Vascularization     |
| 69                  | Left  | Underlying Structures Cannot Be Examined |
| 70                  | Both  | No Findings                              |
|                     |       |  |

#### 2.10 OPHTHALMOSCOPIC EXAMINATIONS **FEMALES**

### PRE-TEST

| ANIMAL            | EYES      | OBSERVATION                |
|-------------------|-----------|----------------------------|
| GROUP 4 (30000 PI | PM)       |                            |
| 71                | ,<br>Both | No Findings                |
| 72                | Both      | No Findings                |
| 73                | Both      | No Findings                |
| 74                | Both      | Pinpoint Corneal Opacities |
| 75                | Both      | No Findings                |
| 76                | Both      | No Findings                |
| 77                | Both      | No Findings                |
| 78                | Both      | No Findings                |
| 79                | Both      | No Findings                |
| 80                | Both      | No Findings                |
| FEMALES           |           |                            |
| AT WEEK 13        |           |                            |
| ANIMAL            | EYES      | OBSERVATION                |
| GROUP 1 (CONTRO   | OL)       |                            |
| 41                | Both      | No Findings                |
| 42                | Right     | Focal Corneal Edema        |
| 42                | Right     | Focal Corneal Opacity      |
| 43                | Both      | No Findings                |
| 44                | Left      | Focal Corneal Opacity      |
| 45                | Both      | No Findings                |
| 46                | Both      | No Findings                |
| 47                | Both      | No Findings                |
| 48                | Left      | Focal Corneal Opacity      |
| 49                | Both      | No Findings                |
| 50                | Right     | Focal Corneal Opacity      |
| GROUP 4 (30000 PI |           | 5 10 10 1                  |
| 71                | Right     | Focal Corneal Opacity      |
| 72                | Both      | No Findings                |
| 73                | Both      | No Findings                |
| 74                | Left      | Focal Corneal Opacity      |
| 75                | Both      | No Findings                |
| 76                | Both      | No Findings                |
| 77                | Left      | Focal Corneal Edema        |
| 77                | Left      | Focal Corneal Opacity      |
| 78                | Both      | No Findings                |
| 79                | Both      | No Findings                |
| 80                | Both      | No Findings                |
|                   |           |                            |

### 2.11 HAEMATOLOGY MALES END OF TREATMENT

| ANIMAL     | WBC<br>10E9/L | Neutrophils<br>%WBC | Lymphocytes<br>%WBC | Monocytes<br>%WBC | Eosinophils<br>%WBC |  |
|------------|---------------|---------------------|---------------------|-------------------|---------------------|--|
| GROUP 1 (0 | CONTROL)      |                     |                     |                   |                     |  |
| 1          | 5.2           | 20.2                | 76.8                | 2.2               | 0.8                 |  |
| 2          | 8.0           | 15.1                | 82.0                | 1.7               | 1.1                 |  |
| 3          | 8.0           | 13.0                | 84.7                | 1.7               | 0.6                 |  |
| 1          | 6.1           | 33.1                | 64.6                | 1.3               | 1.0                 |  |
| 5          | 8.0           | 13.0                | 83.3                | 2.4               | 1.2                 |  |
| 3          | 8.3           | 13.7                | 83.6                | 1.4               | 1.2                 |  |
| 7          | 9.4           | 14.4                | 81.6                | 2.3               | 1.5                 |  |
| 3          | 9.9           | 13.0                | 85.3                | 1.0               | 0.6                 |  |
| 9          | 7.5           | 13.0                | 83.4                | 2.3               | 1.2                 |  |
| 10         | 8.9           | 19.0                | 77.3                | 2.7               | 0.9                 |  |
| 0          | 0.9           | 19.0                | 11.5                | 2.1               | 0.9                 |  |
| ROUP 2 (3  |               | 40.0                | <b></b> .           |                   |                     |  |
| 11         | 5.0           | 16.3                | 78.4                | 2.9               | 2.3                 |  |
| 12         | 6.2           | 16.5                | 79.7                | 2.1               | 1.6                 |  |
| 13         | 8.2           | 15.0                | 83.0                | 1.1               | 1.0                 |  |
| 14         | 6.7           | 11.3                | 84.9                | 1.6               | 2.1                 |  |
| 15         | 6.7           | 15.2                | 81.6                | 1.7               | 1.2                 |  |
| 16         | 7.5           | 18.2                | 78.8                | 1.7               | 1.2                 |  |
| 17         | 7.6           | 18.2                | 78.5                | 1.9               | 1.3                 |  |
| 18         | 7.1           | 11.5                | 84.8                | 2.0               | 1.7                 |  |
| 19         | 6.3           | 14.4                | 82.0                | 2.2               | 1.3                 |  |
| 20         | 8.7           | 19.2                | 78.2                | 1.4               | 1.1                 |  |
| GROUP 3 (1 | 10000 PPM)    |                     |                     |                   |                     |  |
| 21         | 7.5           | 15.7                | 81.2                | 1.5               | 1.4                 |  |
| 22         | 8.3           | 16.3                | 79.0                | 2.5               | 2.2                 |  |
| 23         | 8.4           | 17.9                | 76.8                | 3.7               | 1.5                 |  |
| 24         | 8.4           | 10.2                | 87.3                | 1.5               | 1.0                 |  |
| 25         | 7.1           | 14.7                | 81.6                | 1.6               | 1.9                 |  |
| 26         | 6.3           | 16.9                | 80.8                | 1.1               | 1.1                 |  |
| 27         |               |                     |                     |                   |                     |  |
| <u>2</u> 8 | 7.6           | 24.0                | 71.0                | 1.0               | 4.0                 |  |
| 20<br>29   | 8.6           | 21.0                | 74.3                | 2.5               | 2.1                 |  |
| 30         | 7.3           | 9.7                 | 88.2                | 1.3               | 0.8                 |  |
|            |               | 0.1                 | 00.2                | 1.0               | 0.0                 |  |
|            | 30000 PPM)    | 0.4.0               |                     |                   | . –                 |  |
| 31         | 8.0           | 21.0                | 74.9                | 2.3               | 1.7                 |  |
| 32         | 5.6           | 12.8                | 84.4                | 1.0               | 1.6                 |  |
| 33         | 7.5           | 14.4                | 82.3                | 1.3               | 1.9                 |  |
| 34         | 6.7           | 14.9                | 81.8                | 1.8               | 1.5                 |  |
| 35         | 5.9           | 18.2                | 78.8                | 1.7               | 1.3                 |  |
| 36         | 8.6           | 18.3                | 78.7                | 1.8               | 1.1                 |  |
| 37         | 7.5           | 17.0                | 79.8                | 1.6               | 1.4                 |  |
| 38         | 4.3           | 21.1                | 75.1                | 2.2               | 1.7                 |  |
| 39         | 9.4           | 13.7                | 82.3                | 2.4               | 1.5                 |  |
| 40         | 8.2           | 14.5                | 81.5                | 2.6               | 1.2                 |  |

### MALES END OF TREATMENT

| ANIMAL    | Basophils<br>%WBC | Red blood cells<br>10E12/L | Reticulocytes<br>%RBC | RDW<br>% | Haemoglobin<br>mmol/L |  |
|-----------|-------------------|----------------------------|-----------------------|----------|-----------------------|--|
| GROUP 1 ( | CONTROL)          |                            |                       |          |                       |  |
| 1         | 0.1               | 10.05                      | 2.3                   | 12.3     | 10.8                  |  |
| 2         | 0.1               | 9.03                       | 2.5                   | 12.7     | 9.8                   |  |
| 3         | 0.1               | 9.67                       | 1.9                   | 11.7     | 9.9                   |  |
| 4         | 0.0               | 8.41                       | 2.2                   | 11.8     | 9.0                   |  |
| 5         | 0.2               | 10.24                      | 2.0                   | 11.6     | 10.7                  |  |

000215

### 2.11 HAEMATOLOGY MALES END OF TREATMENT

| ANIMAL    | Basophils<br>%WBC | Red blood cells<br>10E12/L | Reticulocytes<br>%RBC | RDW<br>% | Haemoglobin<br>mmol/L |  |
|-----------|-------------------|----------------------------|-----------------------|----------|-----------------------|--|
| GROUP 1 ( | CONTROL)          |                            |                       |          |                       |  |
| 6         | 0.1               | 9.54                       | 2.5                   | 13.0     | 10.1                  |  |
| 7         | 0.1               | 9.67                       | 1.6                   | 11.9     | 10.1                  |  |
| 8         | 0.1               | 9.43                       | 1.7                   | 12.2     | 9.6                   |  |
| 9         | 0.0               | 8.99                       | 2.4                   | 13.2     | 9.8                   |  |
| 10        | 0.1               | 9.15                       | 2.4                   | 12.9     | 9.6                   |  |
| GROUP 2 ( | ROOD PPM)         |                            |                       |          |                       |  |
| 11        | 0.1               | 9.23                       | 2.1                   | 12.8     | 9.9                   |  |
| 12        | 0.2               | 9.18                       | 1.9                   | 12.6     | 9.7                   |  |
| 13        | 0.0               | 8.96                       | 2.2                   | 12.9     | 9.9                   |  |
| 14        | 0.0               | 8.19                       | 2.4                   | 13.8     | 9.3                   |  |
| 15        | 0.1               | 9.18                       | 2.0                   | 12.2     | 9.5                   |  |
| 16        | 0.1               | 9.16                       | 2.1                   | 12.2     | 9.6                   |  |
| 17        | 0.1               | 8.93                       | 2.5                   | 12.6     | 9.3                   |  |
| 18        | 0.2               | 8.98                       | 2.0                   | 11.6     | 9.7                   |  |
| 19        | 0.1               | 9.03                       | 1.9                   | 13.1     | 9.7                   |  |
|           |                   |                            |                       |          |                       |  |
| 20        | 0.1               | 9.66                       | 2.2                   | 12.7     | 9.8                   |  |
| GROUP 3 ( |                   |                            |                       |          |                       |  |
| 21        | 0.2               | 8.88                       | 2.1                   | 11.9     | 9.7                   |  |
| 22        | 0.1               | 9.57                       | 2.1                   | 11.9     | 9.9                   |  |
| 23        | 0.1               | 9.71                       | 1.9                   | 11.7     | 9.8                   |  |
| 24        | 0.1               | 9.13                       | 2.2                   | 11.6     | 9.6                   |  |
| 25        | 0.1               | 9.61                       | 2.3                   | 12.2     | 9.6                   |  |
| 26        | 0.1               | 8.96                       | 2.3                   | 12.2     | 9.2                   |  |
| 27        |                   |                            |                       |          |                       |  |
| 28        | 0.0               | 9.20                       | 2.1                   | 12.6     | 9.4                   |  |
| 29        | 0.1               | 8.96                       | 2.4                   | 12.5     | 9.4                   |  |
| 30        | 0.0               | 8.82                       | 2.1                   | 11.4     | 9.4                   |  |
| GROUP 4 ( | 80000 PPM)        |                            |                       |          |                       |  |
| 31        | 0.1               | 9.65                       | 2.4                   | 13.4     | 10.0                  |  |
| 32        | 0.2               | 9.93                       | 2.1                   | 11.8     | 10.3                  |  |
| 33        | 0.1               | 9.66                       | 1.9                   | 12.6     | 9.9                   |  |
| 34        | 0.1               | 9.39                       | 2.1                   | 12.3     | 9.7                   |  |
| 35        | 0.1               | 9.68                       | 2.2                   | 12.1     | 10.1                  |  |
| 36        | 0.2               | 9.82                       | 1.9                   | 12.7     | 10.2                  |  |
| 37        | 0.1               | 9.43                       | 2.0                   | 11.9     | 9.8                   |  |
| 38        | 0.1               | 8.33                       | 2.5                   | 13.0     | 8.8                   |  |
| 39        | 0.1               | 9.25                       | 2.3                   | 12.1     | 9.7                   |  |
| 40        | 0.1               | 9.86                       | 2.0                   | 11.5     | 10.1                  |  |

### MALES END OF TREATMENT

| ANIMAL     | Haematocrit<br>L/L | MCV<br>fL | MCH<br>fmol | MCHC<br>mmol/L | Platelets<br>10E9/L |  |
|------------|--------------------|-----------|-------------|----------------|---------------------|--|
| GROUP 1 (0 | CONTROL)           |           | ,           |                |                     |  |
| 1          | 0.531              | 52.8      | 1.07        | 20.33          | 771                 |  |
| 2          | 0.478              | 53.0      | 1.08        | 20.40          | 759                 |  |
| 3          | 0.498              | 51.5      | 1.03        | 19.98          | 883                 |  |
| 4          | 0.432              | 51.4      | 1.07        | 20.78          | 740                 |  |
| 5          | 0.525              | 51.3      | 1.05        | 20.43          | 712                 |  |
| 6          | 0.494              | 51.8      | 1.06        | 20.50          | 893                 |  |
| 7          | 0.494              | 51.1      | 1.04        | 20.39          | 705                 |  |
| 8          | 0.465              | 49.4      | 1.01        | 20.54          | 773                 |  |
| 9          | 0.463              | 51.6      | 1.09        | 21.08          | 793                 |  |
| 10         | 0.474              | 51.7      | 1.05        | 20.31          | 731                 |  |

### 2.11 HAEMATOLOGY MALES END OF TREATMENT

| ANIMAL             | Haematocrit<br>L/L | MCV<br>fL    | MCH<br>fmol  | MCHC<br>mmol/L | Platelets<br>10E9/L |  |
|--------------------|--------------------|--------------|--------------|----------------|---------------------|--|
| GROUP 2 (          | 3000 PPM)          |              |              |                |                     |  |
| 11                 | 0.472              | 51.1         | 1.08         | 21.05          | 695                 |  |
| 12                 | 0.452              | 49.2         | 1.05         | 21.38          | 796                 |  |
| 13                 | 0.470              | 52.4         | 1.11         | 21.15          | 836                 |  |
| 14                 | 0.430              | 52.5         | 1.14         | 21.73          | 600                 |  |
| 15                 | 0.461              | 50.2         | 1.03         | 20.52          | 689                 |  |
| 16                 | 0.469              | 50.8         | 1.04         | 20.46          | 775                 |  |
| 17                 | 0.456              | 51.0         | 1.05         | 20.48          | 724                 |  |
| 18<br>19           | 0.473<br>0.459     | 52.6<br>50.8 | 1.08<br>1.07 | 20.50<br>21.08 | 687<br>832          |  |
| 20                 | 0.459              | 49.4         | 1.01         | 20.48          | 730                 |  |
| GROUP 3 (          | 10000 PPM)         |              |              |                |                     |  |
| 21                 | 0.463              | 52.1         | 1.10         | 21.02          | 707                 |  |
| 22                 | 0.486              | 50.8         | 1.04         | 20.41          | 797                 |  |
| 23                 | 0.489              | 50.3         | 1.01         | 19.97          | 683                 |  |
| 24                 | 0.470              | 51.5         | 1.06         | 20.50          | 728                 |  |
| 25                 | 0.480              | 49.9         | 1.00         | 20.11          | 885                 |  |
| 26                 | 0.450              | 50.2         | 1.03         | 20.56          | 647                 |  |
| 27<br>28           | <br>0.466          | <br>50.7     | 1.03         | <br>20.23      | <br>539             |  |
| 29                 | 0.462              | 51.6         | 1.04         | 20.23          | 858                 |  |
| 30                 | 0.470              | 53.2         | 1.07         | 20.07          | 749                 |  |
| GROUP 4 (          | 30000 PPM)         |              |              |                |                     |  |
| 31                 | 0.497              | 51.5         | 1.04         | 20.21          | 746                 |  |
| 32                 | 0.510              | 51.4         | 1.04         | 20.20          | 775                 |  |
| 33                 | 0.481              | 49.8         | 1.03         | 20.67          | 925                 |  |
| 34                 | 0.470              | 50.1         | 1.03         | 20.54          | 802                 |  |
| 35                 | 0.493              | 50.9         | 1.04         | 20.50          | 805                 |  |
| 36<br>37           | 0.499<br>0.488     | 50.8<br>51.7 | 1.04<br>1.03 | 20.42<br>20.02 | 689<br>690          |  |
| 38                 | 0.400              | 51.7<br>51.2 | 1.06         | 20.70          | 778                 |  |
| 39                 | 0.480              | 51.8         | 1.05         | 20.32          | 717                 |  |
| 40                 | 0.496              | 50.3         | 1.02         | 20.27          | 774                 |  |
| MALES<br>END OF TR | EATMENT            |              |              |                |                     |  |
| ANIMAL             | PT<br>s            | APTT<br>s    |              |                |                     |  |
| GROUP 1 (          | CONTROL)           |              |              |                |                     |  |
| 1                  | 17.8               | 19.1         |              |                |                     |  |
| 2                  | 17.5               | 18.5         |              |                |                     |  |
| 3                  | 17.5               | 19.8         |              |                |                     |  |
| 4                  | 16.9               | 14.1         |              |                |                     |  |
| 5                  | 16.9               | 15.3         |              |                |                     |  |
| 6                  | 16.5               | 14.9         |              |                |                     |  |
| 7                  | 16.3               | 14.9         |              |                |                     |  |
| 8<br>9             | 16.7<br>17.6       | 14.7<br>18.2 |              |                |                     |  |
| 10                 | 16.7               | 14.7         |              |                |                     |  |
| GROUP 2 (          | 3000 PPM)          |              |              |                |                     |  |
| 11                 | 18.7               | 19.3         |              |                |                     |  |
| 12                 | 17.1               | 18.8         |              |                |                     |  |
| 13                 | 17.5               | 21.2         |              |                |                     |  |
| 14                 | 16.6               | 14.2         |              |                |                     |  |
| 15                 | 17.1               | 18.5         |              |                |                     |  |

- Page 29 -

- Page 86 of 249 -

| ANIMAL     | PT        | APTT |
|------------|-----------|------|
|            | S         | S    |
| GROUP 2 (3 | 000 PPM)  |      |
| 16         | 17.1      | 19.6 |
| 17         | 16.5      | 14.2 |
| 18         | 16.9      | 20.7 |
| 19         | 17.6      | 20.0 |
| 20         | 17.3      | 20.1 |
| GROUP 3 (1 | 0000 PPM) |      |
| 21         | 16.4      | 17.9 |
| 22         | 17.1      | 20.1 |
| 23         | 16.5      | 14.2 |
| 24         | 16.3      | 17.7 |
| 25         | 18.3      | 16.5 |
| 26         | 16.1      | 14.7 |
| 27         | 15.3      | 13.4 |
| 28         | 17.0      | 19.5 |
| 29         | 16.8      | 19.1 |
| 30         | 18.9      | 22.6 |
| GROUP 4 (3 | 0000 PPM) |      |
| 31         | 17.1      | 15.3 |
| 32         | 15.5      | 12.8 |
| 33         | 17.4      | 17.8 |
| 34         | 16.9      | 17.2 |
| 35         | 18.4      | 20.7 |
| 36         | 17.0      | 20.9 |
| 37         | 17.0      | 20.9 |
| 38         | 15.8      | 14.4 |
| 39         | 18.2      | 19.5 |
| 40         | 17.5      | 17.3 |

| ANIMAL    | WBC<br>10E9/L | Neutrophils<br>%WBC | Lymphocytes<br>%WBC | Monocytes<br>%WBC | Eosinophils<br>%WBC |  |
|-----------|---------------|---------------------|---------------------|-------------------|---------------------|--|
| GROUP 1 ( | CONTROL)      |                     |                     |                   |                     |  |
| 41        |               | 81.0                | 13.0                | 1.0               | 5.0                 |  |
| 42        | 5.9           | 8.0                 | 89.0                | 2.0               | 1.0                 |  |
| 43        | 2.3           | 20.7                | 75.3                | 1.8               | 2.0                 |  |
| 44        | 5.5           | 11.7                | 84.2                | 2.5               | 1.6                 |  |
| 45        |               | 19.0                | 77.0                | 1.0               | 3.0                 |  |
| 46        | 5.8           | 15.5                | 81.3                | 1.8               | 1.4                 |  |
| 47        | 3.7           | 22.1                | 73.6                | 2.1               | 2.0                 |  |
| 48        | 9.2           | 11.4                | 85.2                | 2.1               | 1.2                 |  |
| 49        | 5.0           | 19.1                | 77.6                | 2.2               | 1.0                 |  |
| 50        | 5.0           | 12.2                | 84.4                | 2.1               | 1.2                 |  |
| GROUP 2 ( | 3000 PPM)     |                     |                     |                   |                     |  |
| 51        | 2.3           | 20.3                | 72.7                | 1.7               | 5.3                 |  |
| 52        | 4.2           | 53.8                | 36.2                | 6.6               | 3.4                 |  |
| 53        | 4.6           | 20.8                | 76.3                | 1.5               | 1.3                 |  |
| 54        | 4.6           | 13.4                | 83.0                | 1.2               | 2.3                 |  |
| 55        | 5.9           | 11.8                | 84.6                | 1.2               | 2.3                 |  |
| 56        | 6.4           | 14.0                | 81.3                | 2.3               | 2.4                 |  |
| 57        | 4.2           | 6.4                 | 90.0                | 2.3               | 1.2                 |  |
| 58        | 2.3           | 20.3                | 76.0                | 1.7               | 1.9                 |  |
| 59        | 3.6           | 16.2                | 81.5                | 1.3               | 1.0                 |  |
| 60        | 5.0           | 9.0                 | 87.5                | 1.9               | 1.5                 |  |

| ANIMAL     | WBC<br>10E9/L | Neutrophils<br>%WBC | Lymphocytes<br>%WBC | Monocytes<br>%WBC | Eosinophils<br>%WBC |  |
|------------|---------------|---------------------|---------------------|-------------------|---------------------|--|
| GROUP 3 (* | 10000 PPM)    |                     |                     |                   |                     |  |
| 61         | 5.7           | 13.3                | 82.9                | 2.2               | 1.5                 |  |
| 62         | 4.5           | 14.4                | 81.2                | 2.9               | 1.4                 |  |
| 63         | 3.3           | 17.1                | 80.0                | 1.5               | 1.3                 |  |
| 64         |               |                     |                     |                   |                     |  |
| 65         | 3.7           | 31.2                | 64.6                | 2.1               | 1.9                 |  |
| 66         | 3.6           | 26.0                | 68.0                | 2.0               | 4.0                 |  |
| 67         | 3.9           | 20.6                | 75.9                | 1.5               | 1.9                 |  |
| 68         | 5.2           | 8.2                 | 89.2                | 1.6               | 0.9                 |  |
| 69         | 4.3           | 17.2                | 78.3                | 3.1               | 1.4                 |  |
| 70         |               |                     |                     |                   |                     |  |
| GROUP 4 (  | 30000 PPM)    |                     |                     |                   |                     |  |
| 71         | 5.4           | 19.0                | 79.0                | 0.0               | 2.0                 |  |
| 72         | 3.6           | 10.6                | 85.4                | 1.7               | 2.1                 |  |
| 73         | 5.5           | 12.5                | 84.0                | 1.6               | 1.9                 |  |
| 74         | 3.1           | 9.0                 | 87.0                | 3.0               | 1.0                 |  |
| 75         | 5.0           | 12.8                | 83.0                | 2.3               | 1.8                 |  |
| 76         | 2.9           | 11.5                | 83.2                | 3.1               | 2.0                 |  |
| 77         | 6.1           | 7.0                 | 90.0                | 1.0               | 2.0                 |  |
| 78         | 2.8           | 12.0                | 83.9                | 2.4               | 1.6                 |  |
| 79         | 5.1           | 9.7                 | 87.1                | 2.0               | 1.2                 |  |
| 80         | 5.3           | 15.9                | 80.0                | 1.3               | 2.8                 |  |

| GROUP 1 (CONTROL)  41   |  |
|---|--|
| 41 0.0 8.06 2.7 11.3 8.8<br>42 0.0 8.79 2.6 10.6 9.7<br>43 0.2 8.50 3.2 10.9 9.1<br>44 0.0 8.11 1.9 11.7 9.4<br>45 0.0 8.08 3.0 11.0 9.2<br>46 0.0 8.18 2.2 11.5 9.4<br>47 0.1 8.74 2.1 10.9 9.5<br>48 0.1 8.84 2.3 10.5 9.7<br>49 0.1 8.13 2.6 14.8 9.7<br>50 0.1 8.33 3.2 11.9 9.1<br>GROUP 2 (3000 PPM)<br>51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 43     0.2     8.50     3.2     10.9     9.1       44     0.0     8.11     1.9     11.7     9.4       45     0.0     8.08     3.0     11.0     9.2       46     0.0     8.18     2.2     11.5     9.4       47     0.1     8.74     2.1     10.9     9.5       48     0.1     8.84     2.3     10.5     9.7       49     0.1     8.13     2.6     14.8     9.7       50     0.1     8.33     3.2     11.9     9.1       GROUP 2 (3000 PPM)       51     0.0     7.83     2.5     10.4     8.8       52     0.0     8.30     2.4     10.9     8.5  |  |
| 44       0.0       8.11       1.9       11.7       9.4         45       0.0       8.08       3.0       11.0       9.2         46       0.0       8.18       2.2       11.5       9.4         47       0.1       8.74       2.1       10.9       9.5         48       0.1       8.84       2.3       10.5       9.7         49       0.1       8.13       2.6       14.8       9.7         50       0.1       8.33       3.2       11.9       9.1         GROUP 2 (3000 PPM)         51       0.0       7.83       2.5       10.4       8.8         52       0.0       8.30       2.4       10.9       8.5 |  |
| 45 0.0 8.08 3.0 11.0 9.2<br>46 0.0 8.18 2.2 11.5 9.4<br>47 0.1 8.74 2.1 10.9 9.5<br>48 0.1 8.84 2.3 10.5 9.7<br>49 0.1 8.13 2.6 14.8 9.7<br>50 0.1 8.33 3.2 11.9 9.1<br>GROUP 2 (3000 PPM)<br>51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 45 0.0 8.08 3.0 11.0 9.2<br>46 0.0 8.18 2.2 11.5 9.4<br>47 0.1 8.74 2.1 10.9 9.5<br>48 0.1 8.84 2.3 10.5 9.7<br>49 0.1 8.13 2.6 14.8 9.7<br>50 0.1 8.33 3.2 11.9 9.1<br>GROUP 2 (3000 PPM)<br>51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 47     0.1     8.74     2.1     10.9     9.5       48     0.1     8.84     2.3     10.5     9.7       49     0.1     8.13     2.6     14.8     9.7       50     0.1     8.33     3.2     11.9     9.1       GROUP 2 (3000 PPM)       51     0.0     7.83     2.5     10.4     8.8       52     0.0     8.30     2.4     10.9     8.5  |  |
| 48 0.1 8.84 2.3 10.5 9.7<br>49 0.1 8.13 2.6 14.8 9.7<br>50 0.1 8.33 3.2 11.9 9.1<br>GROUP 2 (3000 PPM)<br>51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 49 0.1 8.13 2.6 14.8 9.7 50 0.1 8.33 3.2 11.9 9.1<br><b>GROUP 2 (3000 PPM)</b> 51 0.0 7.83 2.5 10.4 8.8 52 0.0 8.30 2.4 10.9 8.5  |  |
| 50 0.1 8.33 3.2 11.9 9.1  GROUP 2 (3000 PPM)  51 0.0 7.83 2.5 10.4 8.8  52 0.0 8.30 2.4 10.9 8.5  |  |
| <b>GROUP 2 (3000 PPM)</b> 51 0.0 7.83 2.5 10.4 8.8 52 0.0 8.30 2.4 10.9 8.5   |  |
| 51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 51 0.0 7.83 2.5 10.4 8.8<br>52 0.0 8.30 2.4 10.9 8.5  |  |
| 52 0.0 8.30 2.4 10.9 8.5  |  |
|   |  |
|   |  |
| 54 0.1 8.13 2.9 11.8 8.8  |  |
| 55 0.1 8.47 2.5 11.4 9.1  |  |
| 56 0.0 8.19 3.1 11.6 8.9  |  |
| 57 0.1 8.11 2.3 11.2 8.8  |  |
| 58 0.1 8.31 2.6 11.0 9.2  |  |
| 59 0.0 7.82 2.7 10.8 8.9  |  |
| 60 0.0 8.35 3.2 11.6 9.1  |  |
| GROUP 3 (10000 PPM)   |  |
| 61 0.2 8.09 2.5 10.6 9.2  |  |
| 62 0.0 8.46 2.5 11.0 9.5  |  |
| 63 0.0 7.77 2.5 10.7 8.9  |  |
| 64  |  |
| 65 0.1 8.15 2.5 11.1 8.7  |  |

| ANIMAL    | Basophils<br>%WBC | Red blood cells<br>10E12/L | Reticulocytes<br>%RBC | RDW<br>% | Haemoglobin<br>mmol/L |  |
|-----------|-------------------|----------------------------|-----------------------|----------|-----------------------|--|
| GROUP 3 ( | 10000 PPM)        |                            |                       |          |                       |  |
| 66 `      | 0.0               | 8.52                       | 2.7                   | 10.8     | 8.6                   |  |
| 67        | 0.2               | 8.35                       | 2.5                   | 11.0     | 9.0                   |  |
| 68        | 0.1               | 8.41                       | 2.3                   | 10.6     | 9.3                   |  |
| 69        | 0.1               | 8.53                       | 2.7                   | 11.2     | 9.2                   |  |
| 70        |                   |                            |                       |          |                       |  |
| GROUP 4 ( | 30000 PPM)        |                            |                       |          |                       |  |
| 71 `      | 0.0               | 8.62                       | 2.7                   | 11.4     | 9.5                   |  |
| 72        | 0.1               | 7.90                       | 2.0                   | 10.1     | 8.8                   |  |
| 73        | 0.1               | 8.63                       | 2.5                   | 11.2     | 9.4                   |  |
| 74        | 0.0               | 8.81                       | 2.2                   | 10.4     | 9.2                   |  |
| 75        | 0.1               | 8.05                       | 2.3                   | 10.5     | 9.2                   |  |
| 76        | 0.1               | 8.28                       | 2.6                   | 11.0     | 9.2                   |  |
| 77        | 0.0               | 8.37                       | 2.4                   | 10.4     | 9.3                   |  |
| 78        | 0.0               | 8.15                       | 2.7                   | 10.8     | 8.9                   |  |
| 79        | 0.0               | 8.64                       | 2.0                   | 10.7     | 9.2                   |  |
| 80        | 0.0               | 8.01                       | 1.9                   | 10.4     | 8.9                   |  |
|           |                   |                            |                       |          |                       |  |

## FEMALES END OF TREATMENT

| ANIMAL    | Haematocrit<br>L/L | MCV<br>fL | MCH<br>fmol | MCHC<br>mmol/L | Platelets<br>10E9/L |  |
|-----------|--------------------|-----------|-------------|----------------|---------------------|--|
| GROUP 1 ( | CONTROL)           |           |             |                |                     |  |
| 41        | 0.427              | 53.0      | 1.10        | 20.66          | 813                 |  |
| 42        | 0.472              | 53.7      | 1.11        | 20.59          | 576                 |  |
| 43        | 0.448              | 52.8      | 1.08        | 20.39          | 755                 |  |
| 44        | 0.436              | 53.7      | 1.16        | 21.56          | 758                 |  |
| 45        | 0.443              | 54.9      | 1.14        | 20.73          | 777                 |  |
| 46        | 0.445              | 54.4      | 1.14        | 21.04          | 693                 |  |
| 47        | 0.454              | 51.9      | 1.08        | 20.90          | 612                 |  |
| 48        | 0.473              | 53.5      | 1.09        | 20.42          | 616                 |  |
| 49        | 0.446              | 54.9      | 1.20        | 21.84          | 742                 |  |
| 50        | 0.443              | 53.2      | 1.09        | 20.44          | 603                 |  |
| GROUP 2 ( | 3000 PPM)          |           |             |                |                     |  |
| 51        | 0.427              | 54.5      | 1.12        | 20.55          | 665                 |  |
| 52        | 0.425              | 51.2      | 1.02        | 20.03          | 898                 |  |
| 53        | 0.409              | 55.4      | 1.21        | 21.79          | 569                 |  |
| 54        | 0.430              | 52.9      | 1.09        | 20.54          | 819                 |  |
| 55        | 0.448              | 52.8      | 1.08        | 20.43          | 833                 |  |
| 56        | 0.430              | 52.4      | 1.08        | 20.67          | 755                 |  |
| 57        | 0.426              | 52.5      | 1.08        | 20.66          | 914                 |  |
| 58        | 0.449              | 54.1      | 1.11        | 20.49          | 859                 |  |
| 59        | 0.417              | 53.4      | 1.13        | 21.25          | 817                 |  |
| 60        | 0.445              | 53.2      | 1.08        | 20.37          | 740                 |  |
| GROUP 3 ( | 10000 PPM)         |           |             |                |                     |  |
| 61        | 0.458              | 56.5      | 1.14        | 20.12          | 804                 |  |
| 62        | 0.465              | 55.0      | 1.12        | 20.37          | 862                 |  |
| 63        | 0.437              | 56.3      | 1.15        | 20.36          | 860                 |  |
| 64        |                    |           |             |                |                     |  |
| 65        | 0.422              | 51.9      | 1.07        | 20.56          | 891                 |  |
| 66        | 0.430              | 50.4      | 1.01        | 20.11          | 778                 |  |
| 67        | 0.438              | 52.5      | 1.07        | 20.46          | 865                 |  |
| 68        | 0.454              | 54.0      | 1.11        | 20.51          | 757                 |  |
| 69        | 0.458              | 53.7      | 1.08        | 20.07          | 1044                |  |
| 70        |                    |           |             |                |                     |  |

000219

| ANIMAL                | Haematocrit                | MCV      | MCH  | MCHC   | Platelets |  |
|-----------------------|----------------------------|----------|------|--------|-----------|--|
|                       | L/L                        | fL       | fmol | mmol/L | 10E9/L    |  |
| GROUP 4 (             |                            |          |      |        |           |  |
| 71                    | 0.458                      | 53.2     | 1.10 | 20.67  | 662       |  |
| 72                    | 0.424                      | 53.6     | 1.12 | 20.84  | 729       |  |
| 73                    | 0.454                      | 52.7     | 1.09 | 20.66  | 829       |  |
| 74                    | 0.452                      | 51.2     | 1.04 | 20.28  | 696       |  |
| 75                    | 0.433                      | 53.7     | 1.14 | 21.24  | 681       |  |
| 76                    | 0.459                      | 55.5     | 1.12 | 20.12  | 676       |  |
| 77                    | 0.452                      | 54.0     | 1.11 | 20.64  | 593       |  |
| 78                    | 0.434                      | 53.2     | 1.10 | 20.61  | 919       |  |
| 79                    | 0.458                      | 53.0     | 1.07 | 20.16  | 778       |  |
| 80                    | 0.433                      | 54.1     | 1.11 | 20.52  | 741       |  |
| FEMALES<br>END OF TR  | EATMENT                    |          |      |        |           |  |
|                       |                            |          |      |        |           |  |
| ANIMAL                | PT                         | APTT     |      |        |           |  |
|                       | S                          | S        |      |        |           |  |
| GROUP 1 (             | CONTROL)                   | ,        | ,    |        |           |  |
| 41                    | 16.8                       | 15.4     |      |        |           |  |
| 42                    | 16.6                       | 18.2     |      |        |           |  |
| 43                    | 15.9                       | 17.1     |      |        |           |  |
| 44                    | 15.7                       | 15.0     |      |        |           |  |
| 45                    | 16.4                       | 16.3     |      |        |           |  |
| 46                    | 16.2                       | 17.0     |      |        |           |  |
|                       |                            |          |      |        |           |  |
| 47                    | 16.3                       | 16.1     |      |        |           |  |
| 48                    | 16.0                       | 15.8     |      |        |           |  |
| 49                    | 17.0                       | 19.5     |      |        |           |  |
| 50                    | 16.1                       | 17.4     |      |        |           |  |
| ODOUD O               | 2000 DDM)                  |          |      |        |           |  |
| GROUP 2 (             |                            |          |      |        |           |  |
| 51                    | 15.6                       | 14.2     |      |        |           |  |
| 52                    | 16.3                       | 19.3     |      |        |           |  |
| 53                    | 15.8                       | 17.0     |      |        |           |  |
| 54                    | 16.8                       | 21.7     |      |        |           |  |
| 55                    | 17.6                       | 18.2     |      |        |           |  |
| 56                    | 15.5                       | 14.8     |      |        |           |  |
| 57                    | 17.2                       | 17.1     |      |        |           |  |
| 58                    | 16.8                       | 17.3     |      |        |           |  |
| 59                    | 16.1                       | 15.5     |      |        |           |  |
| 60                    | 16.5                       | 19.6     |      |        |           |  |
| <b>GROUP 3 (</b> 61   | 1 <b>0000 PPM)</b><br>17.1 | 20.8     |      |        |           |  |
| 62                    | 16.9                       | 15.9     |      |        |           |  |
| 63                    | 17.8                       | 19.1     |      |        |           |  |
|                       |                            |          |      |        |           |  |
| 64<br>65              | <br>16 0                   | <br>17 1 |      |        |           |  |
| 65<br>66              | 16.9                       | 17.1     |      |        |           |  |
| 66                    | 17.1                       | 14.4     |      |        |           |  |
| 67                    | 17.9                       | 20.2     |      |        |           |  |
| 68                    | 18.5                       | 17.6     |      |        |           |  |
| 69                    | 18.1                       | 19.0     |      |        |           |  |
| 70                    |                            |          |      |        |           |  |
| <b>GROUP 4 (</b> 3 71 | 3 <b>0000 PPM)</b><br>16.0 | 14.4     |      |        |           |  |
| 72                    | 16.0                       | 14.3     |      |        |           |  |
| 73                    | 16.9                       | 18.0     |      |        |           |  |
| 73<br>74              | 15.8                       | 15.3     |      |        |           |  |
| 7 <del>4</del><br>75  | 16.3                       | 17.4     |      |        |           |  |
| 13                    | 10.5                       | 17.7     |      |        |           |  |
|                       |                            |          |      |        |           |  |

| ANIMAL     | PT<br>s    | APTT<br>s |
|------------|------------|-----------|
| GROUP 4 (3 | 30000 PPM) |           |
| 76         | 16.6       | 18.2      |
| 77         | 17.4       | 19.2      |
| 78         | 16.8       | 20.9      |
| 79         | 16.3       | 19.8      |
| 80         | 16.1       | 20.2      |

| ANIMAL    | ALAT<br>U/L | ASAT<br>U/L | ALP<br>U/L | Total protein<br>g/L | Albumin<br>g/L |  |
|-----------|-------------|-------------|------------|----------------------|----------------|--|
| GROUP 1 ( | CONTROL)    |             |            |                      |                |  |
| 1 `       | 39.5 ´      | 73.7        | 136        | 65.2                 | 32.9           |  |
| 2         | 31.0        | 74.2        | 127        | 62.3                 | 31.5           |  |
| 3         | 45.8        | 73.7        | 201        | 67.7                 | 33.9           |  |
| 4         | 50.1        | 76.4        | 394        | 63.4                 | 32.5           |  |
| -<br>5    | 55.3        | 86.1        | 159        | 66.0                 | 32.1           |  |
| 6         | 44.3        | 66.3        | 92         | 62.8                 | 31.3           |  |
| 7         | 34.9        | 90.9        | 119        | 64.9                 | 32.7           |  |
| 8         | 34.2        | 74.2        | 127        | 62.9                 | 31.2           |  |
|           |             |             |            |                      |                |  |
| 9         | 55.3        | 84.6        | 136        | 64.0                 | 32.3           |  |
| 10        | 37.4        | 69.2        | 82         | 64.7                 | 33.2           |  |
| GROUP 2 ( | 3000 PPM)   |             |            |                      |                |  |
| 11        | 53.1        | 77.9        | 165        | 62.7                 | 31.7           |  |
| 12        | 43.5        | 69.8        | 101        | 63.6                 | 31.2           |  |
| 13        | 41.5        | 79.6        | 166        | 63.9                 | 31.4           |  |
| 14        | 43.5        | 76.9        | 232        | 61.6                 | 31.2           |  |
| 15        | 35.5        | 80.7        | 209        | 60.2                 | 31.2           |  |
| 16        | 38.1        | 76.4        | 164        | 62.4                 | 31.1           |  |
| 17        | 47.7        | 67.4        | 205        | 63.9                 | 32.3           |  |
| 18        | 40.4        | 71.5        | 98         | 62.6                 | 30.9           |  |
| 19        | 55.7        | 73.8        | 117        | 65.9                 | 31.9           |  |
| 20        | 44.3        | 84.5        | 281        | 67.4                 | 33.3           |  |
| 20        | 44.5        | 04.5        | 201        | 07.4                 | 33.3           |  |
|           | 10000 PPM)  |             |            |                      |                |  |
| 21        | 38.4        | 63.8        | 167        | 64.1                 | 30.9           |  |
| 22        | 39.2        | 69.7        | 95         | 64.5                 | 31.7           |  |
| 23        | 48.4        | 88.1        | 156        | 64.8                 | 31.2           |  |
| 24        | 56.0        | 84.7        | 242        | 64.1                 | 32.7           |  |
| 25        | 50.0        | 66.0        | 151        | 67.3                 | 31.5           |  |
| 26        | 40.7        | 94.3        | 238        | 65.6                 | 32.4           |  |
| 27        | 37.5        | 65.0        | 107        | 63.3                 | 32.3           |  |
| 28        | 45.3        | 80.1        | 275        | 62.2                 | 31.0           |  |
| 29        | 48.1        | 76.7        | 138        | 64.0                 | 32.9           |  |
| 30        | 73.9        | 79.0        | 192        | 65.5                 | 33.0           |  |
| GROUP 4 ( | 30000 PPM)  |             |            |                      |                |  |
| 31        | 46.4        | 80.0        | 310        | 63.9                 | 31.9           |  |
| 32        | 47.2        | 93.9        | 169        | 65.7                 | 32.2           |  |
|           |             |             |            |                      |                |  |
| 33        | 36.8        | 72.5        | 155<br>151 | 66.6                 | 32.4           |  |
| 34        | 50.0        | 69.5        | 151        | 63.6                 | 30.5           |  |
| 35        | 41.7        | 75.0        | 310        | 65.7                 | 33.9           |  |
| 36        | 42.2        | 126.9       | 89         | 64.8                 | 32.3           |  |
| 37        | 41.3        | 73.7        | 217        | 64.5                 | 31.3           |  |
| 38        | 50.3        | 76.8        | 162        | 64.8                 | 32.1           |  |
| 39        | 47.3        | 92.8        | 239        | 65.3                 | 33.3           |  |
| 40        | 35.5        | 73.1        | 111        | 65.3                 | 31.8           |  |

# MALES END OF TREATMENT

| ANIMAL    | Total bilirubin<br>umol/L | Urea<br>mmol/L | Creatinine umol/L | Glucose<br>mmol/L | Cholesterol<br>mmol/L |  |
|-----------|---------------------------|----------------|-------------------|-------------------|-----------------------|--|
| GROUP 1 ( | CONTROL)                  |                |                   |                   |                       |  |
| 1         | 1.9                       | 5.5            | 36.6              | 10.72             | 1.85                  |  |
| 2         | 1.9                       | 4.9            | 36.6              | 10.80             | 1.90                  |  |
| 3         | 1.8                       | 11.1           | 41.3              | 12.91             | 1.93                  |  |
| 4         | 2.1                       | 8.8            | 38.2              | 13.89             | 2.29                  |  |
| 5         | 2.0                       | 6.5            | 39.0              | 10.54             | 2.40                  |  |

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| ANIMAL     | Total bilirubin<br>umol/L | Urea<br>mmol/L | Creatinine<br>umol/L | Glucose<br>mmol/L | Cholesterol<br>mmol/L |  |
|------------|---------------------------|----------------|----------------------|-------------------|-----------------------|--|
| GROUP 1 (0 | CONTROL)                  |                |                      |                   |                       |  |
| 6          | 2.0                       | 5.8            | 39.5                 | 11.77             | 2.19                  |  |
| 7          | 1.9                       | 5.6            | 37.5                 | 9.34              | 2.04                  |  |
| 8          | 1.7                       | 6.4            | 38.8                 | 12.88             | 1.93                  |  |
| 9          | 2.5                       | 6.8            | 39.5                 | 11.85             | 2.13                  |  |
| 10         | 2.3                       | 5.2            | 41.4                 | 11.10             | 1.93                  |  |
| GROUP 2 (3 | 2000 DDM\                 |                |                      |                   |                       |  |
| 11         | 1.7                       | 7.9            | 40.5                 | 10.12             | 2.35                  |  |
| 12         | 1.7                       | 7.9<br>5.1     | 36.6                 | 11.04             | 2.35<br>1.86          |  |
| 1 <u>/</u> |                           |                | 30.0<br>30.0         |                   |                       |  |
| 13         | 1.4                       | 5.1            | 39.0                 | 11.84             | 1.78                  |  |
| 14         | 2.1                       | 8.4            | 39.7                 | 11.99             | 1.85                  |  |
| 15         | 1.4                       | 5.7            | 37.4                 | 11.21             | 2.02                  |  |
| 16         | 1.9                       | 5.1            | 36.9                 | 10.77             | 2.27                  |  |
| 17         | 1.8                       | 6.6            | 38.2                 | 9.93              | 2.18                  |  |
| 18         | 2.1                       | 5.9            | 37.5                 | 10.37             | 2.10                  |  |
| 19         | 1.4                       | 7.3            | 38.8                 | 11.37             | 2.24                  |  |
| 20         | 1.9                       | 9.1            | 40.1                 | 11.58             | 2.11                  |  |
| GROUP 3 (* | 10000 PPM)                |                |                      |                   |                       |  |
| 21         | 1.7                       | 9.7            | 39.0                 | 10.97             | 2.16                  |  |
| 22         | 1.7                       | 5.1            | 35.8                 | 11.18             | 1.96                  |  |
| 23         | 1.7                       | 6.2            | 37.4                 | 10.07             | 2.44                  |  |
| 24         | 2.1                       | 8.0            | 41.3                 | 12.42             | 1.90                  |  |
| 25         | 1.9                       | 8.1            | 42.8                 | 12.82             | 2.12                  |  |
| 26         | 1.5                       | 9.2            | 37.5                 | 8.95              | 2.55                  |  |
| 27         | 1.6                       | 7.4            | 36.2                 | 11.88             | 2.63                  |  |
| 28         | 1.9                       | 8.5            | 37.5                 | 11.25             | 1.87                  |  |
| 29         | 1.9                       | 7.3            | 36.2                 | 10.47             | 2.56                  |  |
| 30         |                           | 7.3<br>11.5    | 36.2<br>39.5         |                   |                       |  |
| JU         | 1.7                       | 11.0           | აყ.ა                 | 11.31             | 1.94                  |  |
| GROUP 4 (3 |                           |                |                      |                   |                       |  |
| 31         | 2.2                       | 7.8            | 39.0                 | 9.05              | 2.39                  |  |
| 32         | 2.4                       | 6.4            | 38.2                 | 8.37              | 2.34                  |  |
| 33         | 2.0                       | 6.1            | 39.7                 | 11.57             | 1.60                  |  |
| 34         | 2.3                       | 6.6            | 38.2                 | 11.51             | 2.06                  |  |
| 35         | 2.1                       | 7.9            | 41.3                 | 12.12             | 2.21                  |  |
| 36         | 2.0                       | 6.8            | 40.1                 | 9.64              | 1.71                  |  |
| 37         | 1.8                       | 7.7            | 43.4                 | 9.79              | 2.57                  |  |
| 38         | 1.9                       | 5.7            | 36.2                 | 10.04             | 2.69                  |  |
| 39         | 2.3                       | 9.0            | 40.1                 | 9.89              | 2.00                  |  |
| 40         | 1.8                       | 5.3            | 36.9                 | 10.65             | 1.81                  |  |

| ANIMAL    | Bile Acids<br>umol/L | Sodium<br>mmol/L | Potassium<br>mmol/L | Chloride<br>mmol/L | Calcium<br>mmol/L |  |
|-----------|----------------------|------------------|---------------------|--------------------|-------------------|--|
| GROUP 1 ( | CONTROL)             |                  |                     |                    |                   |  |
| 1         | 10.6                 | 143.4            | 4.10                | 104                | 2.60              |  |
| 2         | 11.4                 | 142.0            | 3.85                | 104                | 2.55              |  |
| 3         | 12.2                 | 139.9            | 4.23                | 102                | 2.69              |  |
| 4         | 22.9                 | 140.7            | 4.10                | 104                | 2.58              |  |
| 5         | 8.9                  | 140.7            | 3.87                | 103                | 2.60              |  |
| 6         | 10.8                 | 141.2            | 3.94                | 103                | 2.63              |  |
| 7         | 11.0                 | 143.0            | 4.27                | 105                | 2.62              |  |
| 8         | 12.0                 | 143.7            | 3.89                | 105                | 2.57              |  |
| 9         | 38.9                 | 143.8            | 4.09                | 104                | 2.63              |  |
| 10        | 19.1                 | 143.5            | 4.10                | 105                | 2.58              |  |

Betawell L-Arabinose APPENDIX 2

| ANIMAL             | Bile Acids<br>umol/L | Sodium<br>mmol/L | Potassium<br>mmol/L | Chloride<br>mmol/L | Calcium<br>mmol/L |  |
|--------------------|----------------------|------------------|---------------------|--------------------|-------------------|--|
| GROUP 2 (          | 3000 PPM)            |                  |                     |                    |                   |  |
| 11                 | 15.3                 | 140.6            | 3.85                | 103                | 2.51              |  |
| 12                 | 13.3                 | 140.8            | 3.76                | 101                | 2.51              |  |
| 13                 | 10.3                 | 139.4            | 3.72                | 103                | 2.44              |  |
| 14                 | 13.3                 | 142.3            | 4.09                | 106                | 2.52              |  |
| 15                 | 8.0                  | 141.5            | 3.89                | 104                | 2.46              |  |
| 16                 | 11.7                 | 144.6            | 3.87                | 105                | 2.56              |  |
| 17                 | 15.5                 | 143.2            | 4.24                | 105                | 2.64              |  |
| 18                 | 14.0                 | 145.4            | 3.88                | 107                | 2.54              |  |
| 19                 | 13.0                 | 143.1            | 4.03                | 105                | 2.60              |  |
| 20                 | 31.4                 | 143.3            | 4.43                | 104                | 2.69              |  |
| GROUP 3 (          | 10000 PPM)           |                  |                     |                    |                   |  |
| 21 `               | 11.9                 | 141.4            | 3.98                | 103                | 2.53              |  |
| 22                 | 19.2                 | 140.7            | 4.02                | 103                | 2.58              |  |
| 23                 | 16.2                 | 140.6            | 4.22                | 104                | 2.64              |  |
| 24                 | 14.2                 | 140.0            | 4.43                | 104                | 2.59              |  |
| 25                 | 10.9                 | 141.9            | 4.27                | 102                | 2.65              |  |
| 26                 | 12.6                 | 143.4            | 4.74                | 105                | 2.70              |  |
| 27                 | 9.2                  | 143.7            | 4.04                | 105                | 2.63              |  |
| 28                 | 11.1                 | 144.1            | 4.57                | 106                | 2.62              |  |
| 29                 | 31.5                 | 143.7            | 4.04                | 104                | 2.66              |  |
| 30                 | 26.5                 | 142.5            | 4.57                | 104                | 2.71              |  |
| GROUP 4 (          | 30000 PPM)           |                  |                     |                    |                   |  |
| 31                 | 16.2                 | 139.8            | 4.51                | 102                | 2.61              |  |
| 32                 | 20.1                 | 141.9            | 4.15                | 102                | 2.61              |  |
| 33                 | 11.0                 | 140.0            | 3.79                | 102                | 2.57              |  |
| 34                 | 15.4                 | 139.8            | 3.85                | 103                | 2.57              |  |
| 35                 | 18.1                 | 139.6            | 3.55                | 102                | 2.57              |  |
| 36                 | 30.7                 | 143.3            | 4.45                | 105                | 2.59              |  |
| 37                 | 11.1                 | 144.8            | 4.18                | 106                | 2.67              |  |
| 38                 | 25.3                 | 143.0            | 4.05                | 103                | 2.63              |  |
| 39                 | 32.4                 | 143.9            | 4.40                | 106                | 2.67              |  |
| 40                 | 8.8                  | 144.1            | 4.14                | 105                | 2.58              |  |
| MALES<br>END OF TR | REATMENT             |                  |                     |                    |                   |  |
| ANIMAL             | Inorg.Phos           |                  |                     |                    |                   |  |

| Inorg.Phos<br>mmol/L |
|----------------------|
| IIIIIIOI/L           |
|                      |

| GROUP 1 1 2 3 4 5 6 7 8 9 10  | (CONTROL)  1.82 1.71 1.31 1.35 1.63 1.53 1.73 1.40 1.68 1.46 |
|-------------------------------|--|
| <b>GROUP 2</b> 11 12 13 14 15 | (3000 PPM)<br>1.37<br>1.42<br>1.41<br>1.31<br>1.50           |

| ANIMAL               | Inorg.Phos<br>mmol/L |
|----------------------|----------------------|
| GROUP 2 (3           | 8000 PPM)            |
| 16                   | 1.74                 |
| 17                   | 1.48                 |
| 18                   | 1.44                 |
| 19                   | 1.35                 |
| 20                   | 1.46                 |
| GROUP 3 (1           | 10000 PPM)           |
| 21                   | 1.39                 |
| 22                   | 1.35                 |
| 22<br>23             | 1.70                 |
| 24                   | 1.41                 |
| 24<br>25<br>26<br>27 | 1.52                 |
| 26                   | 1.49                 |
| 27                   | 1.24                 |
| 28<br>29             | 1.38                 |
| 29                   | 1.62                 |
| 30                   | 1.46                 |
| GROUP 4 (3           | 80000 PPM)           |
| 31                   | 1.54                 |
| 32                   | 1.55                 |
| 32<br>33             | 1.38                 |
| 34<br>35             | 1.64                 |
| 35                   | 1.01                 |
| 36<br>37             | 1.74                 |
| 37                   | 1.44                 |
| 38                   | 1.42                 |
| 39                   | 1.71                 |
| 40                   | 1.36                 |

| ANIMAL    | ALAT<br>U/L | ASAT<br>U/L | ALP<br>U/L | Total protein<br>g/L | Albumin<br>g/L |  |
|-----------|-------------|-------------|------------|----------------------|----------------|--|
| GROUP 1 ( | CONTROL)    |             |            |                      |                |  |
| 41        | 51.1        | 88.0        | 102        | 60.1                 | 32.4           |  |
| 42        | 34.7        | 66.3        | 64         | 71.7                 | 38.6           |  |
| 43        | 31.2        | 68.6        | 61         | 65.6                 | 34.0           |  |
| 44        | 28.9        | 74.1        | 53         | 63.8                 | 34.3           |  |
| 45        | 35.1        | 72.7        | 81         | 68.6                 | 36.1           |  |
| 46        | 52.5        | 78.7        | 70         | 70.9                 | 37.0           |  |
| 47        | 30.4        | 75.7        | 48         | 66.3                 | 34.5           |  |
| 48        | 51.8        | 72.8        | 91         | 71.6                 | 36.4           |  |
| 49        | 40.7        | 78.7        | 57         | 68.6                 | 35.8           |  |
| 50        | 34.8        | 57.7        | 63         | 72.0                 | 39.0           |  |
| GROUP 2 ( | 3000 PPM)   |             |            |                      |                |  |
| 51 `      | 20.8        | 75.4        | 43         | 65.9                 | 33.7           |  |
| 52        | 68.9        | 135.8       | 67         | 62.9                 | 33.9           |  |
| 53        | 30.9        | 76.2        | 79         | 65.3                 | 33.7           |  |
| 54        | 34.9        | 63.7        | 147        | 67.7                 | 36.3           |  |
| 55        | 42.1        | 75.0        | 111        | 64.6                 | 35.5           |  |
| 56        | 39.0        | 61.8        | 44         | 72.2                 | 37.4           |  |
| 57        | 45.4        | 70.6        | 97         | 67.3                 | 36.2           |  |
| 58        | 30.7        | 69.4        | 78         | 65.4                 | 35.8           |  |
| 59        | 24.2        | 71.8        | 42         | 64.2                 | 33.7           |  |
| 60        | 41.1        | 66.1        | 58         | 69.0                 | 37.0           |  |

| ANIMAL    | ALAT<br>U/L | ASAT<br>U/L | ALP<br>U/L | Total protein<br>g/L | Albumin<br>g/L |  |
|-----------|-------------|-------------|------------|----------------------|----------------|--|
| GROUP 3 ( | 10000 PPM)  |             |            |                      |                |  |
| 61 `      | 58.3        | 74.6        | 155        | 73.2                 | 40.3           |  |
| 62        | 41.5        | 79.9        | 94         | 70.4                 | 38.7           |  |
| 63        | 46.4        | 69.7        | 104        | 71.0                 | 37.9           |  |
| 64        | 45.5        | 86.3        | 82         | 61.5                 | 33.0           |  |
| 65        | 37.3        | 65.6        | 68         | 72.4                 | 38.3           |  |
| 66        | 26.3        | 66.1        | 52         | 71.8                 | 39.1           |  |
| 67        | 39.8        | 71.6        | 92         | 70.1                 | 37.6           |  |
| 68        | 36.8        | 68.4        | 47         | 71.2                 | 38.1           |  |
| 69        | 31.6        | 58.9        | 60         | 69.8                 | 36.7           |  |
| 70        | 60.0        | 85.3        | 57         | 67.3                 | 34.5           |  |
| GROUP 4 ( | 30000 PPM)  |             |            |                      |                |  |
| 71 `      | 43.5        | 61.8        | 65         | 78.8                 | 42.4           |  |
| 72        | 41.7        | 72.4        | 66         | 69.7                 | 36.8           |  |
| 73        | 53.7        | 71.8        | 175        | 67.8                 | 35.2           |  |
| 74        | 35.2        | 95.5        | 44         | 66.3                 | 34.4           |  |
| 75        | 40.3        | 75.5        | 149        | 66.5                 | 34.8           |  |
| 76        | 35.8        | 63.8        | 69         | 68.2                 | 36.9           |  |
| 77        | 48.4        | 60.8        | 65         | 64.6                 | 33.4           |  |
| 78        | 43.2        | 67.1        | 46         | 66.7                 | 34.9           |  |
| 79        | 39.0        | 76.6        | 61         | 68.1                 | 36.0           |  |
| 80        | 49.8        | 71.5        | 53         | 68.8                 | 37.0           |  |

| GROUP 1 (CC | ONTROL)<br>2.2<br>3.2 | 8.0 |      |       | _    | - |
|-------------|-----------------------|-----|------|-------|------|---|
|             | 2.2                   | Ω Λ |      |       |      |   |
|             | 3.2                   | 0.0 | 39.0 | 8.65  | 1.46 |   |
| 42          |                       | 5.1 | 39.7 | 6.76  | 2.18 |   |
| 43          | 2.5                   | 6.7 | 40.5 | 10.53 | 2.29 |   |
| 44          | 2.2                   | 6.0 | 38.2 | 6.28  | 1.76 |   |
| 45          | 2.7                   | 7.4 | 44.4 | 8.61  | 1.85 |   |
| 46          | 2.3                   | 6.2 | 40.5 | 6.69  | 1.92 |   |
| 47          | 3.0                   | 7.1 | 42.8 | 8.92  | 2.04 |   |
| 48          | 2.3                   | 8.1 | 40.5 | 7.71  | 2.11 |   |
| 49          | 2.5                   | 4.8 | 39.0 | 9.58  | 1.72 |   |
| 50          | 2.3                   | 9.2 | 46.7 | 10.26 | 1.70 |   |
| GROUP 2 (30 | 00 PPM)               |     |      |       |      |   |
| 51          | 2.3                   | 5.3 | 45.2 | 7.63  | 1.45 |   |
| 52          | 1.7                   | 9.6 | 42.8 | 8.71  | 1.61 |   |
| 53          | 1.9                   | 7.9 | 44.4 | 8.42  | 1.90 |   |
| 54          | 2.3                   | 8.2 | 46.7 | 9.87  | 1.82 |   |
| 55          | 2.1                   | 7.4 | 46.7 | 10.68 | 1.41 |   |
| 56          | 2.8                   | 6.6 | 46.7 | 8.79  | 2.08 |   |
| 57          | 2.6                   | 6.9 | 38.2 | 9.37  | 1.70 |   |
| 58          | 2.2                   | 6.4 | 42.8 | 9.73  | 1.66 |   |
| 59          | 2.3                   | 6.0 | 47.5 | 7.48  | 1.19 |   |
| 60          | 2.9                   | 5.7 | 43.6 | 12.36 | 1.49 |   |
| GROUP 3 (10 | 000 PPM)              |     |      |       |      |   |
| 61          | 2.2                   | 6.1 | 42.1 | 9.62  | 1.80 |   |
| 62          | 2.3                   | 5.3 | 45.2 | 8.02  | 1.91 |   |
| 63          | 2.1                   | 6.4 | 46.0 | 9.80  | 1.77 |   |
| 64          | 2.3                   | 7.9 | 42.8 | 9.55  | 1.42 |   |
| 65          | 2.0                   | 7.8 | 45.2 | 10.54 | 2.72 |   |

000227

Betawell L-Arabinose APPENDIX 2

#### 2.12 CLINICAL BIOCHEMISTRY FEMALES END OF TREATMENT

| Total bilirubin<br>umol/L | Urea<br>mmol/L   | Creatinine<br>umol/L  | Glucose<br>mmol/L  | Cholesterol<br>mmol/L  |  |
|---------------------------|--|---|--|--|--|
| 0000 PPM)                 |  |   |  |  |  |
| 2.2                       | 5.4  | 43.6  | 6.70   | 1.60   |  |
| 2.5                       | 5.5  | 45.2  | 8.96   | 2.14   |  |
| 2.2                       | 5.6  | 42.1  | 8.23   | 1.95   |  |
| 2.6                       | 7.3  | 42.8  | 7.53   | 1.59   |  |
| 1.7                       | 9.2  | 43.6  | 10.06  | 1.58   |  |
| 0000 PPM)                 |  |   |  |  |  |
| 3.5                       | 5.3  | 37.4  | 8.19   | 2.07   |  |
| 2.2                       | 8.2  | 42.8  | 8.66   | 1.90   |  |
| 1.7                       | 8.4  | 41.3  | 10.18  | 2.16   |  |
| 2.1                       | 6.0  | 42.8  | 9.89   | 1.96   |  |
| 2.1                       | 7.2  | 41.3  | 11.22  | 1.91   |  |
| 2.7                       | 5.2  | 42.1  | 8.32   | 1.78   |  |
| 2.0                       | 7.4  | 36.6  | 11.05  | 1.53   |  |
| 3.3                       | 4.8  | 42.8  | 11.47  | 1.95   |  |
| 3.3                       | 6.7  | 39.0  | 9.67   | 1.70   |  |
| 3.6                       | 6.0  | 41.3  | 10.91  | 1.34   |  |
|                           | umol/L  2000 PPM) 2.2 2.5 2.2 2.6 1.7  2000 PPM) 3.5 2.2 1.7 2.1 2.1 2.7 2.0 3.3 3.3 | umol/L mmol/L  2000 PPM)  2.2 5.4  2.5 5.5  2.2 5.6  2.6 7.3  1.7 9.2  2000 PPM)  3.5 5.3  2.2 8.2  1.7 8.4  2.1 6.0  2.1 7.2  2.7 5.2  2.0 7.4  3.3 4.8  3.3 6.7 | Umol/L   mmol/L   umol/L   umol/L     Umol/L     Umol/L       Umol/L | Umol/L   mmol/L   umol/L   mmol/L   m |  |

| ANIMAL    | Bile Acids<br>umol/L | Sodium<br>mmol/L | Potassium<br>mmol/L | Chloride<br>mmol/L | Calcium<br>mmol/L |  |
|-----------|----------------------|------------------|---------------------|--------------------|-------------------|--|
| GROUP 1 ( | CONTROL)             |                  |                     |                    |                   |  |
| 41        |                      | 140.5            | 3.86                | 103                | 2.60              |  |
| 42        | 9.9                  | 143.0            | 3.81                | 105                | 2.74              |  |
| 43        | 8.4                  | 140.9            | 3.57                | 105                | 2.62              |  |
| 14        | 14.5                 | 142.8            | 3.54                | 105                | 2.58              |  |
| 45        | 16.2                 | 139.6            | 3.69                | 106                | 2.60              |  |
| 46        | 13.7                 | 142.4            | 3.67                | 104                | 2.74              |  |
| 47        | 13.4                 | 141.7            | 3.83                | 106                | 2.69              |  |
| 48        | 19.1                 | 141.6            | 3.99                | 105                | 2.72              |  |
| 49        | 12.0                 | 142.5            | 3.69                | 105                | 2.64              |  |
| 50        | 16.7                 | 141.2            | 3.84                | 103                | 2.73              |  |
| GROUP 2 ( | 3000 PPM)            |                  |                     |                    |                   |  |
| 51 `      | 7.2                  | 140.8            | 3.54                | 107                | 2.51              |  |
| 52        | 14.1                 | 141.3            | 4.38                | 106                | 2.67              |  |
| 53        | 8.5                  | 143.2            | 3.62                | 107                | 2.52              |  |
| 54        | 27.3                 | 142.2            | 3.80                | 105                | 2.67              |  |
| 55        | 17.1                 | 141.5            | 3.60                | 108                | 2.51              |  |
| 56        | 38.1                 | 140.7            | 4.05                | 105                | 2.68              |  |
| 57        | 16.4                 | 142.5            | 3.95                | 106                | 2.70              |  |
| 58        | 11.8                 | 142.8            | 3.47                | 107                | 2.57              |  |
| 59        | 8.3                  | 143.4            | 3.49                | 108                | 2.48              |  |
| 60        | 18.7                 | 141.4            | 3.74                | 105                | 2.68              |  |
| GROUP 3 ( | 10000 PPM)           |                  |                     |                    |                   |  |
| 61 `      | 26.3                 | 142.6            | 3.66                | 104                | 2.78              |  |
| 52        | 13.5                 | 143.3            | 3.42                | 106                | 2.69              |  |
| 33        | 16.7                 | 142.7            | 3.34                | 108                | 2.63              |  |
| 64        | 20.8                 | 141.9            | 3.84                | 106                | 2.59              |  |
| 35        | 7.2                  | 141.9            | 3.41                | 107                | 2.62              |  |
| 66        | 12.6                 | 143.7            | 3.52                | 107                | 2.63              |  |
| 67        | 13.4                 | 142.4            | 3.40                | 107                | 2.60              |  |
| 38        | 19.7                 | 142.7            | 3.55                | 105                | 2.74              |  |
| 39        | 21.2                 | 143.6            | 3.83                | 105                | 2.68              |  |
| 70        | 22.2                 | 143.3            | 4.04                | 104                | 2.66              |  |

| ANIMAL    | Bile Acids<br>umol/L | Sodium<br>mmol/L | Potassium<br>mmol/L | Chloride<br>mmol/L | Calcium<br>mmol/L |  |
|-----------|----------------------|------------------|---------------------|--------------------|-------------------|--|
| GROUP 4 ( | 30000 PPM)           |                  |                     |                    |                   |  |
| 71        | 15.0                 | 141.8            | 3.83                | 103                | 2.81              |  |
| 72        | 15.2                 | 141.1            | 4.16                | 103                | 2.72              |  |
| 73        | 35.4                 | 141.0            | 3.67                | 105                | 2.58              |  |
| 74        | 16.2                 | 141.6            | 3.30                | 104                | 2.64              |  |
| 75        | 20.9                 | 141.9            | 3.59                | 104                | 2.64              |  |
| 76        | 14.3                 | 143.0            | 3.57                | 107                | 2.59              |  |
| 77        | 13.4                 | 141.6            | 3.97                | 102                | 2.65              |  |
| 78        | 27.9                 | 141.6            | 3.42                | 104                | 2.65              |  |
| 79        | 25.1                 | 142.3            | 3.82                | 104                | 2.74              |  |
| 80        | 52.5                 | 141.4            | 3.71                | 104                | 2.71              |  |

#### FEMALES END OF TREATMENT

| ANIMAL | Inorg.Phos |
|--------|------------|
|        | mmol/L     |

| GROUP 1 (41) 42 43 44 45 46 47 48 49 50 | 1.39<br>1.26<br>0.93<br>1.56<br>0.92<br>1.26<br>1.37<br>1.76<br>1.32<br>0.91 |
|---|--|
| <b>GROUP 2 (</b> 51                     | <b>3000 PPM)</b><br>1.15   |
| 51                                      | 1.13   |
| 52                                      | 1.39   |
| 53                                      | 1.21   |
| 54                                      | 1.45   |
| 55                                      | 0.80   |
| 56                                      | 1.03   |
| 57                                      | 1.30   |
| 58                                      | 0.99   |
| 59                                      | 0.98   |

# GROUP 3 (10000 PPM)

1.07

60

| 61 | 0.87 |
|----|------|
| 62 | 1.31 |
| 63 | 0.83 |
| 64 | 0.90 |
| 65 | 0.74 |
| 66 | 0.76 |
| 67 | 0.88 |
| 68 | 1.13 |
| 69 | 1.21 |
| 70 | 1.11 |
|    |      |

# GROUP 4 (30000 PPM)

| 71 | 1.45 |
|----|------|
| 72 | 1.46 |
| 73 | 0.91 |
| 74 | 1.33 |
| 75 | 1.41 |

| ANIMAL | Inorg.Phos |  |
|--------|------------|--|
|        | mmol/L     |  |

# GROUP 4 (30000 PPM)

| 76 | 0.92 |
|----|------|
| 77 | 1.36 |
| 78 | 0.81 |
| 79 | 1.54 |
| 80 | 1.61 |

Betawell L-Arabinose APPENDIX 2

# 2.13 MACROSCOPIC FINDINGS MALES

# ALL NECROPSIES

| ANIMAL       | ORGAN                 | FINDING                                | DAY OF DEATH                               |
|--------------|-----------------------|--|--|
| GROUP 1      | I (CONTROL)           |  |  |
| 1            | ` ,                   | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 2            |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 3            |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 4            |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 5            |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 6            |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 7            |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 8            |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 9            |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 10           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
|              | (0000 DDII)           | rte illianige notea                    | 33/134/134 345/11/35, 35/135 <u>2</u> 3/13 |
| GROUP 2      | 2 (3000 PPM)          | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 12           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 13           | Preputial glands      | Right side: focus/foci, d=5x2 mm, tan. | Scheduled sacrifice, 04Feb2016             |
| 14           | r reputtat glarias    | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 15           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 16           |                       |  | •  |
| 17           | Thyroid aland         | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
|              | Thyroid gland         | Both sides: reduced in size.           | Scheduled sacrifice, 05Feb2016             |
| 18           | Mandibular lymph n    | Right side: discolouration, purple.    | Scheduled sacrifice, 05Feb2016             |
| 19           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 20           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
|              | 3 (10000 PPM)         |  | 0.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1    |
| 21           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 22           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 23           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 24           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 25           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 26           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 27           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 28           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 29           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 30           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| GROUP 4      | 1 (30000 PPM)         |  |  |
| 31           | Bone                  | Sternum: malaligned.                   | Scheduled sacrifice, 04Feb2016             |
| 32           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 33           |                       | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 34           | Thymus                | Focus/foci, many, reddish.             | Scheduled sacrifice, 04Feb2016             |
| 35           | •                     | No findings noted                      | Scheduled sacrifice, 04Feb2016             |
| 36           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 37           | Testes                | Both sides: reduced in size.           | Scheduled sacrifice, 05Feb2016             |
|              | Epididymides          | Both sides: reduced in size.           |  |
| 38           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 39           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
| 40           |                       | No findings noted                      | Scheduled sacrifice, 05Feb2016             |
|              |                       |  |  |
| FEMALES      | S                     |  |  |
| ALL NEC      | ROPSIES               |  |  |
| A N II M A I | ODCAN                 | FINDING                                | DAY OF DEATH                               |
| ANIMAL       | ORGAN                 | FINDING                                | DAY OF DEATH                               |
| GPOUR 4      | L (CONTROL)           |  |  |
| 41           | I (CONTROL)<br>Thymus | Focus/foci many tan                    | Scheduled sacrifice, 04Feb2016             |
| <b>→</b> 1   |                       | Focus/foci, many, tan.                 | Scrieduled Sacrifice, 04Feb2010            |
|              | Axillary lymph node   | Both sides: enlarged.                  |  |
|              | Manadibudae bereiter  | Both sides: discolouration, reddish.   |  |
|              | Mandibular lymph n    | Both sides: discolouration, red-brown. |  |
|              | Skin                  | Shoulder, left side: scab formation,   |  |
|              |                       | several.                               |  |

# 2.13 MACROSCOPIC FINDINGS FEMALES

# ALL NECROPSIES

| ANIMAL   | ORGAN            | FINDING   | DAY OF DEATH   |
|----------|------------------|---|--|
| GROUP '  | I (CONTROL)      |   |  |
|          | ,                | Cheek region, left side: scab formation,        |  |
|          |                  | several.  |  |
|          |                  | Shoulder, right side: scab formation,           |  |
|          |                  | several.  | 0.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1                          |
| 42       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 43       | l Hamisa         | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 44<br>45 | Uterus<br>Uterus | Contains fluid.<br>Contains fluid.              | Scheduled sacrifice, 04Feb2016<br>Scheduled sacrifice, 04Feb2016 |
| 46       | Oterus           | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 40<br>47 | Spleen           | Nodule(s), d=5x4 mm, dark red, soft.            | Scheduled sacrifice, 04Feb2016                                   |
| 48       | Opiceri          | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 49       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 50       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
|          |                  |   |  |
|          | 2 (3000 PPM)     |   | 0  |
| 51       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 52       | Stomach          | Glandular mucosa: focus/foci, several, reddish. | Scheduled sacrifice, 04Feb2016                                   |
|          | Thymus           | Focus/foci, many, reddish.                      |  |
|          | Skin             | Dorso-lumbar region: scab formation,            |  |
|          |                  | many.   | 0.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1                          |
| 53       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 54       | 1.14             | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 55<br>56 | Uterus           | Contains fluid                                  | Scheduled sacrifice, 04Feb2016                                   |
| 56<br>57 | Uterus<br>Uterus | Contains fluid. Contains fluid.                 | Scheduled sacrifice, 04Feb2016<br>Scheduled sacrifice, 04Feb2016 |
| 57<br>58 | Oterus           | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 59       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 60       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| GROUP :  | 3 (10000 PPM)    |   |  |
| 61       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 62       | Ctoruo           | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 63       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 64       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 65       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 66       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 67       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 68       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 69       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 70       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| GROUP 4  | 4 (30000 PPM)    |   |  |
| 71       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 72       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 73       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 74       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 75       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 76       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 77       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 78       | Uterus           | Contains fluid.                                 | Scheduled sacrifice, 04Feb2016                                   |
| 79       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |
| 80       |                  | No findings noted                               | Scheduled sacrifice, 04Feb2016                                   |

| ANIMAL    | BODY W.<br>(GRAM) | BRAIN<br>(GRAM) | HEART<br>(GRAM) | LIVER<br>(GRAM) |  |
|-----------|-------------------|-----------------|-----------------|-----------------|--|
| GROUP 1 ( | CONTROL)          |                 |                 |                 |  |
| 1 `       | 315 <sup>*</sup>  | 1.91            | 0.807           | 6.87            |  |
| 2         | 403               | 2.10            | 1.091           | 8.84            |  |
| 3         | 380               | 2.06            | 0.964           | 10.68           |  |
| 4         | 335               | 2.02            | 0.832           | 7.69            |  |
| 5         | 354               | 2.07            | 0.848           | 7.65            |  |
| 6         | 350               | 1.97            | 0.890           | 8.33            |  |
| 7         | 339               | 2.09            | 0.812           | 7.74            |  |
| 8         | 371               | 1.88            | 0.916           | 8.69            |  |
| 9         | 365               | 1.97            | 0.890           | 8.75            |  |
| 10        | 367               | 1.96            | 0.914           | 8.42            |  |
| 10        | 307               | 1.90            | 0.914           | 0.42            |  |
| GROUP 2 ( | •                 |                 |                 |                 |  |
| 11        | 341               | 1.95            | 0.853           | 8.18            |  |
| 12        | 420               | 2.03            | 1.117           | 10.26           |  |
| 13        | 405               | 2.08            | 0.981           | 9.45            |  |
| 14        | 315               | 1.87            | 0.850           | 7.67            |  |
| 15        | 307               | 2.04            | 0.794           | 6.77            |  |
| 16        | 397               | 2.09            | 0.926           | 9.39            |  |
| 17        | 333               | 1.93            | 0.910           | 8.11            |  |
| 18        | 363               | 1.96            | 0.900           | 9.51            |  |
| 19        | 367               | 2.06            | 0.909           | 8.95            |  |
| 20        | 376               | 2.08            | 0.974           | 8.84            |  |
| CDOUD 2 / | 40000 DDM)        |                 |                 |                 |  |
|           | 10000 PPM)        | 4.00            | 0.040           | 0.50            |  |
| 21        | 329               | 1.96            | 0.813           | 8.58            |  |
| 22        | 406               | 2.03            | 1.024           | 9.45            |  |
| 23        | 367               | 2.08            | 0.886           | 9.24            |  |
| 24        | 343               | 1.87            | 0.825           | 8.38            |  |
| 25        | 433               | 1.99            | 1.124           | 11.24           |  |
| 26        | 386               | 2.13            | 1.179           | 9.23            |  |
| 27        | 389               | 2.04            | 0.985           | 9.45            |  |
| 28        | 349               | 1.92            | 0.825           | 8.66            |  |
| 29        | 339               | 2.02            | 0.884           | 7.80            |  |
| 30        | 360               | 2.00            | 0.943           | 10.02           |  |
| GROUP 4 ( | 30000 PPM)        |                 |                 |                 |  |
| 31        | 321               | 1.89            | 0.821           | 7.94            |  |
| 32        | 357               | 2.05            | 0.859           | 8.18            |  |
| 33        | 364               | 1.96            | 0.929           | 9.12            |  |
|           |                   |                 |                 |                 |  |
| 34        | 336               | 1.96            | 0.942           | 8.41            |  |
| 35        | 365               | 1.99            | 0.898           | 7.82            |  |
| 36        | 377               | 2.06            | 0.964           | 7.84            |  |
| 37        | 314               | 1.82            | 0.740           | 7.37            |  |
| 38        | 439               | 2.01            | 1.097           | 10.61           |  |
| 39        | 331               | 1.99            | 0.896           | 7.49            |  |
| 40        | 403               | 1.94            | 0.980           | 9.16            |  |

## MALES END OF TREATMENT

| ANIMAL    | THYROIDS<br>(GRAM) | THYMUS<br>(GRAM) | KIDNEYS<br>(GRAM) | ADRENALS<br>(GRAM) |  |
|-----------|--------------------|------------------|-------------------|--------------------|--|
| GROUP 1 ( | CONTROL)           |                  |                   |                    |  |
| 1         | 0.022              | 0.243            | 2.05              | 0.044              |  |
| 2         | 0.026              | 0.353            | 2.69              | 0.051              |  |
| 3         | 0.016              | 0.278            | 2.53              | 0.068              |  |
| 4         | 0.016              | 0.289            | 2.11              | 0.038              |  |
| 5         | 0.013              | 0.305            | 2.10              | 0.049              |  |

000232

| ANIMAL               | THYROIDS<br>(GRAM) | THYMUS<br>(GRAM) | KIDNEYS<br>(GRAM) | ADRENALS<br>(GRAM) |  |
|----------------------|--------------------|------------------|-------------------|--------------------|--|
| GROUP 1 (0           | CONTROL)           |                  |                   |                    |  |
| 6                    | 0.013              | 0.379            | 2.11              | 0.047              |  |
| 7                    | 0.017              | 0.326            | 2.06              | 0.051              |  |
| 8                    | 0.015              | 0.323            | 2.22              | 0.037              |  |
| 9                    | 0.009              | 0.366            | 1.98              | 0.039              |  |
| 10                   | 0.022              | 0.311            | 2.06              | 0.049              |  |
| GROUP 2 (3           | ROOD PPM)          |                  |                   |                    |  |
| 11                   | 0.012              | 0.172            | 2.16              | 0.040              |  |
| 12                   | 0.012              | 0.304            | 3.16              | 0.053              |  |
| 13                   | 0.024              | 0.282            | 2.65              | 0.060              |  |
| 14                   | 0.008              | 0.205            | 2.03              | 0.000              |  |
| 15                   |                    |                  | 1.93              | 0.037              |  |
|                      | 0.013              | 0.219            |                   |                    |  |
| 16<br>17             | 0.018              | 0.214            | 2.38              | 0.064              |  |
| 17                   | 0.013              | 0.276            | 2.10              | 0.049              |  |
| 18                   | 0.013              | 0.470            | 2.25              | 0.052              |  |
| 19                   | 0.020              | 0.306            | 2.35              | 0.057              |  |
| 20                   | 0.016              | 0.308            | 2.58              | 0.047              |  |
|                      | 10000 PPM)         |                  |                   |                    |  |
| 21                   | 0.013              | 0.297            | 2.32              | 0.048              |  |
| 22                   | 0.014              | 0.273            | 2.52              | 0.051              |  |
| 23                   | 0.021              | 0.291            | 2.43              | 0.054              |  |
| 24                   | 0.013              | 0.248            | 2.11              | 0.043              |  |
| 25                   | 0.017              | 0.272            | 2.90              | 0.046              |  |
| 26                   | 0.016              | 0.340            | 2.46              | 0.043              |  |
| 27                   | 0.016              | 0.269            | 2.47              | 0.056              |  |
| 28                   | 0.017              | 0.277            | 2.06              | 0.040              |  |
| 29                   | 0.011              | 0.303            | 2.14              | 0.040              |  |
| 30                   | 0.011              | 0.264            | 2.47              | 0.052              |  |
| GROUP 4 (            | 30000 PPM)         |                  |                   |                    |  |
| 31                   | 0.010              | 0.175            | 2.05              | 0.036              |  |
| 32                   | 0.020              | 0.333            | 2.24              | 0.045              |  |
| 33                   | 0.017              | 0.257            | 2.23              | 0.047              |  |
| 34                   | 0.017              | 0.263            | 2.23              | 0.047              |  |
| 3 <del>4</del><br>35 | 0.011              | 0.250            | 2.50              | 0.050              |  |
| 36                   | 0.013              | 0.242            |                   | 0.050              |  |
|                      |                    |                  | 2.29              |                    |  |
| 37                   | 0.013              | 0.297            | 1.77              | 0.041              |  |
| 38                   | 0.012              | 0.369            | 2.79              | 0.041              |  |
| 39                   | 0.014              | 0.254            | 1.88              | 0.040              |  |
| 40                   | 0.017              | 0.335            | 2.34              | 0.052              |  |

#### MALES END OF TREATMENT

| ANIMAL     | SPLEEN<br>(GRAM) | TESTES<br>(GRAM) | PROSTATE GLAND<br>(GRAM) | EPIDIDYMIDES<br>(GRAM) |
|------------|------------------|------------------|--------------------------|------------------------|
| GROUP 1 (C | CONTROL)         |                  |                          |                        |
| 1          | 0.346            | 3.62             | 1.040                    | 1.191                  |
| 2          | 0.581            | 3.45             | 0.930                    | 1.214                  |
| 3          | 0.584            | 3.45             | 1.348                    | 1.187                  |
| 4          | 0.368            | 3.71             | 0.833                    | 1.184                  |
| 5          | 0.471            | 3.83             | 0.765                    | 1.297                  |
| 6          | 0.569            | 3.44             | 1.025                    | 1.125                  |
| 7          | 0.458            | 3.50             | 0.976                    | 1.128                  |
| 8          | 0.483            | 3.51             | 1.134                    | 1.211                  |
| 9          | 0.511            | 3.47             | 0.842                    | 1.046                  |
| 10         | 0.596            | 3.38             | 0.952                    | 1.284                  |

000233

Betawell L-Arabinose APPENDIX 2

| ANIMAL    | SPLEEN<br>(GRAM) | TESTES<br>(GRAM) | PROSTATE GLAND<br>(GRAM) | EPIDIDYMIDES<br>(GRAM) |
|-----------|------------------|------------------|--------------------------|------------------------|
| GROUP 2 ( | 3000 PPM)        |                  |                          |                        |
| 11        | 0.493            | 3.50             | 0.805                    | 1.080                  |
| 12        | 0.602            | 3.77             | 0.568                    | 1.209                  |
| 13        | 0.642            | 3.80             | 1.168                    | 1.375                  |
| 14        | 0.585            | 3.35             | 0.872                    | 1.096                  |
| 15        | 0.482            | 3.44             | 0.623                    | 1.129                  |
| 16        | 0.529            | 3.57             | 0.884                    | 1.137                  |
| 17        | 0.546            | 3.24             | 1.145                    | 1.102                  |
| 18        | 0.556            | 3.21             | 0.772                    | 1.043                  |
| 19        | 0.476            | 3.59             | 0.969                    | 1.222                  |
| 20        | 0.599            | 3.24             | 1.147                    | 1.184                  |
| 20        | 0.599            | 3.24             | 1.147                    | 1.104                  |
|           | 10000 PPM)       |                  |                          |                        |
| 21        | 0.501            | 3.33             | 0.683                    | 1.142                  |
| 22        | 0.608            | 4.00             | 0.894                    | 1.419                  |
| 23        | 0.467            | 3.50             | 0.881                    | 1.247                  |
| 24        | 0.419            | 3.49             | 1.074                    | 1.158                  |
| 25        | 0.601            | 3.64             | 0.952                    | 1.302                  |
| 26        | 0.555            | 3.74             | 0.579                    | 1.182                  |
| 27        | 0.583            | 3.93             | 0.720                    | 1.320                  |
| 28        | 0.473            | 3.44             | 0.792                    | 1.169                  |
| 29        | 0.482            | 3.45             | 0.868                    | 1.146                  |
| 30        | 0.610            | 3.98             | 0.684                    | 1.209                  |
| GROUP 4 ( | 30000 PPM)       |                  |                          |                        |
| 31 `      | 0.470            | 3.36             | 0.655                    | 0.988                  |
| 32        | 0.482            | 3.79             | 1.107                    | 1.254                  |
| 33        | 0.525            | 3.64             | 1.081                    | 1.239                  |
| 34        | 0.459            | 3.65             | 0.850                    | 1.218                  |
| 35        | 0.505            | 3.79             | 0.940                    | 1.310                  |
| 36        | 0.672            | 3.82             | 1.174                    | 1.266                  |
| 37        | 0.384            | 1.83             | 0.741                    | 0.693                  |
| 38        | 0.633            | 3.67             | 1.107                    | 1.192                  |
| 39        | 0.547            | 3.20             | 0.762                    | 1.074                  |
| 40        | 0.581            | 3.68             | 0.901                    | 1.168                  |
| MALES     | REATMENT         |                  |                          |                        |

ANIMAL SEMINAL VESICLES

(GRAM)

1.465 1.820 1.166

0.961

**GROUP 1 (CONTROL)** 1.538 1 2 3 4 5 1.711 1.299 0.977 1.716 6 7 0.978 0.930 1.707 1.501 8 9 10 1.506 GROUP 2 (3000 PPM) 11 1.461

12 13

14 15

Final Report 25Mar16 09h13

ANIMAL SEMINAL VESICLES

(GRAM)

#### GROUP 2 (3000 PPM) 16 17 1.210 1.377 1.289 18 19 1.685 1.585 20 **GROUP 3 (10000 PPM)** 21 1.518 22 23 1.743 1.846 24 1.517 25 1.380 26 1.373 27 1.621 28 1.122 29 1.655 30 1.335 GROUP 4 (30000 PPM) 31 1.174

31 1.174 32 1.574 33 1.922 34 1.554 35 1.806 36 1.464 37 1.509 38 1.654 39 1.518 40 1.709

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) MALES END OF TREATMENT

| ANIMAL    | BODY W.<br>(GRAM) | BRAIN<br>(%) | HEART<br>(%) | LIVER<br>(%) |  |
|-----------|-------------------|--------------|--------------|--------------|--|
| GROUP 1 ( | CONTROL)          |              |              |              |  |
| 1         | 315 <sup>′</sup>  | 0.61         | 0.256        | 2.18         |  |
| 2         | 403               | 0.52         | 0.271        | 2.19         |  |
| 3         | 380               | 0.54         | 0.254        | 2.81         |  |
| 4         | 335               | 0.60         | 0.248        | 2.29         |  |
| 5         | 354               | 0.59         | 0.240        | 2.16         |  |
| 6         | 350               | 0.56         | 0.254        | 2.38         |  |
| 7         | 339               | 0.62         | 0.240        | 2.28         |  |
| 8         | 371               | 0.51         | 0.247        | 2.34         |  |
| 9         | 365               | 0.54         | 0.244        | 2.40         |  |
| 10        | 367               | 0.53         | 0.249        | 2.29         |  |
|           |                   |              |              |              |  |
| GROUP 2 ( |                   | 0.57         | 0.250        | 2.40         |  |
| 11        | 341               | 0.57         | 0.250        |              |  |
| 12        | 420               | 0.48         | 0.266        | 2.44         |  |
| 13        | 405               | 0.51         | 0.242        | 2.33         |  |
| 14        | 315               | 0.59         | 0.270        | 2.43         |  |
| 15        | 307               | 0.66         | 0.259        | 2.21         |  |
| 16        | 397               | 0.53         | 0.233        | 2.36         |  |
| 17        | 333               | 0.58         | 0.273        | 2.44         |  |
| 18        | 363               | 0.54         | 0.248        | 2.62         |  |
| 19        | 367               | 0.56         | 0.248        | 2.44         |  |
| 20        | 376               | 0.55         | 0.259        | 2.35         |  |
| GROUP 3 ( | 10000 PPM)        |              |              |              |  |
| 21 `      | 329               | 0.59         | 0.247        | 2.61         |  |
| 22        | 406               | 0.50         | 0.252        | 2.33         |  |
| 23        | 367               | 0.57         | 0.241        | 2.52         |  |
| 24        | 343               | 0.55         | 0.241        | 2.44         |  |
| 25        | 433               | 0.46         | 0.260        | 2.60         |  |
| 26        | 386               | 0.55         | 0.305        | 2.39         |  |
| 27        | 389               | 0.52         | 0.253        | 2.43         |  |
| 28        | 349               | 0.55         | 0.236        | 2.48         |  |
| 29        | 339               | 0.60         | 0.261        | 2.30         |  |
| 30        | 360               | 0.56         | 0.262        | 2.78         |  |
| GROUP # / | 30000 PPM)        |              |              |              |  |
| 31        | 321               | 0.59         | 0.256        | 2.47         |  |
| 32        | 357               | 0.57         | 0.230        | 2.47         |  |
| 33        | 364               | 0.54         | 0.255        | 2.51         |  |
| 34        | 336               | 0.54         | 0.280        | 2.50         |  |
|           |                   |              |              |              |  |
| 35        | 365               | 0.55         | 0.246        | 2.14         |  |
| 36        | 377               | 0.55         | 0.256        | 2.08         |  |
| 37        | 314               | 0.58         | 0.236        | 2.35         |  |
| 38        | 439               | 0.46         | 0.250        | 2.42         |  |
| 39        | 331               | 0.60         | 0.271        | 2.26         |  |
| 40        | 403               | 0.48         | 0.243        | 2.27         |  |

| ANIMAL    | THYROIDS<br>(%) | THYMUS<br>(%) | KIDNEYS<br>(%) | ADRENALS<br>(%) |  |
|-----------|-----------------|---------------|----------------|-----------------|--|
| GROUP 1 ( | CONTROL)        |               |                |                 |  |
| 1         | 0.007           | 0.077         | 0.65           | 0.014           |  |
| 2         | 0.006           | 0.088         | 0.67           | 0.013           |  |
| 3         | 0.004           | 0.073         | 0.67           | 0.018           |  |
| 4         | 0.005           | 0.086         | 0.63           | 0.011           |  |
| 5         | 0.004           | 0.086         | 0.59           | 0.014           |  |

000237

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) MALES END OF TREATMENT

| ANIMAL    | THYROIDS<br>(%) | THYMUS<br>(%)  | KIDNEYS<br>(%)           | ADRENALS<br>(%) |  |
|-----------|-----------------|----------------|--------------------------|-----------------|--|
| GROUP 1 ( | CONTROL)        |                |                          |                 |  |
| 6         | 0.004           | 0.108          | 0.60                     | 0.013           |  |
| 7         | 0.005           | 0.096          | 0.61                     | 0.015           |  |
| 8         | 0.004           | 0.087          | 0.60                     | 0.010           |  |
| 9         | 0.002           | 0.100          | 0.54                     | 0.011           |  |
| 10        | 0.006           | 0.085          | 0.56                     | 0.013           |  |
| GROUP 2 ( | 2000 DDM\       |                |                          |                 |  |
| 11        | 0.004           | 0.050          | 0.63                     | 0.012           |  |
| 12        | 0.004           | 0.072          | 0.75                     | 0.012           |  |
| 13        | 0.000           | 0.072          | 0.75                     | 0.015           |  |
| 14        | 0.003           | 0.065          | 0.68                     | 0.013           |  |
| 15        | 0.003           | 0.065          | 0.63                     | 0.012           |  |
| 16        | 0.004           | 0.071          | 0.60                     | 0.022           |  |
| 17        | 0.004           | 0.054          | 0.63                     | 0.016           |  |
|           |                 |                |                          |                 |  |
| 18        | 0.003           | 0.129          | 0.62                     | 0.014           |  |
| 19        | 0.005           | 0.083          | 0.64                     | 0.016           |  |
| 20        | 0.004           | 0.082          | 0.68                     | 0.013           |  |
| GROUP 3 ( | 10000 PPM)      |                |                          |                 |  |
| 21        | 0.004           | 0.090          | 0.70                     | 0.015           |  |
| 22        | 0.003           | 0.067          | 0.62                     | 0.013           |  |
| 23        | 0.006           | 0.079          | 0.66                     | 0.015           |  |
| 24        | 0.004           | 0.072          | 0.61                     | 0.013           |  |
| 25        | 0.004           | 0.063          | 0.67                     | 0.011           |  |
| 26        | 0.004           | 0.088          | 0.64                     | 0.011           |  |
| 27        | 0.004           | 0.069          | 0.64                     | 0.014           |  |
| 28        | 0.005           | 0.079          | 0.59                     | 0.011           |  |
| 29        | 0.003           | 0.089          | 0.63                     | 0.012           |  |
| 30        | 0.003           | 0.073          | 0.69                     | 0.014           |  |
| GROUP 4 ( | 30000 PPM)      |                |                          |                 |  |
| 31        | 0.003           | 0.055          | 0.64                     | 0.011           |  |
| 32        | 0.006           | 0.093          | 0.63                     | 0.013           |  |
| 33        | 0.005           | 0.071          | 0.61                     | 0.013           |  |
| 34        | 0.003           | 0.078          | 0.60                     | 0.010           |  |
| 35        | 0.003           | 0.068          | 0.68                     | 0.014           |  |
| 36        | 0.004           | 0.064          | 0.61                     | 0.014           |  |
| 37        | 0.003           | 0.004          | 0.56                     | 0.013           |  |
|           | 0.004           |                | 0.64                     | 0.013           |  |
| 38        | 0.003           | 0.084<br>0.077 | 0.6 <del>4</del><br>0.57 | 0.009           |  |
| 39        |                 |                |                          |                 |  |
| 40        | 0.004           | 0.083          | 0.58                     | 0.013           |  |

| ANIMAL     | SPLEEN<br>(%) | TESTES<br>(%) | PROSTATE GLAND (%) | EPIDIDYMIDES (%) |
|------------|---------------|---------------|--------------------|------------------|
| GROUP 1 (0 | CONTROL)      |               |                    |                  |
| 1          | 0.110         | 1.15          | 0.330              | 0.378            |
| 2          | 0.144         | 0.86          | 0.231              | 0.301            |
| 3          | 0.154         | 0.91          | 0.355              | 0.312            |
| 4          | 0.110         | 1.11          | 0.249              | 0.353            |
| 5          | 0.133         | 1.08          | 0.216              | 0.366            |
| 6          | 0.163         | 0.98          | 0.293              | 0.321            |
| 7          | 0.135         | 1.03          | 0.288              | 0.333            |
| 8          | 0.130         | 0.95          | 0.306              | 0.326            |
| 9          | 0.140         | 0.95          | 0.231              | 0.287            |
| 10         | 0.162         | 0.92          | 0.259              | 0.350            |

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) MALES END OF TREATMENT

| ANIMAL               | SPLEEN<br>(%)  | TESTES<br>(%) | PROSTATE GLAND<br>(%) | EPIDIDYMIDES (%) |
|----------------------|----------------|---------------|-----------------------|------------------|
| GROUP 2 (            | 3000 PPM)      |               |                       |                  |
| 11                   | 0.145          | 1.03          | 0.236                 | 0.317            |
| 12                   | 0.143          | 0.90          | 0.135                 | 0.288            |
| 13                   | 0.159          | 0.94          | 0.288                 | 0.340            |
| 14                   | 0.186          | 1.06          | 0.277                 | 0.348            |
| 15                   | 0.157          | 1.12          | 0.203                 | 0.368            |
| 16                   | 0.133          | 0.90          | 0.223                 | 0.286            |
| 17                   | 0.164          | 0.97          | 0.344                 | 0.331            |
| 18                   | 0.153          | 0.88          | 0.213                 | 0.287            |
| 19                   | 0.130          | 0.98          | 0.264                 | 0.333            |
| 20                   | 0.159          | 0.86          | 0.305                 | 0.315            |
| 20                   | 0.100          | 0.00          | 0.000                 | 0.010            |
|                      | 10000 PPM)     |               |                       |                  |
| 21                   | 0.152          | 1.01          | 0.208                 | 0.347            |
| 22                   | 0.150          | 0.99          | 0.220                 | 0.350            |
| 23                   | 0.127          | 0.95          | 0.240                 | 0.340            |
| 24                   | 0.122          | 1.02          | 0.313                 | 0.338            |
| 25                   | 0.139          | 0.84          | 0.220                 | 0.301            |
| 26                   | 0.144          | 0.97          | 0.150                 | 0.306            |
| 27                   | 0.150          | 1.01          | 0.185                 | 0.339            |
| 28                   | 0.136          | 0.99          | 0.227                 | 0.335            |
| 29                   | 0.142          | 1.02          | 0.256                 | 0.338            |
| 30                   | 0.169          | 1.11          | 0.190                 | 0.336            |
| GROUP 4 (            | 30000 PPM)     |               |                       |                  |
| 31                   | 0.146          | 1.05          | 0.204                 | 0.308            |
| 32                   | 0.135          | 1.06          | 0.204                 | 0.351            |
| 33                   | 0.144          | 1.00          | 0.297                 | 0.340            |
| 34                   | 0.144          | 1.00          | 0.257                 | 0.363            |
| 3 <del>4</del><br>35 | 0.138          | 1.09          | 0.258                 | 0.359            |
| 36                   | 0.136<br>0.178 | 1.04          | 0.256                 | 0.336            |
| 36<br>37             | 0.176          | 0.58          | 0.236                 | 0.336            |
| 3 <i>1</i><br>38     | 0.122          | 0.84          | 0.252                 | 0.221            |
| 38<br>39             |                |               | 0.232                 | 0.272<br>0.324   |
|                      | 0.165          | 0.97          |                       |                  |
| 40                   | 0.144          | 0.91          | 0.224                 | 0.290            |
| MALES<br>END OF TR   | REATMENT       |               |                       |                  |
|                      |                |               |                       |                  |

(%)

0.349 0.449 0.370

0.313

**GROUP 1 (CONTROL)** 0.488 0.425 1 2 3 4 5 0.342 0.292 0.485 6 7 0.279 0.274 0.460 0.411 8 9 10 0.410 GROUP 2 (3000 PPM) 11 0.428 12 13

14 15

Betawell L-Arabinose APPENDIX 2

#### 2.14 ORGAN/BODY WEIGHT RATIOS (%) **MALES END OF TREATMENT**

ANIMAL SEMINAL VESICLES (%)

GROUP 2 (3000 PPM) 0.305 0.414 16 17 0.355 18 19 0.459 0.422 20

#### GROUP 3 (10000 PPM)

0.461 0.429 21 22 23 0.503 24 0.442 25 0.319 26 0.356 27 0.417 28 0.321 29 0.488 30 0.371

### GROUP 4 (30000 PPM)

| 0.366 |
|-------|
| 0.441 |
| 0.528 |
| 0.463 |
| 0.495 |
| 0.388 |
| 0.481 |
| 0.377 |
| 0.459 |
| 0.424 |
|       |

Final Report 25Mar16 09h13

| GROUP 1 (C<br>41<br>42<br>43<br>44<br>45<br>46<br>47 | ONTROL) 237 235 242 221 227 236 | 1.96<br>1.90<br>1.95 | 0.671<br>0.731 | 6.47 |  |
|--|---------------------------------|----------------------|----------------|------|--|
| 42<br>43<br>44<br>45<br>46<br>47                     | 235<br>242<br>221<br>227        | 1.90                 |                | 6.47 |  |
| 43<br>44<br>45<br>46<br>47                           | 242<br>221<br>227               |                      | 0.731          |      |  |
| 44<br>45<br>46<br>47                                 | 221<br>227                      | 1.95                 | 0.731          | 5.44 |  |
| 44<br>45<br>46<br>47                                 | 221<br>227                      |                      | 0.776          | 6.25 |  |
| 45<br>46<br>47                                       | 227                             | 1.76                 | 0.633          | 5.00 |  |
| 46<br>47   |                                 | 1.96                 | 0.716          | 5.44 |  |
| 47   |                                 | 2.01                 | 0.682          | 6.03 |  |
|  | 257                             | 2.00                 | 0.702          | 5.94 |  |
| 48   | 205                             | 1.81                 | 0.625          | 5.95 |  |
| 49   | 253                             | 1.96                 | 0.760          | 6.38 |  |
| 50   | 215                             | 1.82                 | 0.646          | 5.56 |  |
|  |                                 | 1.02                 | 0.010          | 0.00 |  |
| <b>GROUP 2 (3)</b><br>51                             | <b>000 РРМ)</b><br>233          | 2.03                 | 0.718          | 6.22 |  |
| 52   | 233<br>242                      | 1.89                 | 0.718          | 6.34 |  |
|  | 211                             | 2.00                 |                | 5.61 |  |
| 53   |                                 |                      | 0.599          |      |  |
| 54   | 215                             | 1.92                 | 0.682          | 6.23 |  |
| 55   | 222                             | 1.81                 | 0.639          | 5.57 |  |
| 56   | 232                             | 1.90                 | 0.721          | 7.39 |  |
| 57   | 238                             | 1.91                 | 0.684          | 6.41 |  |
| 58   | 243                             | 1.94                 | 0.802          | 6.09 |  |
| 59   | 223                             | 1.86                 | 0.670          | 5.81 |  |
| 60   | 231                             | 1.94                 | 0.690          | 6.01 |  |
| <b>GROUP 3 (10</b>                                   |                                 |                      |                |      |  |
| 61   | 207                             | 1.93                 | 0.658          | 6.55 |  |
| 62   | 212                             | 1.87                 | 0.678          | 5.34 |  |
| 63   | 229                             | 1.86                 | 0.690          | 6.99 |  |
| 64   | 235                             | 1.93                 | 0.692          | 5.83 |  |
| 65   | 217                             | 1.82                 | 0.638          | 6.21 |  |
| 66   | 228                             | 1.86                 | 0.656          | 5.79 |  |
| 67   | 231                             | 1.83                 | 0.652          | 5.93 |  |
| 68   | 230                             | 1.87                 | 0.692          | 5.45 |  |
| 69   | 206                             | 2.02                 | 0.617          | 5.16 |  |
| 70   | 239                             | 1.91                 | 0.663          | 6.13 |  |
| GROUP 4 (3)  | 0000 PPM)                       |                      |                |      |  |
| 71   | 216                             | 1.85                 | 0.735          | 6.17 |  |
| 72   | 217                             | 1.82                 | 0.599          | 6.03 |  |
| 73   | 252                             | 1.89                 | 0.727          | 7.12 |  |
| 74   | 241                             | 1.88                 | 0.741          | 6.17 |  |
| 75   | 233                             | 1.92                 | 0.691          | 6.72 |  |
| 76   | 204                             | 1.64                 | 0.663          | 5.12 |  |
| 77<br>77   | 223                             | 1.92                 | 0.726          | 7.34 |  |
| 78   | 252                             | 1.91                 | 0.804          | 7.06 |  |
| 79   | 235                             | 1.92                 | 0.778          | 6.00 |  |
| 80   | 204                             | 1.91                 | 0.668          | 5.90 |  |

| ANIMAL    | THYROIDS<br>(GRAM) | THYMUS<br>(GRAM) | KIDNEYS<br>(GRAM) | ADRENALS<br>(GRAM) |  |
|-----------|--------------------|------------------|-------------------|--------------------|--|
| GROUP 1 ( | CONTROL)           |                  |                   |                    |  |
| 41        | 0.018              | 0.309            | 1.80              | 0.073              |  |
| 42        | 0.012              | 0.375            | 1.59              | 0.058              |  |
| 43        | 0.018              | 0.196            | 1.75              | 0.072              |  |
| 44        | 0.013              | 0.291            | 1.44              | 0.060              |  |
| 45        | 0.012              | 0.346            | 1.71              | 0.064              |  |

| ANIMAL          | THYROIDS<br>(GRAM)         | THYMUS<br>(GRAM) | KIDNEYS<br>(GRAM) | ADRENALS<br>(GRAM) |  |
|-----------------|----------------------------|------------------|-------------------|--------------------|--|
| GROUP 1 (       | CONTROL)                   |                  |                   |                    |  |
| 46              | 0.012                      | 0.329            | 1.65              | 0.071              |  |
| 47              | 0.020                      | 0.238            | 1.70              | 0.079              |  |
| 48              | 0.016                      | 0.234            | 1.46              | 0.064              |  |
| 49              | 0.021                      | 0.264            | 1.80              | 0.062              |  |
| 50              | 0.012                      | 0.432            | 1.40              | 0.062              |  |
|                 | 2000 DDM)                  |                  |                   |                    |  |
| GROUP 2 (       |                            | 0.346            | 1.67              | 0.085              |  |
| 51<br>52        | 0.017                      |                  |                   |                    |  |
| 52              | 0.013                      | 0.294            | 1.79              | 0.072              |  |
| 53              | 0.017                      | 0.288            | 1.54              | 0.070              |  |
| 54              | 0.012                      | 0.255            | 1.55              | 0.062              |  |
| 55              | 0.008                      | 0.309            | 1.45              | 0.071              |  |
| 56              | 0.016                      | 0.312            | 1.66              | 0.065              |  |
| 57              | 0.013                      | 0.239            | 1.91              | 0.069              |  |
| 58              | 0.018                      | 0.259            | 1.65              | 0.071              |  |
| 59              | 0.013                      | 0.368            | 1.67              | 0.077              |  |
| 60              | 0.010                      | 0.308            | 1.58              | 0.065              |  |
| GROUP 3 (       | 10000 PPM)                 |                  |                   |                    |  |
| 61              | 0.010                      | 0.267            | 1.63              | 0.062              |  |
| 62              | 0.013                      | 0.268            | 1.55              | 0.067              |  |
| 63              | 0.012                      | 0.271            | 1.61              | 0.064              |  |
| 64              | 0.013                      | 0.239            | 1.63              | 0.070              |  |
| 35              | 0.011                      | 0.225            | 1.49              | 0.060              |  |
| 66              | 0.014                      | 0.362            | 1.60              | 0.059              |  |
| 37<br>37        | 0.013                      | 0.291            | 1.63              | 0.057              |  |
| 57<br>58        | 0.017                      | 0.330            | 1.64              | 0.065              |  |
| 56<br>59        | 0.008                      | 0.245            | 1.38              | 0.069              |  |
| 70              | 0.008                      | 0.326            | 1.69              | 0.059              |  |
|                 |                            |                  |                   |                    |  |
| GROUP 4 (<br>71 | <b>30000 PPM)</b><br>0.012 | 0.297            | 1.42              | 0.056              |  |
| <br>72          | 0.015                      | 0.302            | 1.43              | 0.039              |  |
| 73              | 0.019                      | 0.218            | 1.78              | 0.067              |  |
| 74              | 0.015                      | 0.371            | 1.53              | 0.067              |  |
| 75              | 0.020                      | 0.332            | 1.64              | 0.080              |  |
| 76              | 0.020                      | 0.300            | 1.50              | 0.067              |  |
| 77              | 0.009                      | 0.244            | 1.64              | 0.067              |  |
|                 |                            |                  |                   |                    |  |
| 78<br>70        | 0.015                      | 0.254            | 1.92              | 0.082              |  |
| 79<br>20        | 0.013                      | 0.289            | 1.64              | 0.066              |  |
| 80              | 0.014                      | 0.331            | 1.41              | 0.055              |  |

# **END OF TREATMENT**

| ANIMAL    | SPLEEN<br>(GRAM) | OVARIES<br>(GRAM) | UTERUS<br>(GRAM) |  |
|-----------|------------------|-------------------|------------------|--|
| GROUP 1 ( | CONTROL)         |                   |                  |  |
| 41        | 0.354            | 0.123             | 0.490            |  |
| 42        | 0.416            | 0.150             | 0.659            |  |
| 43        | 0.457            | 0.136             | 0.696            |  |
| 44        | 0.344            | 0.124             | 0.893            |  |
| 45        | 0.327            | 0.162             | 0.760            |  |
| 46        | 0.473            | 0.125             | 0.501            |  |
| 47        | 0.579            | 0.165             | 0.500            |  |
| 48        | 0.472            | 0.097             | 0.497            |  |
| 49        | 0.432            | 0.146             | 1.061            |  |
| 50        | 0.432            | 0.117             | 1.243            |  |

- Page 111 of 249 -

| ANIMAL    | SPLEEN<br>(GRAM) | OVARIES<br>(GRAM) | UTERUS<br>(GRAM) |  |
|-----------|------------------|-------------------|------------------|--|
|           |                  |                   |                  |  |
| GROUP 2 ( | 3000 PPM)        |                   |                  |  |
| 51        | 0.496            | 0.155             | 1.319            |  |
| 52        | 0.395            | 0.161             | 0.643            |  |
| 53        | 0.455            | 0.157             | 0.941            |  |
| 54        | 0.421            | 0.141             | 0.580            |  |
| 55        | 0.370            | 0.141             | 0.927            |  |
| 56        | 0.473            | 0.144             | 1.623            |  |
| 57        | 0.530            | 0.166             | 1.027            |  |
| 58        | 0.412            | 0.165             | 0.678            |  |
| 59        | 0.478            | 0.167             | 0.968            |  |
| 60        | 0.444            | 0.123             | 1.057            |  |
| GROUP 3 ( | 10000 PPM)       |                   |                  |  |
| 61        | 0.373            | 0.131             | 0.587            |  |
| 62        | 0.445            | 0.109             | 0.482            |  |
| 63        | 0.460            | 0.156             | 0.791            |  |
| 64        | 0.426            | 0.160             | 0.457            |  |
| 65        | 0.454            | 0.162             | 1.239            |  |
| 66        | 0.365            | 0.155             | 0.646            |  |
| 67        | 0.303            | 0.135             | 0.640            |  |
| 68        |                  |                   |                  |  |
|           | 0.384            | 0.139             | 0.907            |  |
| 69        | 0.445            | 0.129             | 1.239            |  |
| 70        | 0.464            | 0.126             | 0.541            |  |
|           | 30000 PPM)       |                   |                  |  |
| 71        | 0.390            | 0.133             | 0.709            |  |
| 72        | 0.416            | 0.135             | 1.657            |  |
| 73        | 0.559            | 0.120             | 0.528            |  |
| 74        | 0.425            | 0.157             | 0.415            |  |
| 75        | 0.487            | 0.125             | 0.199            |  |
| 76        | 0.521            | 0.134             | 1.164            |  |
| 77        | 0.461            | 0.173             | 0.490            |  |
| 78        | 0.555            | 0.158             | 0.996            |  |
| 79        | 0.396            | 0.163             | 0.424            |  |
| 80        | 0.456            | 0.135             | 0.529            |  |

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) FEMALES END OF TREATMENT

| ANIMAL                  | BODY W.<br>(GRAM)        | BRAIN<br>(%) | HEART<br>(%) | LIVER<br>(%) |  |
|-------------------------|--------------------------|--------------|--------------|--------------|--|
| GROUP 1 (               | CONTROL)                 |              |              |              |  |
| 41 `                    | 237                      | 0.83         | 0.283        | 2.73         |  |
| 42                      | 235                      | 0.81         | 0.311        | 2.31         |  |
| 43                      | 242                      | 0.81         | 0.321        | 2.58         |  |
| 44                      | 221                      | 0.80         | 0.286        | 2.26         |  |
| 45                      | 227                      | 0.86         | 0.315        | 2.40         |  |
| 46                      | 236                      | 0.85         | 0.289        | 2.56         |  |
| 47                      | 257                      | 0.78         | 0.273        | 2.31         |  |
| 48                      | 205                      | 0.88         | 0.305        | 2.90         |  |
| 49                      | 253                      | 0.77         | 0.300        | 2.52         |  |
| 50                      | 215                      | 0.84         | 0.300        | 2.58         |  |
| 50                      | 213                      | 0.04         | 0.300        | 2.30         |  |
| GROUP 2 (               |                          |              |              |              |  |
| 51                      | 233                      | 0.87         | 0.308        | 2.67         |  |
| 52                      | 242                      | 0.78         | 0.307        | 2.62         |  |
| 53                      | 211                      | 0.95         | 0.284        | 2.66         |  |
| 54                      | 215                      | 0.89         | 0.317        | 2.90         |  |
| 55                      | 222                      | 0.82         | 0.288        | 2.51         |  |
| 56                      | 232                      | 0.82         | 0.311        | 3.18         |  |
| 57                      | 238                      | 0.80         | 0.287        | 2.69         |  |
| 58                      | 243                      | 0.80         | 0.330        | 2.50         |  |
| 59                      | 223                      | 0.84         | 0.300        | 2.61         |  |
| 60                      | 231                      | 0.84         | 0.299        | 2.60         |  |
|                         |                          |              |              |              |  |
|                         | 10000 PPM)               |              |              |              |  |
| 61                      | 207                      | 0.93         | 0.318        | 3.16         |  |
| 62                      | 212                      | 0.88         | 0.320        | 2.52         |  |
| 63                      | 229                      | 0.81         | 0.301        | 3.05         |  |
| 64                      | 235                      | 0.82         | 0.294        | 2.48         |  |
| 65                      | 217                      | 0.84         | 0.294        | 2.86         |  |
| 66                      | 228                      | 0.82         | 0.288        | 2.54         |  |
| 67                      | 231                      | 0.79         | 0.282        | 2.57         |  |
| 68                      | 230                      | 0.81         | 0.301        | 2.37         |  |
| 69                      | 206                      | 0.98         | 0.300        | 2.50         |  |
| 70                      | 239                      | 0.80         | 0.277        | 2.56         |  |
| CPOUR # #               | 30000 DDM/               |              |              |              |  |
| <b>GROUP 4</b> (-<br>71 | <b>30000 PPM)</b><br>216 | 0.86         | 0.240        | 2.96         |  |
|                         |                          |              | 0.340        | 2.86         |  |
| 72<br>72                | 217                      | 0.84         | 0.276        | 2.78         |  |
| 73<br>74                | 252                      | 0.75         | 0.288        | 2.83         |  |
| 74                      | 241                      | 0.78         | 0.307        | 2.56         |  |
| 75<br>                  | 233                      | 0.82         | 0.297        | 2.88         |  |
| 76                      | 204                      | 0.80         | 0.325        | 2.51         |  |
| 77                      | 223                      | 0.86         | 0.326        | 3.29         |  |
| 78                      | 252                      | 0.76         | 0.319        | 2.80         |  |
| 79                      | 235                      | 0.82         | 0.331        | 2.55         |  |
| 80                      | 204                      | 0.94         | 0.327        | 2.89         |  |

| ANIMAL | THYROIDS<br>(%) | THYMUS<br>(%) | KIDNEYS<br>(%) | ADRENALS<br>(%) |  |
|--------|-----------------|---------------|----------------|-----------------|--|
|        | CONTROL)        |               |                |                 |  |
| 41     | 0.008           | 0.130         | 0.76           | 0.031           |  |
| 42     | 0.005           | 0.160         | 0.68           | 0.025           |  |
| 43     | 0.007           | 0.081         | 0.72           | 0.030           |  |
| 44     | 0.006           | 0.132         | 0.65           | 0.027           |  |
| 45     | 0.005           | 0.152         | 0.75           | 0.028           |  |

000244

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) FEMALES END OF TREATMENT

|            | (%)        | (%)   | (%)  | ADRENALS<br>(%) |  |
|------------|------------|-------|------|-----------------|--|
| GROUP 1 (0 | CONTROL)   |       |      |                 |  |
| 16         | 0.005      | 0.139 | 0.70 | 0.030           |  |
| 47         | 0.008      | 0.093 | 0.66 | 0.031           |  |
| 48         | 0.008      | 0.114 | 0.71 | 0.031           |  |
| 49         | 0.008      | 0.104 | 0.71 | 0.025           |  |
| 50         | 0.006      | 0.201 | 0.65 | 0.029           |  |
| GROUP 2 (3 | ROOD PPM)  |       |      |                 |  |
| 51<br>51   | 0.007      | 0.148 | 0.72 | 0.036           |  |
| 52         | 0.007      | 0.121 | 0.74 | 0.030           |  |
| 53         | 0.003      | 0.121 | 0.73 | 0.033           |  |
| 54<br>54   | 0.006      | 0.119 | 0.73 | 0.033           |  |
| 55         | 0.004      | 0.119 | 0.65 | 0.029           |  |
| 56         | 0.004      | 0.139 | 0.03 | 0.032           |  |
| 56<br>57   | 0.007      | 0.134 | 0.71 | 0.026           |  |
|            |            | 0.100 |      |                 |  |
| 58<br>50   | 0.007      |       | 0.68 | 0.029           |  |
| 59<br>30   | 0.006      | 0.165 | 0.75 | 0.035           |  |
| 60         | 0.005      | 0.133 | 0.68 | 0.028           |  |
|            | 10000 PPM) |       |      |                 |  |
| 31         | 0.005      | 0.129 | 0.79 | 0.030           |  |
| 62         | 0.006      | 0.126 | 0.73 | 0.032           |  |
| 63         | 0.005      | 0.118 | 0.70 | 0.028           |  |
| 64         | 0.006      | 0.102 | 0.69 | 0.030           |  |
| 35         | 0.005      | 0.104 | 0.69 | 0.028           |  |
| 36         | 0.006      | 0.159 | 0.70 | 0.026           |  |
| 67         | 0.006      | 0.126 | 0.70 | 0.025           |  |
| 38         | 0.008      | 0.143 | 0.71 | 0.028           |  |
| 69         | 0.004      | 0.119 | 0.67 | 0.033           |  |
| 70         | 0.005      | 0.136 | 0.71 | 0.021           |  |
| GROUP 4 (3 | 30000 PPM) |       |      |                 |  |
| 71         | 0.006      | 0.138 | 0.66 | 0.026           |  |
| 72         | 0.007      | 0.139 | 0.66 | 0.018           |  |
| 73         | 0.007      | 0.087 | 0.71 | 0.027           |  |
| 74         | 0.006      | 0.154 | 0.63 | 0.028           |  |
| 75         | 0.009      | 0.142 | 0.71 | 0.034           |  |
| 76         | 0.004      | 0.147 | 0.73 | 0.033           |  |
| 77         | 0.004      | 0.109 | 0.73 | 0.033           |  |
| 78         | 0.006      | 0.109 | 0.76 | 0.027           |  |
| 79         | 0.006      | 0.101 | 0.70 | 0.033           |  |
| 79<br>30   | 0.000      | 0.162 | 0.70 | 0.026           |  |
| JU         | 0.007      | 0.102 | 0.03 | 0.021           |  |

| ANIMAL    | SPLEEN<br>(%) | OVARIES<br>(%) | UTERUS<br>(%) |  |
|-----------|---------------|----------------|---------------|--|
| GROUP 1 ( | CONTROL)      |                |               |  |
| 41        | 0.149         | 0.052          | 0.207         |  |
| 42        | 0.177         | 0.064          | 0.280         |  |
| 43        | 0.189         | 0.056          | 0.288         |  |
| 44        | 0.156         | 0.056          | 0.404         |  |
| 45        | 0.144         | 0.071          | 0.335         |  |
| 46        | 0.200         | 0.053          | 0.212         |  |
| 47        | 0.225         | 0.064          | 0.195         |  |
| 48        | 0.230         | 0.047          | 0.242         |  |
| 49        | 0.171         | 0.058          | 0.419         |  |
| 50        | 0.201         | 0.054          | 0.578         |  |

Betawell L-Arabinose APPENDIX 2

# 2.14 ORGAN/BODY WEIGHT RATIOS (%) FEMALES END OF TREATMENT

| ANIMAL    | SPLEEN     | OVARIES | UTERUS |  |
|-----------|------------|---------|--------|--|
|           | (%)        | (%)     | (%)    |  |
| GROUP 2 ( | 3000 PPM)  |         |        |  |
| 51        | 0.213      | 0.067   | 0.566  |  |
| 52        | 0.163      | 0.067   | 0.266  |  |
| 53        | 0.216      | 0.074   | 0.446  |  |
| 54        | 0.196      | 0.066   | 0.270  |  |
| 55        | 0.167      | 0.064   | 0.418  |  |
| 56        | 0.204      | 0.062   | 0.700  |  |
| 57        | 0.223      | 0.070   | 0.432  |  |
| 58        | 0.170      | 0.068   | 0.279  |  |
| 59        | 0.214      | 0.075   | 0.434  |  |
| 60        | 0.192      | 0.053   | 0.458  |  |
| GROUP 3 ( | 10000 PPM) |         |        |  |
| 61        | 0.180      | 0.063   | 0.284  |  |
| 62        | 0.210      | 0.051   | 0.227  |  |
| 63        | 0.201      | 0.068   | 0.345  |  |
| 64        | 0.181      | 0.068   | 0.194  |  |
| 65        | 0.209      | 0.075   | 0.571  |  |
| 66        | 0.160      | 0.068   | 0.283  |  |
| 67        | 0.161      | 0.054   | 0.277  |  |
| 68        | 0.167      | 0.060   | 0.394  |  |
| 69        | 0.216      | 0.063   | 0.601  |  |
| 70        | 0.194      | 0.053   | 0.226  |  |
| GROUP 4 ( | 30000 PPM) |         |        |  |
| 71        | 0.181      | 0.062   | 0.328  |  |
| 72        | 0.192      | 0.062   | 0.764  |  |
| 73        | 0.222      | 0.048   | 0.210  |  |
| 74        | 0.176      | 0.065   | 0.172  |  |
| 75        | 0.209      | 0.054   | 0.085  |  |
| 76        | 0.255      | 0.066   | 0.571  |  |
| 77        | 0.207      | 0.078   | 0.220  |  |
| 78        | 0.220      | 0.063   | 0.395  |  |
| 79        | 0.169      | 0.069   | 0.180  |  |
| 80        | 0.224      | 0.066   | 0.259  |  |

# 2.15 KEY TO MISSING VALUES/REMARKS CLINICAL LABORATORY INVESTIGATIONS

# **End of Treatment**

| Haematology:                      |   |
|-----------------------------------|---|
| Animal(s):                        |   |
| 41, 45                            | <br>= Technical error for WBC   |
| 27, 64, 70                        | <br>= EDTA sample clotted   |
| 64, 70                            | <br>= Citrate sample clotted  |
| 28, 41, 42, 45, 66,<br>71, 74, 77 | Differential leucocyte count was also performed manually because of a technical error / an abnormal plot in the automated count and these |
| , ,                               | manual results are reported   |

| Clinical Biochemistry: |   |  |  |
|------------------------|---|--|--|
| Serum sa               | Serum sample of the following animal was haemolytic. Therefore the following parameter was not included |  |  |
| in the tab             | ples:   |  |  |
| Animal                 | Bile acids (µmol/L)   |  |  |
| 41                     | 11.6  |  |  |

Betawell L-Arabinose Project 509991

# **APPENDIX 3 CERTIFICATE OF ANALYSIS**

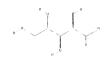
Final Report - Page 1 -

- Page 117 of 249 -

Certificate of analysis Specification date: 15.06.2015

# Certificate of analysis

: Betawell<sup>®</sup> Ara-P Product name



| Component                            | Value           |
|--------------------------------------|-----------------|
| Arabinose                            | 99.9 wt%        |
| Glucose                              | <0.01 wt%       |
| Mannose                              | <0.01 wt%       |
| Rhamnose                             | 0.01 wt%        |
| Xylose                               | 0.03 wt%        |
| Fucose                               | <0.01 wt%       |
| Galactose                            | 0.04 wt%        |
| Galacturonic acid                    | <0.01 wt%       |
| Beet pectin derived oligosaccharides | 0.02 wt%        |
| Water content                        | 0.1 wt%         |
| Solubility ( 10% in water)           | < 20 Hazen      |
| Clarity                              | 0.85 - 0.90 FNU |

CAS-Nr.

: 5328-37-0 (for L-Arabinose)

Origin

: Sugar beet

Batch number Batch size

: C32-1 : total 40 kg.

Product number

Appearance (color) : Whitish to white

: 7000 (Cosun internal number)

Appearance (form)

: Powder

Smell

: Neutral

Infrared spectrum

: Conforms to structure

Minimum purity

: > 99 wt% of Dry Solids (L-arabinose, method: HPLC (C18-aq), PDA)

Functionality

: food ingredient (USA, Asia), flavor ingredient (for EU see Regulation 872/2012),

cosmetic ingredient.

Storage conditions

: Dry, keep out of sunshine.

Shelf life

: The expiry date of this product is 24 months after the production date indicated on this certificate of analysis when properly stored and maintained.

Production date

: 15.05.2015

Betawell Ara-P, powder of arabinose page 1 of 2



Certificate of analysis Specification date: 15.06.2015

#### Additional specifications:

| Test                          | Method              | Maximum      |
|-------------------------------|---------------------|--------------|
| Total Viable Count / g (30°C) | ISO 4833:2003       | 1000 CFU / g |
| Yeasts / g                    | ISO 7954:1987       | 20 CFU / g   |
| Moulds / g                    | ISO 7954:1987       | 20 CFU / g   |
| Staph. aureus / g             | ISO 6888-3 :2003    | Absent       |
| Salmonella / 50g              | ISO 6579:2002       | Absent       |
| E. coli / g                   | ISO 16649-2:2001    | Absent       |
| Bacillus cereus / g           | ISO 7932:2004       | 100 CFU / g  |
| Coliforms / g                 | ISO 4832:2006       | Absent       |
| Enterobacteria / g            | ISO 21528-1:2004    | Absent       |
| Listeria / g                  | ISO 11290-1:1997    | Absent       |
| Clostridium perfringens/g     | ISO 7937:2004       | Absent       |
| Faecal Streps/g               | External laboratory | Absent       |
| Aflatoxins                    | External laboratory | < 0.1 μg/kg  |

| Metals  | Value (ppm) |
|---------|-------------|
| Arsenic | <0.01       |
| Lead    | <0.01       |
| Mercury | <0.0001     |
| Cadmium | <0.005      |
| Tin     | <0.01       |
| Copper  | <0.01       |
| Silver  | <0.05       |
| Bismuth | <0.2        |

This powder is produced from sugar beet grown in the Netherlands and Germany. This material has been checked for compliance with international pesticide tolerance legislation, does not contain and/or has not been in contact with genetically modified organisms, does not contain any ingredient with an animal origin and does not contain any known allergen.

Cosun Biobased Products B.V.
P.O. Box 3411, 4800 MG Breda, The Netherlands
Tel +31 76 530 33 33, Fax +31 76 530 32 06

The information and recommendations in this leaflet are to the best of our knowledge, information and belief accurate at the date of publication. Nothing herein is to be construed as warranty expressed or implied. In all cases it is the responsibility of users to determine the applicability of such information or the suitability of any products for their own particular purpose.

Betawell Ara-P, powder of arabinose page 2 of 2

#### 206781/B:



# Certificate of analysis

Product name : Betawell® L-Arabinose

| Component                              | Amount (wt% Dry Solids) |
|--|-------------------------|
| Arabinose                              | >99.0                   |
| Rhamnose                               | <0.5                    |
| Galactose                              | <0.1                    |
| Other sugars (fucose, mannose, xylose) | <0.1                    |
| Beet pectin derived oligosaccharides   | <1.0                    |
| Total metal content                    | <0.1 ppm                |
| Moisture content                       | <0.3                    |

Appearance (form) : crystalline powder Preparation date : April, 2015

Purity : > 99.0% of (method: HPLC (C18-aq), PDA)

Functionality: food supplement (USA, Asia), flavor ingredient (USA, for EU see Regulation

872/2012), cosmetic ingredient.

Storage conditions : Room temperature

Shelf life : The expiry date of this product is 12 months after the preparation date indicated

on this certificate of analysis when properly stored and maintained.

Specification date : 13.08.2015

Cosun Biobased Products B.V. Borchwerf 4M, 4704 RG Roosendaal, The Netherlands Tel +31 76 530 33 33, Fax +31 76 530 32 06

The information and recommendations in this leaflet are to the best of our knowledge, information and betief accurate at the date of publication. Nothing herein is to be construed as warranty expressed or implied. In all cases it is the responsibility of users to determine the applicability of such information or the suitability of any products for their own particular purpose.

Betawell L-Arabinose Project 509991

# **APPENDIX 4 PHASE REPORT DIET ANALYSIS**

Final Report - Page 1 -

- Page 121 of 249 -

# 1. CONTENTS

Betawell L-Arabinose

| CONTENTS              | 2                |
|-----------------------|------------------|
| REPORT APPROVAL       | 3                |
|                       |                  |
|                       |                  |
|                       |                  |
|                       |                  |
|                       |                  |
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|                       |                  |
|                       |                  |
| o. 1.2. Otday campioo |                  |
|                       |                  |
| ABLES                 |                  |
|                       |                  |
| ble 1 QC samples      | 8                |
|                       |                  |
|                       |                  |
|                       |                  |
| ble 5 Stability test  |                  |
| ıb<br>ıb              | ole 1 QC samples |

# 2. REPORT APPROVAL

Charles River Den Bosch

(b) (6)

Signature

Name: J. Ciric, PhD.

Title: Principal Scientist

**Analytical Chemistry** 

Date: 08 November 2016

## 3. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation, homogeneity and stability of the test item in diets, according to the method available at Consun Food Technology Centre (non-GLP).

## Accuracy of preparation

The concentrations analysed in the diets of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 80% and 120%).

A minimal response at the retention time of the test item was observed in the chromatograms of the Group 1 diet prepared for use in Week 13. In all other diets of Group 1, no test item was detected.

# **Homogeneity**

The diets of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10%).

# Stability

Diets at the entire range were stable when stored at room temperature for at least 9 days.

Final Report - Page 4 -

#### 4. INTRODUCTION

# 4.1. Study schedule analytical phase

Experimental starting date : 17 December 2016 Experimental completion date : 29 January 2016

### 4.2. Purpose of the study

The purpose of the analytical phase was to determine the accuracy of preparation, homogeneity and stability of the test item in diets, according to the method available at Consun Food Technology Centre (non-GLP)

#### 5. MATERIALS AND METHODS

#### 5.1. Reagents

Water Tap water purified by a Milli-Q water purification system

(Millipore, Bedford, MA, USA)

All reagents were of analytical grade, unless specified otherwise.

### 5.2. Study samples

Accuracy, homogeneity and stability were determined for diets prepared for use during treatment.

Samples of approximately 60 g or 250 g were taken from the diets. For determination of accuracy, samples were taken at the random position or at top, middle and bottom position (90%, 50% and 10% height). The samples taken at 90%, 50% and 10% height were also used for the determination of the homogeneity of the diets. For determination of stability, additional samples were taken at random position and stored at room temperature under normal laboratory light conditions for 9 days.

Duplicate samples of approximately 2 g of Group 1 and Group2, 0.7 g of Group 3 and 1 g of Group 4 of the powder diets were accurately weighed into glass vessels. The samples were extracted at 225 rpm with 100 mL (Group 1, 2 and 3) or 500 mL (Group 4) water. The shaking time was 30 minutes. The solutions were filtered through a 0.2 µm Spartan 30/0.2 RC filter (Whatman, Dassel, Germany).

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore the samples were send to the sponsor for analysis.

# 5.3. Analytical method

# 5.3.1. Analytical conditions

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V.. The analysis of the samples was done at the Cosun Food Technology Centre (CFTC). CFTC is a sister company of Cosun Biobased Products B.V. and is specialized in sugar analysis and therefore is well-found with necessary equipment for the analysis of Betawell L-Arabinose in diet.

# 5.3.2. Preparation of solutions

### Quality control (QC) samples

Approximately 2 g (for the low QC samples) and 1 g (for the high QC samples) blank powder diet was spiked with the test item at a target concentration of 3000 or 30000 ppm. After spiking, the test item was allowed to absorb to the diet for at least 30 minutes. The QC samples were treated similarly as the study samples (see paragraph 5.2 'Study samples').

Final Report - Page 5 -

## 5.4. Electronic systems for data acquisition

Temperature, relative humidity and/or atmospheric pressure during sample storage and/or performance of the studies was monitored continuously using the following program:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA).

#### 5.5. Formulas

Analysed concentration (C<sub>A</sub>)  $C_A = \frac{(R-b)}{a} \times \frac{V \times d}{w} \ \ [ppm]$ 

where:

w = weight sample [g]

V = volume extraction solvent [mL]

d = dilution factor

Recovery  $\frac{C_A}{C_N} \times 100 \ \ [\%]$ 

where:

 $C_N = nominal concentration [ppm]$ 

Accuracy  $\frac{C_A}{C_T} \times 100 \text{ [\%]}$ 

where:

 $C_T$  = target concentration [ppm]

Relative difference (relative diff.)  $\frac{C_t - C_0}{C_0} \times 100 \text{ [\%]}$ 

where:

C<sub>t</sub> = mean concentration of stored samples [ppm] C<sub>0</sub> = mean concentration of non-stored samples [ppm]

## 5.6. Specifications

Preparation of diets was considered acceptable if the mean accuracy was in the range 80 - 120% of the target concentration and was considered homogeneous if the coefficient of variation was  $\leq 10\%$ . Diets were considered stable if the relative difference between the stored and freshly taken samples was  $\leq 10\%$ .

#### 6. RESULTS

#### 6.1. Samples

# 6.1.1. QC samples

The results for the QC samples are given in Table 1.

The mean recoveries of the QC samples were within the criterion range of 80 - 120%. It demonstrated that the analytical method was adequate for the determination of the test item in the study samples.

# 6.1.2. Study samples

The results of the study samples are given in Table 2 to Table 4

# Accuracy of preparation

The concentrations analysed in the diets of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 80% and 120%).

A minimal response at the retention time of the test item was observed in the chromatograms of the Group 1 diet prepared for use in Week 13. In all other diets of Group 1, no test item was detected.

# Homogeneity

The diets of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10%).

#### Stability

Analysis of Group 2 and Group 4 diets after storage yielded a relative difference of  $\leq$  10%. Based on this, the diets were found to be stable during storage at room temperature for at least 9 days.

Final Report - Page 7 -

- Page 127 of 249 -

# **TABLES**

Table 1 QC samples

| Date of     | Date of analysis | Target        | Nominal       | Analysed      | Accuracy | Mean     |
|-------------|------------------|---------------|---------------|---------------|----------|----------|
| preparation |                  | concentration | concentration | concentration |          | accuracy |
|             |                  | [ppm]         | [ppm]         | [ppm]         | [%]      | [%]      |
|             |                  |               |               |               |          |          |
| 17-Dec-2015 | 18-Dec-2015      | 3000          | 3090          | 3227          | 104      | 104      |
|             |                  |               | 3156          | 3284          | 104      | n.a.     |
|             |                  |               |               |               |          |          |
| 17-Dec-2015 | 18-Dec-2015      | 10000         | 29584         | 29838         | 101      | 101      |
|             |                  |               | 31379         | 31995         | 102      | n.a.     |
|             |                  |               |               |               |          |          |
| 27-Jan-2016 | 29-Jan-2016      | 3000          | 3090          | 3190          | 103      | 103      |
|             |                  |               | 2991          | 3046          | 102      | n.a.     |
|             |                  |               |               |               |          |          |
| 27-Jan-2016 | 29-Jan-2016      | 10000         | 29691         | 29886         | 101      | 100      |
|             |                  |               | 30647         | 30745         | 100      | n.a.     |
|             |                  |               |               |               |          |          |

Table 2 Accuracy and homogeneity test – Week 1

| Group | Date of preparation | Date of analysis | Sample<br>position | Concentration [ppm] |                | Accura<br>[%]   | -   | Homogeneity<br>(coefficient of<br>variation) |  |
|-------|---------------------|------------------|--------------------|---------------------|----------------|-----------------|-----|--|--|
|       |                     |                  |                    | Target              | Analysed       | Individual Mean |     | [%]  |  |
| 1     | 17-Dec-2015         | 18-Dec-2015      | 50% height         | 0.00                | n.d.           | n.a.            |     |  |  |
| '     | 17-Dec-2015         | 16-Dec-2015      | 50 % Height        | 0.00                | n.d.           | n.a.            |     |  |  |
| 2     | 17-Dec-2015         | 18-Dec-2015      | 90% height         | 3000<br>3000        | 3177<br>3038   | 106<br>101      |     |  |  |
|       |                     |                  | 50% height         | 3000<br>3000        | 3090<br>3082   | 103<br>103      | 103 | 1.5  |  |
|       |                     |                  | 10% height         | 3000<br>3000        | 3088<br>3057   | 103<br>102      |     |  |  |
| 3     | 17-Dec-2015         | 18-Dec-2015      | 50% height         | 10000<br>10000      | 10143<br>10113 | 101<br>101      | 101 | n.a.   |  |
| 4     | 17-Dec-2015         | 18-Dec-2015      | 90% height         | 30000<br>30000      | 29626<br>28623 | 99<br>95        |     |  |  |
|       |                     |                  | 50% height         | 30000<br>30000      | 30876<br>29974 | 103<br>100      | 100 | 3.1  |  |
|       |                     |                  | 10% height         | 30000<br>30000      | 31096<br>30572 | 104<br>102      |     |  |  |

n.d. Not detected.

n.a. Not applicable.

Table 3 Accuracy and homogeneity test – Week 6

| Group | Date of preparation | Date of analysis | Sample<br>position                     | Concentration<br>[ppm]                             |  | Accuracy<br>[%]                        |      | Homogeneity (coefficient of variation) |  |
|-------|---------------------|------------------|--|--|--|--|------|--|--|
|       |                     |                  |  | Target   | Analysed   | Individual                             | Mean | [%]                                    |  |
| 1     | 17-Dec-2015         | 18-Dec-2015      | 50% height                             | 0.0<br>0.00  | n.d.<br>n.d  | n.a.<br>n.a.                           |      |  |  |
| 2     | 17-Dec-2015         | 18-Dec-2015      | 90% height<br>50% height<br>10% height | 3000<br>3000<br>3000<br>3000<br>3000<br>3000       | 3127<br>3076<br>3077<br>3055<br>3018<br>3116       | 104<br>103<br>103<br>102<br>101<br>104 | 103  | 1.3                                    |  |
| 3     | 17-Dec-2015         | 18-Dec-2015      | 50% height                             | 10000<br>10000                                     | 10312<br>9868                                      | 103<br>99                              | 101  | n.a.                                   |  |
| 4     | 17-Dec-2015         | 18-Dec-2015      | 90% height<br>50% height<br>10% height | 30000<br>30000<br>30000<br>30000<br>30000<br>30000 | 30125<br>30392<br>30030<br>29904<br>29751<br>30362 | 100<br>101<br>100<br>100<br>99<br>101  | 100  | 0.84                                   |  |

n.d. Not detected.

Table 4 Accuracy and homogeneity test – Week 13

| Group | Date of preparation | Date of analysis | Sample<br>position                     | Concentration [ppm]                                |  | Accuracy<br>[%]                        |      | Homogeneity (coefficient of variation) |  |
|-------|---------------------|------------------|--|--|--|--|------|--|--|
|       |                     |                  |  | Target   | Analysed   | Individual                             | Mean | [%]                                    |  |
| 1     | 27-Jan-2016         | 29-Jan-2016      | 50% height                             | 0.00<br>0.00                                       | 69<br>70   | n.a.<br>n.a.                           |      |  |  |
| 2     | 27-Jan-2016         | 29-Jan-2016      | 90% height<br>50% height<br>10% height | 3000<br>3000<br>3000<br>3000<br>3000<br>3000       | 3040<br>3000<br>3015<br>3005<br>3005<br>3025       | 101<br>100<br>101<br>100<br>100<br>101 | 101  | 0.51                                   |  |
| 3     | 27-Jan-2016         | 29-Jan-2016      | 50% height                             | 10000<br>10000                                     | 9873<br>9757                                       | 99<br>98                               | 98   | n.a.                                   |  |
| 4     | 27-Jan-2016         | 29-Jan-2016      | 90% height<br>50% height<br>10% height | 30000<br>30000<br>30000<br>30000<br>30000<br>30000 | 30050<br>31111<br>29949<br>28168<br>30152<br>30347 | 100<br>104<br>100<br>94<br>101<br>101  | 100  | 3.2                                    |  |

n.d. Not detected.

n.a. Not applicable.

n.a. Not applicable.

Table 5 Stability test

| Group | Date of analysis |             | -     | oncentration<br>om] | Relative diff. |  |  |
|-------|------------------|-------------|-------|---------------------|----------------|--|--|
|       | t=0 t=** days    |             |       |                     | [%]            |  |  |
| 2     | 17-Dec-2015      | 18-Dec-2015 | 3089  | 3222 <sup>2</sup>   | 4.3            |  |  |
| 4     | 17-Dec-2015      | 18-Dec-2015 | 30128 | 30957 <sup>3</sup>  | 2.8            |  |  |

Mean of six samples at t=0 hours taken at 10%, 50% and 90% height (see Table 2).

Mean of two samples at t=\*\* days taken at random position. Individual results were 3189 and 3255 ppm.

Mean of two samples at t=\*\* days taken at random position. Individual results were 30859 and 31056 ppm.

# **APPENDIX 5 PHASE REPORT HISTOPATHOLOGY**

Final Report - Page 1 -

# TABLE OF CONTENTS

| 1. | SUMMARY                        | 3 |
|----|--------------------------------|---|
| 2. | INTRODUCTION                   | 4 |
|    | STUDY DESIGN                   |   |
| 4. | METHODS                        | 4 |
|    | 4.1. Macroscopic Examination   | 4 |
|    | 4.2. Organ Weights             | 5 |
|    | 4.3. Microscopic Examination   | 5 |
|    | 4.4. Internal Peer Review      | 6 |
| 5. | RESULTS                        |   |
|    | 5.1. Mortality                 | 7 |
|    | 5.2. Clinical Pathology        | 7 |
|    | 5.3. Macroscopic Findings      | 7 |
|    | 5.4. Organ Weights             | 7 |
|    | 5.5. Microscopic Findings      | 7 |
| 6. | CONCLUSIONS                    |   |
| 7. | REPORT AUTHENTICATION          | 9 |
| Q  | APPENDIX HISTOPATHOLOGY TARLES | 1 |

#### 1. SUMMARY

Pathomorphologic examination was performed on 80 Wistar Han rats (40 males, 40 females) which had been subjected to a 90-day oral (diet) toxicity study with the test item **Betawell L-Arabinose**.

The rats were assigned to four dose groups, each containing 10 males and 10 females. The rats of the control Group 1 received standard powder rodent diet without test item. Dose Groups 2, 3 and 4 received the test item at dietary inclusion levels of 3000, 10000 and 30000 ppm, respectively.

At the end of the treatment period all rats from all Groups were killed and subjected to complete necropsies. Histopathologic examination was performed on an extensive list of organs and tissues from all Group 1 and 4 animals as well as all organs with macroscopic findings from all rats.

There were no unscheduled deaths.

There were no test item-related macroscopic findings.

There were no test item-related organ weight changes.

There were no test item-related microscopic findings.

After a 90-day diet toxicity study in Wistar Han rats with the test item **Betawell L-Arabinose** there were no test item-related findings in males and females treated up to 30000 ppm.

#### 2. INTRODUCTION

The nature and purpose of this toxicity study was to assess the toxic potential of the test substance when administered to rats via the diet for a period of 13 weeks. This study should provide part of a rational basis for toxicological risk assessment in man. The oral route was selected as it is the route of intended human use.

This pathology report addresses the anatomical pathology endpoints of the study. It is based on the study protocol and any protocol amendment.

#### 3. STUDY DESIGN

Male and female Wistar Han rats, approximately 6 weeks of age on study Day 1, were administered Betawell L-Arabinose via diet for at least 90 consecutive days as indicated in the following table.

| Group  | Dose level | Number of animals |         | Animal numbers |         |  |
|--------|------------|-------------------|---------|----------------|---------|--|
| Number | (ppm)      | Males             | Females | Males          | Females |  |
| 1      | 0          | 10                | 10      | 1-10           | 41-50   |  |
| 2      | 3000       | 10                | 10      | 11-20          | 51-60   |  |
| 3      | 10000      | 10                | 10      | 21-30          | 61-70   |  |
| 4      | 30000      | 10                | 10      | 31-40          | 71-80   |  |

#### 4. METHODS

## 4.1. Macroscopic Examination

Complete *postmortem* examinations were performed on all animals. Animals were anesthetized using isoflurane and subsequently exsanguinated. At the time of necropsy, the following tissues and organs were collected and placed in 10% neutral-buffered formalin fixative unless otherwise noted:

| Identification marks: not processed              | Ovaries  |
|--|--|
| Adrenal glands                                   | Pancreas                                       |
| Aorta  | Peyer's patches [jejunum, ileum] if detectable |
| Brain [cerebellum, mid-brain, cortex] [7 levels] | Pituitary gland                                |
| Caecum   | (Preputial gland)                              |
| Cervix   | Prostate gland                                 |
| (Clitoral gland)                                 | Rectum   |
| Colon  | Salivary glands - mandibular, sublingual       |
| Duodenum   | Sciatic nerve                                  |
| Epididymides *                                   | Seminal vesicles including coagulating gland   |
| Eyes with optic nerve [if detectable] and        | (Skeletal muscle)                              |
| Harderian gland *                                | Skin   |
| Female mammary gland area                        | Spinal cord -cervical, midthoracic, lumbar     |
| (Femur including joint)                          | Spleen   |
| Heart  | Sternum with bone marrow                       |
| Ileum  | Stomach  |
| Jejunum  | Testes *                                       |
| Kidneys  | Thymus   |
| Larynx   | Thyroid including parathyroid [if detectable]  |
| (Lacrimal gland, exorbital)                      | (Tongue)                                       |
| Liver  | Trachea  |
| Lung, infused with formalin                      | Urinary bladder                                |
| Lymph nodes - mandibular, mesenteric             | Uterus   |

| (Nasopharynx) | Vagina            |
|---------------|-------------------|
| Oesophagus    | All gross lesions |

Tissues/organs mentioned in parentheses were not examined by the pathologist.

\* Initially fixed in modified Davidson's solution.

## 4.2. Organ Weights

The following organ weights (and terminal body weight) were recorded from all animals at the scheduled necropsy:

| Adrenal glands | Spleen  |
|----------------|---|
| Brain          | Testes  |
| Epididymides   | Thymus  |
| Heart          | Uterus (including cervix)                     |
| Kidneys        | Prostate                                      |
| Liver          | Seminal vesicles including coagulating glands |
| Ovaries        | Thyroid including parathyroid                 |

Paired organs were weighed together. Absolute organ weights were reported and organ to terminal body weights were calculated and presented in the main study report.

In the discussion of organ weights, statistical significance refers to the p  $\leq$  0.05 level. The discussion of organ weights refers to group mean values unless stated otherwise.

# 4.3. Microscopic Examination

Microscopic examination of routinely prepared hematoxylin-eosin stained paraffin sections was performed on all tissues collected at necropsy (with exceptions as indicated on the tissue list above) from all control group and 30000 ppm treated animals. Gross lesions were examined from all animals and correlated to microscopic findings if possible.

The animal data and macroscopic findings were electronically transferred from the necropsy raw data files of ToxData system® into the computer system PathData®. Stained histologic sections were examined by light microscopy in the period 08 – 21 March 2016 and the microscopic findings were recorded by the undersigned pathologist using on-line input under pathology number 41607 JOL.

Severity grades were assigned to non-neoplastic histopathologic diagnoses, as presented in the following table. Severity grades were assigned based on the severity of alterations in the examined histologic sections and may not reflect the overall severity of the pathologic process in the entire tissue, organ, or animal. The PathData® histopathology tables contain all of the recorded data and serve as the basis for this narrative report.

In the separate pathology tables file, all macroscopic and microscopic findings are given for each animal in text form under "Text of Gross and Microscopic Findings". The incidence of microscopic findings is also presented in tabular form: "Incidence table - all microscopic findings". Incidence tables were created by computer.

Histopathological changes were described according to distribution, severity and morphological character.

Severity scores were assigned as follows:

Present Finding present, grading not scored.

5

| Grade  | 1 | Minimal/very few/very small.             |
|--------|---|--|
| Grade  | 2 | Slight/few/small.                        |
| Grade  | 3 | Moderate/moderate number/moderate size.  |
| Grade  | 4 | Marked/many/large.                       |
| Grade  | 5 | Massive/extensive number/extensive size. |
| N.A.D. |   | No Abnormality Detected                  |

## 4.4. Internal Peer Review

Pathology findings were subjected to an internal review conducted by Hetty van den Brink-Knol, DVM (Dutch CRP/TP Certified Toxicologic Pathologist). Following the peer review, a consensus was reached between the study pathologist and the peer review pathologist with regard to diagnoses and interpretation. Histopathology data entries in PathData® and pathology data presented in the pathology report reflect this consensus.

6

#### 5. RESULTS

# 5.1. Mortality

There were no premature decedents in the study.

## 5.2. Clinical Pathology

Clinical pathology data were evaluated and discussed by the study pathologist and the study director. Clinical pathology results are presented in the main toxicology report.

# 5.3. Macroscopic Findings

There were no test item-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

# 5.4. Organ Weights

There were no test item-related alterations in organ weights.

All organ weight differences observed, including those that reached statistical significance, were considered incidental and unrelated to the administration of the test item.

# 5.5. Microscopic Findings

There were no test item-related microscopic observations.

All of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There was no test item-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

# 6. CONCLUSIONS

After a 90-day diet toxicity study in Wistar Han rats with the test item **Betawell L-Arabinose** there were no test item-related findings in males and females treated up to 30000 ppm.

# 7. REPORT AUTHENTICATION

I, the undersigned, was responsible for the histopathology evaluation and reporting of the pathology data. The histopathology data in this report were compiled by me, and they reflect accurately the primary data records. Histopathology tables were created in PathData® under number 41607 JOL.

FINAL histopathology tables generated 07-November-2016

Project 509991 Pathology Report

Report and Histopathology Tables Submitted By:

(b) (6)

Joost Lensen, PhD

Dutch ERPTP Certified Toxicologic Pathologist

Study Pathologist

07-100-2016

Date

# 8. APPENDIX HISTOPATHOLOGY TABLES

Final Report 1

| PATHOLOGY REPORT (FINAL)   | PAGE<br>TOX   | :   |      | I<br>509991 |  |
|--|---|-----|------|-------------|--|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V.  | PATHOL. NO.: 41607<br>FINALIZED : 07-NOV<br>PathData®System V6. |     |      |             |  |
| TABLE OF CONTENTS  |   |     |      |             |  |
|  | PAGE  | E : |      |             |  |
|  |   |     |      |             |  |
| EXPLANATION OF CODES AND SYMBOLS   |   |     |      | 1           |  |
| SUMMARY TABLES  NUMBER OF ANIMALS WITH  MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0  Incidence table - All microscopic findings |   |     | 2 -  | - 12        |  |
| INDIVIDUAL ANIMAL DATA TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)   |   |     | 13 - | - 27        |  |
| ANIMAL HEADING DATA DOSE GROUP 01  |   |     |      | 28          |  |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROU   | P 01  |     | 29 - | - 55        |  |
| ANIMAL HEADING DATA DOSE GROUP 02  |   |     |      | 56          |  |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROU   | P 02  |     | 57 - | - 68        |  |
| ANIMAL HEADING DATA DOSE GROUP 03  |   |     |      | 69          |  |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROU   | P 03  |     | 70 - | - 80        |  |
| ANIMAL HEADING DATA DOSE GROUP 04  |   |     |      | 81          |  |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROU   | P 04  |     | 82 - | - 106       |  |

PATHOLOGY REPORT (FINAL)

PAGE : 1/106

TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

EXPLANATION OF CODES AND SYMBOLS

# CODES AND SYMBOLS USED AT ANIMAL LEVEL:

M = Male animal F = Female animal

K0 = Terminal sacrifice group

## CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = Gross observation checked off histologically
U = Tissue not present for histologic examination

' = Histologic examination not required
+ = Organ examined, findings present

- = Organ examined, no pathologic findings noted (AOFT only)

( = Only one of paired organs examined/present

## CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = Minimal / very few / very small

GRADE 2 = Slight / few / small

GRADE 3 = Moderate / moderate number / moderate size

P = Finding present, severity not scored ( = Finding unilateral in paired organs

\* = Comment in text of individual animal data

| PATHOLOGY REE<br>SUMMARY TABLE                  |  |   |                                 |                                 |   | PAGE : 2/106<br>TOX : 509991 |
|---|--|---|---------------------------------|---------------------------------|---|------------------------------|
| TEST ITEM TEST SYSTEM SPONSOR                   | : Betawell<br>: RAT, 90-<br>: Cosun Bi | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |                                 |                                 |   |                              |
| NUMBER OF ANI<br>STATUS AT NEC<br>Incidence tak | CROPSY: KO                             |   |                                 |                                 |   | Y ORGAN/GROUP/SEX            |
| Ι   | SEX :<br>DOSE GROUP:<br>NO.ANIMALS:    | 01  | 02<br>10                        | 03<br>10                        | 04  | MALE                         |
| HEART   | N.A.D. :                               | 10<br>9   | _                               | -<br>-                          | 10<br>10                                  |                              |
| - Infiltrate                                    | inflamm. : Grade 1:                    | 1   | -<br>-                          | -<br>-                          | -<br>-                                    |                              |
| LUNG  | N.A.D. :                               | 10  | _<br>_                          | -<br>-                          | 10 5                                      |                              |
| - Alveolar ma - Inflamm. pe - Osseus meta       | Grade 1: Grade 2: eribronch.: Grade 1: | 4<br>2<br>2<br>3<br>3<br>-<br>-   | -<br>-<br>-<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>-<br>-<br>- | 3<br>2<br>1<br>2<br>2<br>2<br>2<br>1<br>1 |                              |
| THYMUS  | N.A.D. :                               | 10<br>8   | _<br>_                          | -<br>-                          | 10<br>9                                   |                              |
| - Congestion<br>- Hyperplasia                   | a, epith.:<br>Grade 1:<br>Grade 2:     | 2<br>1<br>1   | -<br>-<br>-<br>-                | -<br>-<br>-<br>-                | 1<br>-<br>-<br>-                          |                              |
| TRACHEA   | N.A.D. :                               | 10  | _<br>_                          | -<br>-                          | 10  |                              |
| - Infiltrate - Ectasia suk                      | Grade 1:                               | 2<br>2<br>1<br>1  | -<br>-<br>-<br>-                | -<br>-<br>-<br>-                | 2<br>2<br>-<br>-                          |                              |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPO<br>SUMMARY TABLES   |  |                            |                       |                       |                            | PAGE : 3/106<br>TOX : 509991  |  |  |  |  |  |
|--|--|----------------------------|-----------------------|-----------------------|----------------------------|---|--|--|--|--|--|
| TEST ITEM TEST SYSTEM SPONSOR  | : Betawell<br>: RAT, 90-<br>: Cosun Bi | Day,                       | Diet                  |                       | B.V.                       | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |  |  |  |  |  |
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0 Incidence table - All microscopic findings |  |                            |                       |                       |                            |   |  |  |  |  |  |
|  | SE GROUP:                              | 01<br>10                   | 02<br>10              |                       | 04<br>10                   | MALE  |  |  |  |  |  |
| THYROID GLAND  | N.A.D. :                               | 4                          |                       | -                     | 10                         |   |  |  |  |  |  |
| - Hypertrophy  |  | 6<br>5                     | _                     | -<br>-<br>-           | 7<br>6<br>1                |   |  |  |  |  |  |
| STOMACH  | N.A.D. :                               | 10<br>5                    | _<br>_<br>_           | _<br>_<br>_           | 10<br>9                    |   |  |  |  |  |  |
| - Inflammation - Cyst(s) - Vacuolation,  | Grade 1:<br>Grade 1:                   | 1<br>1<br>2<br>2<br>2<br>2 | _                     | -<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>1<br>1 |   |  |  |  |  |  |
| PEYER'S PATCHE   | S :                                    | 10<br>9                    | _<br>_<br>_           | <u>-</u><br>-         | 10<br>9                    |   |  |  |  |  |  |
| - Mineralizati   | on :<br>Grade 2:                       | _                          | -<br>-<br>-           | -<br>-                | 1<br>1                     |   |  |  |  |  |  |
| LIVER  | N.A.D. :                               | 10                         |                       | _<br>_                | 10                         |   |  |  |  |  |  |
| - Infiltrate i - Single cell - Fibrosis  | Grade 1:                               | 9<br>9<br>-<br>-<br>-      | -<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>- | 10<br>10<br>1<br>1<br>1    |   |  |  |  |  |  |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>SUMMARY TABLES                                    |   |               |               |                   | PAGE : 4/106<br>TOX : 509991 |
|---|---|---------------|---------------|-------------------|------------------------------|
| TEST ITEM : Betawell TEST SYSTEM : RAT, 90- SPONSOR : Cosun B                 | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |               |               |                   |                              |
| NUMBER OF ANIMALS WITH N<br>STATUS AT NECROPSY: KO<br>Incidence table - All m |   |               |               |                   | Y ORGAN/GROUP/SEX            |
| SEX :<br>DOSE GROUP:<br>NO.ANIMALS:   | 01<br>10  | 02<br>10      | 03<br>10      | 04<br>10          | MALE                         |
| SPLEEN : - Hematopoiesis incr. : Grade 1: Grade 2:                            | 10<br>6<br>4<br>2   | -<br>-<br>-   | -<br>-<br>-   | 10<br>3<br>2<br>1 |                              |
| - Pigmentation, hemos.: Grade 1: Grade 2: Grade 3:                            | 9<br>4<br>5<br>-  | -<br>-<br>-   | -<br>-<br>-   | 10<br>6<br>4<br>- |                              |
| MESENT. LYMPH NODE : N.A.D. :   | 10<br>6   | <u>-</u><br>- | <u>-</u><br>- | 10<br>6           |                              |
| - Incr. macrophages : Grade 1: Grade 2:                                       |   | -<br>-<br>-   | -<br>-<br>-   | 4<br>4<br>–       |                              |
| PANCREAS : N.A.D. :   | 10  | <u>-</u>      | _<br>_        | 10                |                              |
| - Atrophy, acinar : Grade 1:  | 1   | -<br>-        | -<br>-        | 1 1               |                              |
| MANDIB.LYMPH NODES : N.A.D. :   | 10<br>10  | 1<br>-        | -<br>-        | 10<br>10          |                              |
| - Erythrocytes, sinus : Grade 2:  | -<br>-  | 1             | -<br>-        | -<br>-<br>-       |                              |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>SUMMARY TABLES   | PAGE : 5/106<br>TOX : 509991  |
|--|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Product  | PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 PathData®System V6.2e2 |
| NUMBER OF ANIMALS WITH MICROSCOPIC FIRSTATUS AT NECROPSY: KO Incidence table - All microscopic fine  |   |
| SEX : DOSE GROUP: 01 02 03 NO.ANIMALS: 10 10 10  |   |
| KIDNEYS : 10   | - 10<br>- 4   |
| - Infiltrate inflamm.: 1 - Grade 1: 3 - Grade 1: | <br><br>- 1<br>- 6<br>- 6   |
| Grade 2: 1 Basophilia, tubule : 3 Grade 1: 3   | <br>- 1<br>- 1  |
| ADRENAL GLANDS : 10  | - 10<br>- 7   |
| - Vacuol. fasciculata: 3 - Grade 1: 3 -  | - 3<br>- 3  |
| PITUITARY GLAND : 10 N.A.D. : 9 -  | - 10<br>- 8   |
| - Cyst(s) : 1 Grade 1: 1   | - 2<br>- 2  |
| SCIATIC NERVE, LEFT : 10   | - 10<br>- 9   |
| - Demyelination : Grade 1:   | - 1<br>- 1  |
| TESTES : 10  | - 10<br>- 9   |
| - Atrophy, tubular : Grade 3:  | - 1<br>- 1  |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPO<br>SUMMARY TABLES                   |   |          |             |             |             | PAGE : 6/106<br>TOX : 509991            |
|--|---|----------|-------------|-------------|-------------|---|
| TEST ITEM TEST SYSTEM SPONSOR                      | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |          |             |             |             |   |
| NUMBER OF ANIM<br>STATUS AT NECR<br>Incidence tabl | OPSY: KO  |          |             |             |             | BY ORGAN/GROUP/SEX                      |
|  | X :<br>SE GROUP:<br>.ANIMALS:   | 01<br>10 | 02<br>10    |             | 04<br>10    | MALE                                    |
| EPIDIDYMIDES                                       | N.A.D. :  | 10<br>10 |             | <u>-</u>    | 10          |   |
| - Cell debris,                                     | luminal:<br>Grade 2:  | -<br>-   | -<br>-<br>- | -<br>-      | 1<br>1      |   |
| PROSTATE GLAND                                     | :<br>N.A.D. :   | 10<br>9  | _<br>_      | _<br>_<br>_ | 10          |   |
| - Infiltrate i                                     | nflamm.:<br>Grade 1:<br>Grade 2:  |          | -<br>-<br>- | -<br>-<br>- | 2<br>2<br>- |   |
| LARYNX   | :<br>N.A.D. :   | 10       | _<br>_      | -<br>-      | 10<br>10    |   |
| - Ectasia subm                                     | glands: Grade 1: Grade 2:   | 2        | -           | -<br>-<br>- | -<br>-<br>- |   |
| EYES   | N.A.D. :  | 10       |             | <u>-</u>    | 10<br>10    |   |
| - Atrophy reti                                     | nal :<br>Grade 2:   | 1<br>1   | _           | -<br>-      | -<br>-<br>- |   |
| BONE, STERNUM                                      | N.A.D. :  | 10<br>10 | _<br>_      | <u>-</u>    | 10<br>9     |   |
| - Developm. ar                                     |   | -        | _           | _           | 1           | • |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT<br>SUMMARY TABLES   | (FINAL)                |                                     |             |             |             |  | PAGE<br>TOX | : | 7/ 106<br>509991 |  |
|--|------------------------|-------------------------------------|-------------|-------------|-------------|--|-------------|---|------------------|--|
| TEST ITEM : B TEST SYSTEM : R SPONSOR : C  | ED :                   | 41607 JOL<br>07-NOV-16<br>em V6.2e2 |             |             |             |  |             |   |                  |  |
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0 Incidence table - All microscopic findings |                        |                                     |             |             |             |  |             |   |                  |  |
|  | :<br>GROUP:<br>IIMALS: |                                     | 02<br>10    | 03<br>10    | 04<br>10    |  |             |   | MALE             |  |
| BONE MARROW, STER  | RNUM :<br>A.D. :       |                                     | _<br>_      | _<br>_      | 10<br>9     |  |             |   |                  |  |
| - Increased adipo  | cytes:                 | -<br>-                              | -<br>-      | -<br>-      | 1           |  |             |   |                  |  |
| PREPUTIAL GLANDS - Dilation Gr   | :<br>:<br>:ade 3:      | -<br>-<br>-                         | 1<br>1<br>1 | -<br>-<br>- | -<br>-<br>- |  |             |   |                  |  |

Group 01, CONTROL, males: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, males: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, males: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, males: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPOSUMMARY TABLES                      |   |                  |                            |                                 |                                 | PAGE : 8/106<br>TOX : 509991 |
|---|---|------------------|----------------------------|---------------------------------|---------------------------------|------------------------------|
| TEST ITEM TEST SYSTEM SPONSOR                     | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |                  |                            |                                 |                                 |                              |
| NUMBER OF ANIM<br>STATUS AT NECE<br>Incidence tab | ROPSY: KO   |                  |                            |                                 |                                 | Y ORGAN/GROUP/SEX            |
| DC  | EX :<br>DSE GROUP:<br>D.ANIMALS:  | 01<br>10         | 02<br>10                   | 03<br>10                        | 04<br>10                        | FEMALE                       |
| HEART   | N.A.D. :  |                  | _<br>_                     | -<br>-                          | 10                              |                              |
| - Myxomatous,                                     | valvular:<br>Grade 2:   | -<br>-           | -<br>-<br>-                | -<br>-                          | 1<br>1                          | ••••••                       |
| LUNG  | N.A.D. :  | 10               | <u>-</u>                   | _<br>_                          | 10<br>6                         |                              |
| - Alveolar mad                                    | Grade 1: Grade 2: cibronch.: Grade 1:                                     | _                | -<br>-<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>-<br>-<br>- | 2<br>2<br>-<br>2<br>2<br>1<br>- |                              |
| THYMUS  | N.A.D. :  | 10<br>10         | 1 -                        | <u>-</u>                        | 10<br>10                        |                              |
| - Congestion                                      | :   |                  | 1                          | _                               | _                               |                              |
| TRACHEA   | N.A.D. :  | 10               | <u>-</u>                   | _<br>_                          | 10<br>10                        |                              |
| - Infiltrate : - Ectasia subr                     | Grade 1:  | 1<br>1<br>1<br>1 | -<br>-<br>-<br>-           | -<br>-<br>-<br>-                | -<br>-<br>-<br>-                |                              |

Group 01, CONTROL, females: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, females: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, females: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, females: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORE SUMMARY TABLES                                   | RT (FINAL)   |   |                                 |                                 |   | PAGE : 9/106<br>TOX : 509991  |
|---|--|---|---------------------------------|---------------------------------|---|---|
| TEST SYSTEM   | : Betawell<br>: RAT, 90-1<br>: Cosun Bio               | Day, I                                      | Diet                            |                                 | B.V.  | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |
| NUMBER OF ANIMA<br>STATUS AT NECRO<br>Incidence table             | OPSY: KO   |   |                                 |                                 |   | BY ORGAN/GROUP/SEX  |
|   | X :<br>SE GROUP:<br>.ANIMALS:                          | 01<br>10                                    | 02<br>10                        | 03<br>10                        | 04<br>10                                    | FEMALE  |
| THYROID GLAND   | N.A.D. :   | 10<br>10                                    | _<br>_                          | -<br>-                          | 10<br>9                                     |   |
| - Thymus, ector   | pic :  | -   | _                               | _                               | 1   |   |
| STOMACH   | :<br>N.A.D. :  | 10<br>10                                    | 1 -                             | -<br>-                          | 10  |   |
| <ul><li>Inflammation</li><li>Hemorrhage</li><li>Cyst(s)</li></ul> | gland: Grade 1: Grade 2: Grade 1:                      | -<br>-<br>-<br>-<br>-                       | 1<br>1<br>1<br>1<br>-           | -<br>-<br>-<br>-<br>-           | -<br>-<br>-<br>-<br>2<br>2                  |   |
| LIVER   | :<br>N.A.D. :  | 10 2  | <u>-</u><br>-                   |                                 | 10  | · · · · · · · · · · · · · · · · · · ·                                     |
| - Infiltrate in   | nflamm.:<br>Grade 1:                                   | 8<br>8                                      | -<br>-                          | -<br>-                          | 9   |   |
| SPLEEN - Hematopoiesis - Pigmentation                             | Grade 1: Grade 2: , hemos.: Grade 1: Grade 2: Grade 3: | 10<br>9<br>6<br>3<br>10<br>4<br>3<br>3<br>1 | -<br>-<br>-<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>-<br>-<br>- | 10<br>8<br>4<br>4<br>10<br>2<br>5<br>3<br>- |   |

Group 01, CONTROL, females: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, females: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, females: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, females: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>SUMMARY TABLES  | PAGE : 10/106<br>TOX : 509991                                       |
|---|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V.             | PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 PathData®System V6.2e2 |
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY OF STATUS AT NECROPSY: KO Incidence table - All microscopic findings | RGAN/GROUP/SEX  |
| SEX : DOSE GROUP: 01 02 03 04 NO.ANIMALS: 10 10 10  | FEMALE  |
| MESENT. LYMPH NODE : 10 10 N.A.D. : 6 - 9   |   |
| - Incr. macrophages : 3 1 Grade 1: 3 1 Grade 2:   |   |
| - Lymphangiectasis : 1 Grade 1: 1   |   |
| MANDIB.LYMPH NODES : 10 10 N.A.D. : 9 10  |   |
| - Erythrophagocytosis: 1 Grade 2: 1   |   |
| : 10 10<br>N.A.D.: 8 8  |   |
| - Infiltrate inflamm.: 1 Grade 1: 1 - Casts : 1 - Mineralization : 2 1 Grade 1: 1 Grade 2: 2 1 Grade 2: 2           |   |
| ADRENAL GLANDS : 10 10 N.A.D.: 9 - 10   |   |
| - Infiltrate inflamm. : 1 Grade 1: 1  | •                             |

Group 01, CONTROL, females: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, females: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, females: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, females: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>SUMMARY TABLES   | PAGE : 11/106<br>TOX : 509991   |
|--|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V.  | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY OR STATUS AT NECROPSY: K0 Incidence table - All microscopic findings  | GAN/GROUP/SEX   |
| SEX : DOSE GROUP: 01 02 03 04 NO.ANIMALS: 10 10 10   | FEMALE  |
| SCIATIC NERVE, LEFT : 10 10 N.A.D. : 9 9   |   |
| - Demyelination : 1 1 Grade 1: 1 1   | •••••   |
| UTERUS : 10 7 5 10 N.A.D. : 5 - 6  |   |
| - Cyclic dilation : 5 7 5 4  | •••••   |
| VAGINA : 10 7 5 10 - Cycle: Proestrus : 3 2 2 3 - Cycle: Estrus : 3 5 3 1 - Cycle: Metestrus : 2 3 - Cycle: Diestrus : 2 - 3   |   |
| SKIN/SUBCUTIS : 10 1 - 10 N.A.D.: 9 10   |   |
| - Inflammation adnexal: - 1 Grade 2: - 1 Grade 2: 1 Grade 2: 1 Grade 2: 1 1 | ••••••  |
| LARYNX : 10 10 N.A.D. : 9 - 8  |   |
| - Infiltrate inflamm.: 1 1 Grade 1: 1 1 - Ectasia subm. glands: 1 Grade 1: 1 Grade 2:  |   |

Group 01, CONTROL, females: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, females: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, females: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, females: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>SUMMARY TABLES   |                  |                  |                  |                  | PAGE : 12/106<br>TOX : 509991 |  |  |  |  |  |  |
|--|------------------|------------------|------------------|------------------|-------------------------------|--|--|--|--|--|--|
| TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 4 TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 0 SPONSOR : Cosun Biobased Products B.V. PathData®System |                  |                  |                  |                  |                               |  |  |  |  |  |  |
| NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: KO Incidence table - All microscopic findings                     |                  |                  |                  |                  |                               |  |  |  |  |  |  |
| SEX : DOSE GROUP: NO.ANIMALS:  | -                | 02<br>10         | 03<br>10         | 04<br>10         | FEMALE                        |  |  |  |  |  |  |
| EYES : N.A.D. :  | 10               | _                | -<br>-           | 10<br>10         |                               |  |  |  |  |  |  |
| - Atrophy retinal : Grade 2:   |                  |                  | -<br>-<br>-      | -<br>-<br>-      |                               |  |  |  |  |  |  |
| BONE MARROW, STERNUM : N.A.D. :  | 10<br>7          | _                | <u>-</u><br>-    | 10               |                               |  |  |  |  |  |  |
| - Increased adipocytes:<br>Grade 1:  | 3                |                  | -<br>-           | 2 2              |                               |  |  |  |  |  |  |
| AXILLARY LYMPH NODES: - Hyperplasia lymphoid:  | 1<br>1<br>1<br>1 | -<br>-<br>-<br>- | -<br>-<br>-<br>- | -<br>-<br>-<br>- |                               |  |  |  |  |  |  |

Group 01, CONTROL, females: Betawell L-Arabinose (0 PPM)
Group 02, 3000 PPM, females: Betawell L-Arabinose (3000 PPM)
Group 03, 10000 PPM, females: Betawell L-Arabinose (10000 PPM)
Group 04, 30000 PPM, females: Betawell L-Arabinose (30000 PPM)

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | )        |             |                                       |                                       |                                       |                                       | AGE<br>OX                             |                                       |                                       | 3/ 106<br>509991                      |  |  |
|---|----------|-------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|--|
| TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NO SPONSOR : Cosun Biobased Products B.V. PathData®System V6 |          |             |                                       |                                       |                                       |                                       |                                       |                                       |                                       |                                       |  |  |
| TABLE OF INDIVIDUAL MICE DOSE GROUP : 01, CONT  |          |             | FINDI                                 | NGS (2                                | AOFT)                                 |                                       | 1 1 1 1                               |                                       |                                       |                                       |  |  |
| ANIMAL NUMBER :   | 1<br>4K0 | 2<br>MK0    | 3<br>MK0                              |                                       |                                       | 6<br>MK0                              | 7<br>MK0                              | _                                     | 9<br>MK0                              | _                                     |  |  |
| HEART - Infiltrate inflamm.   | -        | +<br>1.     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     |  |  |
| AORTA   | -<br>-   | · · · · · · | · · · · ·<br>-                        | · · · · · ·                           | · · · · · -                           | · · · · · · · · · · · ·               | · · · · · · -                         | · · · · · ·                           | · · · · · ·                           | -                                     |  |  |
| LUNG - Alveolar macrophages - Inflamm. peribronch.  | +<br>1.  | -           | +                                     | •                                     | <br>+<br>2.                           | · · · · · · · · · · · · · · · · · · · | ·····<br>+<br>1.                      | · · · · · · · · · · · · · · · · · · · | ·····<br>+<br>1.                      | <br>+<br>1.                           |  |  |
| THYMUS - Hyperplasia, epith.  |          | -<br>-      | -<br>-                                | -<br>-                                | +<br>1.                               | -<br>-                                | -<br>-                                | -<br>-                                | -<br>-                                | +<br>2.                               |  |  |
| TRACHEA - Infiltrate inflamm Ectasia subm. glands   | +<br>1.  | -           | +                                     | · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>1.                               |  |  |
| ESOPHAGUS   | -        | -           | -                                     |                                       |                                       | -                                     | -                                     | -                                     |                                       | -                                     |  |  |
| THYROID GLAND - Hypertrophy foll. c.  | 1.       |             | 2.                                    | •                                     |                                       |                                       |                                       | -<br>-                                | +<br>1.                               | +<br>1.                               |  |  |
| PARATHYROID GLANDS  | _        | _           | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | ( -                                   | _                                     |  |  |
| STOMACH - Inflammation forest Cyst(s) - Vacuolation, lim. r.  | +<br>1.  | -           | -<br>:                                | +<br>+                                | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>+                                | + 1.                                  | +<br>1.                               |  |  |
| DUODENUM  | _        | -           | · · · · · -                           |                                       | -                                     | · · · · · ·                           | -<br>-                                |                                       | · · · · · ·                           | · · · · · · · · · · · ·               |  |  |
| JEJUNUM   | _        | _           | _                                     | _                                     | _                                     | _                                     | _                                     | _                                     | _                                     | _                                     |  |  |
| ILEUM   | _        | _           | -                                     | -                                     | -                                     | _                                     | -                                     | -                                     | · · · · · ·                           | -                                     |  |  |
| PEYER'S PATCHES - Mineralization  | -        | -           | · · · · · · · · · · · · · · · · · · · | ·····                                 | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>2.                               | · · · · · · · · · · · · · · · · · · · |  |  |
| CECUM   | _        | _           | _                                     | · · · · · · · ·                       | · · · · · ·<br>-                      | · · · · · ·                           | -<br>-                                | -<br>-                                | · · · · · ·                           | -<br>-                                |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA  | )        |             |          |                                       |   |             | AGE<br>OX | :   |                         | 4/ 106<br>509991                      |  |  |  |  |
|---|----------|-------------|----------|---------------------------------------|---|-------------|-----------|---|-------------------------|---------------------------------------|--|--|--|--|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. |          |             |          |                                       |   |             |           | PATHOL. NO.: 41607 JOI<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |                         |                                       |  |  |  |  |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 01, CON   |          |             | FINDI    | NGS (A                                | AOFT)                                   |             |           |   |                         |                                       |  |  |  |  |
| ANIMAL NUMBER :   | 1<br>MK0 | _           | 3<br>MK0 | 4<br>MK0                              | -                                       | 6<br>MK0    | 7<br>MK0  | 8<br>MK0  | 9<br>MK0                | -                                     |  |  |  |  |
| COLON   | _        |             |          |                                       |   |             |           | _   |                         |                                       |  |  |  |  |
| RECTUM  |          | · · · · · · |          |                                       | _                                       | · · · · · · | -         | · · · · · ·   | · · · · · · · · · · · · |                                       |  |  |  |  |
| LIVER - Infiltrate inflamm.   | -        | +           | +        | +                                     | +                                       | +           | +         | +   |                         | +                                     |  |  |  |  |
| SPLEEN - Hematopoiesis incr Pigmentation, hemos.  | +        |             |          | +<br>1.                               |   | 2.          | 1.        | +<br>1.<br>2.   | 2.                      | 1.                                    |  |  |  |  |
| MESENT. LYMPH NODE - Incr. macrophages  |          | +<br>2.     | -        |                                       | -                                       | +           | _         | +<br>1.   | +                       | _                                     |  |  |  |  |
| PANCREAS - Atrophy, acinar  |          |             | -        | -                                     | 1.                                      |             |           |   |                         |                                       |  |  |  |  |
| MANDIB.LYMPH NODES  | -        | _           |          |                                       | - · · · ·                               |             | -         | · · · · · ·   | _                       | · · · · · · · ·                       |  |  |  |  |
| SUBLINGUAL GLANDS   | -        | _           | _        | -                                     | _                                       | _           | _         | _   | -                       | -                                     |  |  |  |  |
| MANDIBULAR GLANDS   | -        | _           | _        | _                                     | _                                       | _           | _         | _   | _                       | _                                     |  |  |  |  |
| KIDNEYS - Infiltrate inflamm Hyaline droplet acc Basophilia, tubule                                     | +<br>1.  | ( 1.<br>1.  | -        | +                                     | -<br>·                                  | +<br>1.     | -<br>·    | +   | +<br>2.                 | <br>+<br>1.                           |  |  |  |  |
| URINARY BLADDER   | · · · ·  |             |          | · · · · · · · · · · · · · · · · · · · | - · · · · · · · · · · · · · · · · · · · | -           | -         | · · · · · ·   | · · · · · ·             | -                                     |  |  |  |  |
| ADRENAL GLANDS - Vacuol. fasciculata  | -        |             | -        | +<br>1.                               | +<br>1.                                 | +<br>1.     |           | · · · · · · · · · · · · · · · · · · ·                                     | -<br>-                  | · · · · · · · · · · · · · · · · · · · |  |  |  |  |
| BRAIN   | -        | _           | _        | _                                     | -                                       | _           | _         | · · · · · · ·   | _                       | -<br>-                                |  |  |  |  |
| PITUITARY GLAND - Cyst(s)   |          |             |          |                                       |   |             |           | · · · · · · · · · · · · · · · · · · ·                                     | -<br>-                  | +<br>1.                               |  |  |  |  |
| SCIATIC NERVE, LEFT   | _        | _           | _        | _                                     | _                                       | _           | -         | -<br>-  | -<br>-                  | -<br>-                                |  |  |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA  | L)       |                                       |       |         |             |   | AGE<br>OX   |   |             | 5/ 106<br>509991 |  |  |
|---|----------|---------------------------------------|-------|---------|-------------|---|---|---|-------------|------------------|--|--|
| TEST SYSTEM : RAT, 90-Day, Diet                 |          |                                       |       |         |             |   | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData@System V6.2e2 |   |             |                  |  |  |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 01, CON |          |                                       | FINDI | NGS (.  | AOFT)       |   |   |   |             |                  |  |  |
| ANIMAL NUMBER :                                 | 1<br>MK0 | 2<br>MK0                              |       |         |             |   |   |   | 9<br>MK0    |                  |  |  |
| TESTES  |          | _                                     |       |         |             |   |   |   |             | _                |  |  |
|   | _        | _                                     | _     | -       | _           | _ | _   | _ | _           | -                |  |  |
| PROSTATE GLAND - Infiltrate inflamm.            |          |                                       | -     |         |             | - | +<br>2.   | - | -           |                  |  |  |
| SEMINAL VESICLES                                | _        | _                                     | _     | -       | -           | - | -   | _ | -           | -                |  |  |
| COAGULATING GLANDS                              | _        | _                                     | _     | _       | _           | _ | ( -   | _ | _           | _                |  |  |
| SKIN/SUBCUTIS                                   |          | · · · · · ·                           |       |         | · · · · · · |   |   |   | · · · · · · |                  |  |  |
| LARYNX - Ectasia subm. glands                   | -        | -                                     | -     | +<br>2. | -           | - | +<br>1.   | - | -           | -                |  |  |
| EYES - Atrophy retinal                          | -        | · · · · · · · · · · · · · · · · · · · | _     | _       | _           | + | _   | _ | _           | _                |  |  |
| OPTIC NERVES                                    |          |                                       |       |         |             |   |   |   |             |                  |  |  |
| HARDERIAN GLANDS                                |          | · · · · ·                             |       |         |             |   |   |   |             |                  |  |  |
| SPINAL CORD, CERVIC.                            | _        | _                                     | _     | _       | _           | _ | _   | _ | _           | -                |  |  |
| SPINAL CORD, THORAC.                            | -        | _                                     | _     | -       | -           | - | -   | _ | -           | -                |  |  |
| SPINAL CORD, LUMBAR                             | _        | _                                     | _     | _       | _           | _ | _   | _ | -           | _                |  |  |
| BONE, STERNUM                                   | _        | _                                     | _     | _       | _           | _ | _   | _ | _           | _                |  |  |
| BONE MARROW, STERNUM                            | -        | _                                     | -     | -       | -           | - | -   | _ | -           | -                |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA  | L)            |             |             |                                       |             |                                       | AGE<br>OX                             |   |                                       | 6/ 106<br>509991                      |  |  |
|---|---------------|-------------|-------------|---------------------------------------|-------------|---------------------------------------|---------------------------------------|---|---------------------------------------|---------------------------------------|--|--|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. |               |             |             |                                       |             |                                       |                                       | PATHOL. NO.: 41607 JOI<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |                                       |                                       |  |  |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 01, COI   |               | OPIC 1      | FINDI       | NGS (.                                | AOFT)       |                                       |                                       |   |                                       |                                       |  |  |
| ANIMAL NUMBER :   | 41<br>FK0     | 42<br>FK0   | 43<br>FK0   |                                       |             | 46<br>FK0                             | 47<br>FK0                             |   |                                       | 50<br>FK0                             |  |  |
| HEART   | _             | _           | _           | _                                     | _           | _                                     | _                                     | _   | _                                     | _                                     |  |  |
| AORTA   | -             | -           | -           | -                                     | -           | -                                     | -                                     | -   | -                                     | -                                     |  |  |
| LUNG - Inflamm. peribronch.   | -             | -           | +<br>1.     | +                                     | _           | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·                                     | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |  |  |
| THYMUS  | -G            |             | -           |                                       |             |                                       | -                                     | -   |                                       | -                                     |  |  |
| TRACHEA - Infiltrate inflamm Ectasia subm. glands   | -             | -<br>·      | -           | +                                     | -           | -                                     | +                                     | -   | -                                     | -                                     |  |  |
| ESOPHAGUS   | -             | -           | -           | · · · · ·                             | · · · · ·   | · · · · ·                             | · · · · · ·                           | · · · · · ·   | -                                     | -                                     |  |  |
| THYROID GLAND   | · · · · · · - | · · · · · · | · · · · · · | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           | · · · · · ·   | · · · · · ·                           | -                                     |  |  |
| PARATHYROID GLANDS  |               | ( -         |             |                                       |             |                                       | ( -                                   |   | · · · · · ·                           | -                                     |  |  |
| STOMACH   | · · · · · ·   | -           |             |                                       |             |                                       |                                       |   |                                       |                                       |  |  |
| DUODENUM  | · · · · · ·   |             |             | · · · · · ·                           | · · · · · · |                                       | · · · · · ·                           |   | · · · · · -                           | -                                     |  |  |
| JEJUNUM   | · · · · · ·   |             |             |                                       | · · · · · · | · · · · · ·                           | · · · · · ·                           | · · · · · ·   | · · · · · -                           | · · · · · · ·                         |  |  |
| ILEUM   | · · · · · ·   | · · · · · · |             | · · · · · ·                           | · · · · ·   |                                       | · · · · ·                             | · · · · · ·   | · · · · · ·                           |                                       |  |  |
| PEYER'S PATCHES   | · · · · · ·   | · · · · · · | · · · · · · | · · · · · ·                           | · · · · ·   | · · · · · ·                           | · · · · · ·                           | · · · · · ·   | · · · · · ·                           | -                                     |  |  |
| CECUM   | · · · · · ·   |             | -           | · · · · · ·                           | · · · · ·   | · · · · · ·                           | · · · · ·                             |   | · · · · · ·                           |                                       |  |  |
| COLON   | · · · · · ·   | · · · · · · | · · · · · · | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           |   | · · · · · ·                           |                                       |  |  |
| RECTUM  | · · · · · ·   | · · · · · · | · · · · · · | · · · · · ·                           | · · · · ·   | · · · · ·                             | · · · · · ·                           | · · · · · ·   | · · · · · ·                           |                                       |  |  |
| LIVER - Infiltrate inflamm.   | <br>+<br>1.   | <br>+<br>1. | <br>+<br>1. | · · · · · · · · · · · · · · · · · · · | <br>+<br>1. | <br>+<br>1.                           | <br>+<br>1.                           | <br>+<br>1.   | · · · · · · · · · · · · · · · · · · · | <br>+<br>1.                           |  |  |
|   |               |             |             |                                       |             |                                       |                                       |   |                                       |                                       |  |  |

| PATHOLOGY REPORT (FINA INDIVIDUAL ANIMAL DATA   | L)                                    |                                       |               |  |                                       |                                       | AGE<br>OX                             |   |                                       | 7/ 106<br>509991                        |  |  |  |  |
|---|---------------------------------------|---------------------------------------|---------------|--|---------------------------------------|---------------------------------------|---------------------------------------|---|---------------------------------------|---|--|--|--|--|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. |                                       |                                       |               |  |                                       |                                       |                                       | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |                                       |   |  |  |  |  |
| TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT) DOSE GROUP : 01, CONTROL                                |                                       |                                       |               |  |                                       |                                       |                                       |   |                                       |   |  |  |  |  |
| ANIMAL NUMBER :   | 41<br>FK0                             | 42<br>FK0                             | 43<br>FK0     | 44<br>FK0                              | 45<br>FK0                             | 46<br>FK0                             | 47<br>FK0                             | 48<br>FK0   | 49<br>FK0                             | 50<br>FK0                               |  |  |  |  |
| SPLEEN - Hematopoiesis incr Pigmentation, hemos Hyperplasia lymphoid                                    | +<br>2.<br>1.                         |                                       | +<br>1.<br>2. | +<br>1.<br>3.                          | +<br>1.<br>3.                         | +<br>2.<br>1.                         | +G<br>1.<br>3.                        | +<br>2.<br>1.   | +<br>1.<br>2.                         | +<br>1.<br>2.                           |  |  |  |  |
| MESENT. LYMPH NODE - Incr. macrophages - Lymphangiectasis - Sinus histiocytosis                         |                                       |                                       | +<br>1.       | ······································ | +<br>1.                               | · · · · · · · · · · · · · · · · · · · | +<br>1.                               | ······································                                    | ······<br>-<br>·<br>·                 | · · · · · · · · · · · · · · · · · · ·   |  |  |  |  |
| PANCREAS  | _                                     | - · · · · ·                           | · · · · ·     | · · · · · ·                            | -                                     | · · · · ·                             | · · · · ·                             | · · · · ·   | · · · · ·                             | -                                       |  |  |  |  |
| MANDIB.LYMPH NODES - Erythrophagocytosis  | +G<br>2.                              | _                                     | -<br>-        | -<br>-                                 | · · · · · · · · · · · · · · · · · · · | -<br>-                                | -<br>-                                | · · · · · · · · · · · · · · · · · · ·                                     | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·   |  |  |  |  |
| SUBLINGUAL GLANDS   | _                                     |                                       | · · · · · ·   | · · · · · ·                            | - · · · · ·                           | · · · · · ·                           | · · · · · ·                           | · · · · · ·   | · · · · · ·                           | -                                       |  |  |  |  |
| MANDIBULAR GLANDS   | _                                     | -                                     | -             | · · · · · ·                            | -                                     | · · · · ·                             | · · · · ·                             | · · · · · ·   | · · · · ·                             | -                                       |  |  |  |  |
| KIDNEYS - Mineralization  | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>2.       | -<br>-                                 | -<br>-                                | -<br>-                                | + ( 2.                                | -<br>-  | -<br>-                                | · · · · · · · · · · · · · · · · · · ·   |  |  |  |  |
| URINARY BLADDER   | -                                     | -                                     | 0             | -                                      | -                                     | -                                     | -                                     | · · · · ·   | -                                     | -                                       |  |  |  |  |
| ADRENAL GLANDS - Infiltrate inflamm.  | -                                     | -                                     | -             | · · · · · · · · · · · · · · · · · · ·  | _                                     | <br>+<br>( 1.                         | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·                                     | · · · · · · · · · · · · · · · · · · · | -<br>-                                  |  |  |  |  |
| BRAIN   | -                                     | -                                     | -             | -                                      | -                                     | -                                     | -                                     | · · · · · ·   | -                                     | - · · · · · · · · · · · · · · · · · · · |  |  |  |  |
| PITUITARY GLAND   | -                                     | · · · · · ·<br>-                      | · · · · · ·   | -                                      | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           |   | · · · · · ·                           | -                                       |  |  |  |  |

...... 

OVARIES - - - - - - - - -

UTERUS - +G - +G +G - - +G +G - - - +G +G - Cyclic dilation . P. P. P. P. P. P.

OVARIES

| PATHOLOGY REPORT (FINA INDIVIDUAL ANIMAL DATA                                  |             |   |                                       |                                       |                                       |                                       | AGE<br>OX                             |                                       |                                       | 8/ 106<br>509991                      |
|--|-------------|---|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| TEST ITEM : Betawe<br>TEST SYSTEM : RAT, 9<br>SPONSOR : Cosun                  | V.          | PATHOL. NO.: 41607 JOFINALIZED : 07-NOV-PathData®System V6.20 |                                       |                                       |                                       |                                       |                                       |                                       |                                       |                                       |
| TABLE OF INDIVIDUAL MI DOSE GROUP : 01, CO                                     |             | OPIC I  | FINDI                                 | NGS (                                 | AOFT)                                 |                                       |                                       |                                       |                                       |                                       |
| ANIMAL NUMBER :  | 41<br>FK0   |   |                                       |                                       |                                       |                                       |                                       | 48<br>FK0                             |                                       |                                       |
| CERVIX   | _           | _   | _                                     |                                       |                                       | _                                     | _                                     | _                                     | _                                     | _                                     |
| VAGINA - Cycle: Proestrus - Cycle: Estrus - Cycle: Metestrus - Cycle: Diestrus | +<br>•<br>• | P.  | Р.                                    |                                       | P.                                    |                                       | P.                                    | <br>+<br>P.                           |                                       |                                       |
| MAMMARY GLAND  | · · · · · · | · · · · · · · · · · · ·                                       | · · · · ·                             | · · · · · ·                           | · · · · ·                             | · · · · · ·                           | -                                     | · · · · · ·                           | · · · · · -                           |                                       |
| SKIN/SUBCUTIS - Inflamm. exudative - Erosion/ulcer                             | +G          | -   | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |
| LARYNX - Infiltrate inflamm.   | _           | -   | <br>+<br>1.                           |                                       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · ·<br>-                      | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |
| EYES - Atrophy retinal   | +           | _   |                                       |                                       |                                       | · · · · · · · · · · · · · · · · · · · |                                       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |
| OPTIC NERVES   | ( -         |   | ( -                                   | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | · · · · · · · · · · · · · · · · · · · |
| HARDERIAN GLANDS   | _           | -   | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     |
| SPINAL CORD, CERVIC.   | -           | · · · · · · · · · · · ·                                       | · · · · · -                           | · · · · · ·                           | · · · · · ·                           | · · · · · · · ·                       | · · · · · ·                           | · · · · · ·                           | · · · · · -                           | -                                     |
| SPINAL CORD, THORAC.   | -           | · · · · · · · · · · · · · · · · · · ·                         | · · · · · · -                         |                                       |                                       | -                                     | · · · · · · -                         | -                                     | · · · · · -                           | -                                     |
| SPINAL CORD, LUMBAR  | · · · · · · |   |                                       | · · · · · ·                           |                                       |                                       | · · · · ·                             |                                       | · · · · · -                           |                                       |
| BONE, STERNUM  | · · · · · · |   | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | · · · · · ·                           | · · · · · · · · · · · · · · · · · · · |
| BONE MARROW, STERNUM - Increased adipocytes                                    | _           | +   | _                                     | +                                     | _                                     | _                                     | <br>+<br>1.                           | _                                     | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |
| AXILLARY LYMPH NODES - Hyperplasia lymphoid - Congestion                       | 2.<br>P.    |   |                                       |                                       |                                       |                                       |                                       |                                       |                                       | , , , , , ,                           |
|  |             | • •   | <b>.</b> .                            | <b>.</b> .                            | <b></b>                               |                                       | <b></b>                               | <b></b>                               | <b></b>                               | <b></b>                               |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE : 19/106<br>TOX : 509991   |
|---|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |
| TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT) DOSE GROUP : 02, 3000 PPM                               |   |
| ANIMAL NUMBER:  11 12 13 14 15  MKO MKO MKO MKO MKO MKO MKO   | 16 17 18 19 20<br>30 MK0 MK0 MK0 MK0                                      |
| THYROID GLAND ' ' ' '   | ' -G ' ' '  |
| MANDIB.LYMPH NODES ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' '  | ' +G ' ' (2.  |
| PREPUTIAL GLANDS ' '+G ' ' - Dilation (3.   | ,                                   |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA               | ٦)        |                |         |           |         |          | AGE<br>OX |           |           | 0/ 106<br>509991           |
|--|-----------|----------------|---------|-----------|---------|----------|-----------|-----------|-----------|----------------------------|
| TEST ITEM : Betawell TEST SYSTEM : RAT, 90 SPONSOR : Cosun H | Day       | , Die          | t       | ts B.     | V.      | F        | INALI     | ZED       | : 07-1    | 07 JOL<br>NOV-16<br>V6.2e2 |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 02, 300              |           |                | FINDI   | NGS (     | AOFT)   |          |           |           |           |                            |
| ANIMAL NUMBER :  | 51<br>FK0 |                |         | 54<br>FK0 |         |          |           | 58<br>FK0 | 59<br>FK0 |                            |
| THYMUS - Congestion  | ,         | +G<br>P.       | ,       | ,         | 1       | '        | •         | ,         | ,         | ,                          |
| STOMACH - Inflammation, gland Hemorrhage                     |           | +G<br>1.<br>2. | , , , , |           |         | , , , ,  |           |           |           |                            |
| - Cyclic dilation  | +G<br>P.  |                |         |           |         | +G<br>P. |           |           |           | +G<br>P.                   |
| VAGINA - Cycle: Proestrus - Cycle: Estrus                    | +<br>P.   |                | +<br>P. |           | +<br>P. | •        | •         |           | +<br>P.   | +<br>P.                    |
| SKIN/SUBCUTIS - Inflammation adnexal - Erosion/ulcer         |           | +G<br>2.<br>2. |         |           |         |          |           |           |           |                            |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA   | PAGE : 21/106<br>TOX : 509991 |  |  |  |  |  |  |  |  |
|--|-------------------------------|--|--|--|--|--|--|--|--|
| TEST ITEM : Betawell L-Arabinose PATHOL. NO.: TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : SPONSOR : Cosun Biobased Products B.V. PathData®Syst |                               |  |  |  |  |  |  |  |  |
| TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT) DOSE GROUP : 03, 10000 PPM   |                               |  |  |  |  |  |  |  |  |
| ANIMAL NUMBER: 61 62 63 64 65 FKO FKO FKO FKO FKO FF   |                               |  |  |  |  |  |  |  |  |
|  | +G +G ' +G '<br>P. P. P.      |  |  |  |  |  |  |  |  |
| VAGINA + ' ' + - Cycle: Proestrus P Cycle: Estrus P.   | + + ' + '<br>P.<br>P. P.      |  |  |  |  |  |  |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA                      | )                                     |                                       |                                       |             |                                       |                                       | AGE<br>OX                             | :                                       |                                       | 2/ 106<br>509991                        |
|---|---------------------------------------|---------------------------------------|---------------------------------------|-------------|---------------------------------------|---------------------------------------|---------------------------------------|---|---------------------------------------|---|
| TEST ITEM : Betawel TEST SYSTEM : RAT, 90 SPONSOR : Cosun B         | F                                     | INALI                                 | ZED :                                 | : 07-1      | 07 JOL<br>NOV-16<br>V6.2e2            |                                       |                                       |   |                                       |   |
| TABLE OF INDIVIDUAL MIC DOSE GROUP : 04, 300                        |                                       |                                       | FINDI                                 | NGS (2      | AOFT)                                 |                                       |                                       |   |                                       |   |
| ANIMAL NUMBER :   | 31<br>MK0                             | 32<br>MK0                             | 33<br>MK0                             |             | 35<br>MK0                             |                                       | 37<br>MK0                             |   | 39<br>MK0                             | _                                       |
| HEART   | _                                     |                                       | _                                     |             |                                       |                                       |                                       | _                                       | _                                     |   |
| AORTA   | · · · ·                               |                                       | · · · · ·                             |             |                                       | · · · · · ·                           | -                                     | · · · · · ·                             | · · · · · · · · · · · · · · · · · · · |   |
| LUNG - Alveolar macrophages - Inflamm. peribronch Osseus metaplasia |                                       | +<br>1.                               | +                                     |             | <br>+<br>1.                           | ······<br>+<br>1.                     | <br>+<br>2.                           | - · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                  |
| THYMUS - Congestion   | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                | +G<br>P.    | · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · · | -<br>-                                  | -<br>-                                | · · · · · · · · · · · · · · · · · · ·   |
| TRACHEA - Infiltrate inflamm.                                       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>1.     | +<br>1.                               | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | - · · · · · · · · · · · · · · · · · · · | -<br>-                                | -<br>-                                  |
| ESOPHAGUS   | · · · ·                               | -                                     | -                                     | -           | -                                     | -                                     | -                                     | · · · · · · · · · · · ·                 | · · · · · · · ·                       | -                                       |
| THYROID GLAND - Hypertrophy foll. c.                                | _                                     | _                                     | +                                     | +           | +                                     | +                                     | _                                     | +<br>1.                                 | +                                     | +                                       |
| PARATHYROID GLANDS  | · · · ·                               | ( -                                   | -                                     | -           | ( -                                   | ( -                                   | -                                     | · · · · · ·                             | · · · · · ·                           | ( -                                     |
| STOMACH - Vacuolation, lim. r.                                      | _                                     | _                                     | · · · · · · · · · · · · · · · · · · · | <br>+<br>1. | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | - · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · ·   |
| DUODENUM  | · · · ·                               | · · · · · ·                           | · · · · ·                             |             | · · · · ·                             | · · · · · ·                           | · · · · · ·                           | · · · · · ·                             | _                                     | · · · · · · ·                           |
| JEJUNUM   | · · · · ·                             | · · · · · ·                           | · · · · · · · · · · · · · · · · · · · | · · · · · · | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           | - · · · · · · · · · · · · · · · · · · · | _                                     | · · · · · · · · -                       |
|   | · · · ·                               | · · · · · · -                         | · · · · · · · · · · · · · · · · · · · | · · · · · · | · · · · · · -                         | · · · · · · -                         | · · · · · · -                         | - · · · · · · · · · · · · · · · · · · · | - · · · · · · · ·                     | · · · · · · · · · · · · · · · · · · ·   |
| PEYER'S PATCHES - Mineralization                                    | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                | +<br>2*     | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                  | -<br>-                                | · · · · · · · · · · · · · · · · · · ·   |
| CECUM   | _                                     | -                                     |                                       |             | · · · · · · · · · · · · · · · · · · · |                                       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·   | -<br>-                                | - · · · · · · · · · · · · · · · · · · · |
| COLON   | -<br>                                 |                                       |                                       |             | -<br>                                 | -<br>                                 | -<br>                                 | -<br>                                   | -<br>· · · · · -                      | -<br>                                   |
|   |                                       |                                       |                                       |             |                                       |                                       |                                       |   |                                       |   |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA                      | L)        |             |                                       |                                       |                                       |             | AGE<br>OX                             |                                       |                                       | 3/ 106<br>509991           |
|---|-----------|-------------|---------------------------------------|---------------------------------------|---------------------------------------|-------------|---------------------------------------|---------------------------------------|---------------------------------------|----------------------------|
| TEST ITEM : Betawe. TEST SYSTEM : RAT, 90 SPONSOR : Cosun I         | )-Day     | , Die       | t                                     | ts B.                                 | V.                                    | F           | INALI                                 | ZED                                   | : 07-                                 | 07 JOL<br>NOV-16<br>V6.2e2 |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 04, 300                     |           |             | FINDI                                 | NGS (.                                | AOFT)                                 |             |                                       |                                       |                                       |                            |
| ANIMAL NUMBER :   | 31<br>MK0 |             |                                       | 34<br>MK0                             |                                       |             | 37<br>MK0                             | 38<br>MK0                             | 39<br>MK0                             | 40<br>MK0                  |
| LIVER - Infiltrate inflamm Single cell necrosis - Fibrosis          | +<br>1.   | +<br>1.     | +<br>1.                               |                                       |                                       |             | +<br>1.                               |                                       | +<br>1.                               | +<br>1.                    |
| SPLEEN - Hematopoiesis incr Pigmentation, hemos.                    | 1.        | + 2.        | +                                     | +<br>2.<br>2.                         |                                       | +<br>1.     | + 1.                                  | +<br>1.<br>1.                         | + 1.                                  | + 2.                       |
| MESENT. LYMPH NODE - Incr. macrophages                              | -         | -           | + 1.                                  | -                                     | -                                     | -           | + 1.                                  | + 1.                                  | -                                     | +<br>1.                    |
| PANCREAS - Atrophy, acinar  | -<br>-    | -<br>-      | -<br>-                                | -<br>-                                | -<br>-                                | -<br>-      | -<br>-                                | -<br>-                                | +<br>1.                               | -<br>-                     |
| MANDIB.LYMPH NODES  | -         | _           | _                                     | _                                     | _                                     | · · · · ·   | _                                     | _                                     | _                                     | _                          |
| SUBLINGUAL GLANDS   | -         |             | _                                     | -                                     | -                                     | -           | -                                     | -                                     | -                                     | -                          |
| MANDIBULAR GLANDS   | -         | · · · · · · | · · · · · ·                           | -<br>-                                | - · · · · ·                           | · · · · · · |                                       | · · · · · ·                           |                                       | · · · · · · · · · · · ·    |
| KIDNEYS - Nephrogenic rest - Hyaline droplet acc Basophilia, tubule | +         |             | +<br>1.                               | <br>+<br>( P.<br>1.                   | · · · · · · · · · · · · · · · · · · · | <br>+<br>1. | <br>+<br>1.<br>( 1.                   | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>1.                    |
| URINARY BLADDER   | -         | -           | · · · · ·                             | · · · · ·                             | · · · · ·                             | -           |                                       | · · · · ·                             | · · · · ·                             | -                          |
| ADRENAL GLANDS - Vacuol. fasciculata                                |           | +<br>1.     |                                       | · · · · · · · · · · · · · · · · · · · | -<br>-                                | -           | +<br>1.                               | -<br>-                                | +<br>1.                               | -<br>-                     |
| BRAIN   | _         | _           | -                                     | -                                     | -                                     | -           | · · · · · ·                           | -                                     | · · · · · ·                           | -                          |
| PITUITARY GLAND - Cyst(s)   | +<br>1.   | -           | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +                                     | ·····       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |                            |
| SCIATIC NERVE, LEFT - Demyelination                                 | -         | -           | -                                     | -                                     |                                       | -           |                                       | + 1.                                  |                                       | -                          |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA             |                                       |                                       |                                       |                                       |                                       |                                       | AGE<br>OX                             |                                       | : 2<br>:                              | 4/ 106<br>509991                      |
|--|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| TEST ITEM : Betawell TEST SYSTEM : RAT, 90- SPONSOR : Cosun Bi | Day                                   | , Die                                 | t                                     | ts B.                                 | V.                                    | F                                     | INALI                                 | ZED                                   | : 07-                                 | 07 JOL<br>NOV-16<br>V6.2e2            |
| TABLE OF INDIVIDUAL MICR DOSE GROUP : 04, 3000                 |                                       |                                       | FINDI                                 | NGS (                                 | AOFT)                                 |                                       |                                       |                                       |                                       |                                       |
| ANIMAL NUMBER :  | 31<br>IK0                             | 32<br>MK0                             |                                       |                                       |                                       | 36<br>MK0                             |                                       | 38<br>MK0                             |                                       | -                                     |
| TESTES - Atrophy, tubular                                      |                                       |                                       | •                                     |                                       |                                       |                                       | 3.                                    |                                       |                                       | •                                     |
| EPIDIDYMIDES - Cell debris, luminal                            |                                       |                                       |                                       | -                                     | _                                     | _                                     | +G                                    | -                                     | -                                     | _                                     |
| PROSTATE GLAND - Infiltrate inflamm.                           | _                                     | _                                     | _                                     | _                                     |                                       | · · · · · · · · · · · · · · · · · · · |                                       |                                       |                                       | · · · · · · · · · · · · · · · · · · · |
| SEMINAL VESICLES   | _                                     | -                                     | _                                     | _                                     | _                                     | _                                     | _                                     | _                                     | _                                     | -                                     |
| COAGULATING GLANDS   | -                                     | -                                     | -                                     | -                                     | -                                     | _                                     | -                                     | -                                     | -                                     | -                                     |
| SKIN/SUBCUTIS  | -                                     | -                                     | -                                     | -                                     | _                                     | _                                     | -                                     | -                                     | _                                     | -                                     |
| LARYNX   | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     |
| EYES   | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | _                                     |
| OPTIC NERVES   | -                                     | _                                     | _                                     | _                                     | ( –                                   | _                                     | -                                     | ( –                                   | _                                     | _                                     |
| HARDERIAN GLANDS   | _                                     | -                                     | _                                     | -                                     | _                                     | _                                     | -                                     | _                                     | -                                     | -                                     |
| SPINAL CORD, CERVIC.   | -                                     | -                                     | -                                     | -                                     | -                                     | _                                     | -                                     | -                                     | -                                     | -                                     |
| ,  | -                                     | · · · · ·                             |                                       |                                       |                                       |                                       |                                       |                                       |                                       |                                       |
| SPINAL CORD, LUMBAR  | -                                     | -                                     | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | -                                     | -                                     |
| BONE, STERNUM - Developm. artifact                             | +<br>P.                               |                                       | -<br>-                                | -<br>-                                | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -                                     |
| BONE MARROW, STERNUM - Increased adipocytes                    | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | <br>+<br>1.                           | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · |
| BONE   | -G                                    |                                       |                                       |                                       |                                       | • • • • • •                           |                                       |                                       | • • • • • •                           | 1                                     |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA                        |   |             |             |               |                                       |                                       | AGE<br>OX   |                                       |                                       | 5/ 106<br>509991                       |  |  |
|---|---|-------------|-------------|---------------|---------------------------------------|---------------------------------------|-------------|---------------------------------------|---------------------------------------|--|--|--|
| TEST ITEM : Betawer TEST SYSTEM : RAT, S SPONSOR : Cosun              | F   | INALI       | ZED         | : 07-         | 07 JOL<br>NOV-16<br>V6.2e2            |                                       |             |                                       |                                       |  |  |  |
|   | TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)  DOSE GROUP : 04, 30000 PPM |             |             |               |                                       |                                       |             |                                       |                                       |  |  |  |
| ANIMAL NUMBER :   | 71<br>FK0   | 72<br>FK0   | 73<br>FK0   |               | 75<br>FK0                             |                                       | 77<br>FK0   |                                       | 79<br>FK0                             | 80<br>FK0                              |  |  |
| HEART - Myxomatous, valvular  | -<br>-  | -           | -           |               | -                                     | -                                     | -           | -                                     | -                                     | + 2.                                   |  |  |
| AORTA   | · · · · · · · · · · · · · · · · · · ·                                       | · · · · · · | · · · · · · | · · · · · ·   | · · · · · ·                           | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           | -                                      |  |  |
| LUNG - Alveolar macrophages - Inflamm. peribronch - Osseus metaplasia | -<br>5 .<br>  | +<br>1.     | 1.          | 1.            | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | <br>+<br>1. | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | ······································ |  |  |
| THYMUS  | _   | -           | -           | -             | -                                     | -                                     | -           | -                                     | -                                     | -                                      |  |  |
| TRACHEA   | · · · · · · · -   |             | -           | · · · · · ·   | -                                     | · · · · · ·                           | · · · · · · | -                                     |                                       | -                                      |  |  |
| ESOPHAGUS   |   | · · · · ·   |             | · · · · ·     | · · · · · ·                           | · · · · · ·                           | · · · · ·   | · · · · · ·                           | · · · · · ·                           | -                                      |  |  |
| THYROID GLAND - Thymus, ectopic                                       | _   | -           | _           | +             |                                       | _                                     | _           | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·  |  |  |
| PARATHYROID GLANDS  | · · · · · · · · · · · · · · · · · · ·                                       |             | · · · · · · | · · · · · ·   | · · · · ·                             |                                       | · · · · · · |                                       | · · · · · ·                           |  |  |  |
| - Cyst(s)   | -   | -           | -           | +             | +<br>1.                               | -                                     |             | ·····                                 | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · ·  |  |  |
| DUODENUM  | -<br>-  |             | · · · · · · | · · · · · ·   | · · · · · ·                           | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           | -                                      |  |  |
| JEJUNUM   | · · · · · · · · · · · · · · · · · · ·                                       | · · · · · · |             |               |                                       |                                       |             | · · · · · ·                           |                                       |  |  |  |
| ILEUM   | · · · · · · · · · · · · · · · · · · ·                                       | · · · · · · | -           | -             |                                       |                                       |             |                                       | · · · · · -                           | · · · · · · ·                          |  |  |
| PEYER'S PATCHES   | · · · · · · · · · · · · · · · · · · ·                                       | · · · · · · | -           | · · · · · · - | -                                     | · · · · · ·                           | · · · · · · | -                                     | · · · · · -                           | · · · · · · · · · · · · · · · · · · ·  |  |  |
| CECUM   | · · · · · · · · · · · · · · · · · · ·                                       | · · · · · · | · · · · · · | · · · · · -   | · · · · · ·                           | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · -                           |  |  |  |
| COLON   | · · · · · · · ·   |             | · · · · · · | · · · · · ·   | · · · · ·                             | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           |  |  |  |
| RECTUM  | · · · · · · · · · · · · · · · · · · ·                                       | -           | · · · · · · | · · · · · ·   | -                                     | · · · · · ·                           | · · · · · · | · · · · · ·                           | · · · · · ·                           | -                                      |  |  |
|   |   |             |             |               |                                       |                                       |             |                                       |                                       |  |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA               | ٦)   |             |                                       |                                       |                                       |                                       | AGE<br>OX                             | :                                     |                                       | 6/ 106<br>509991                        |  |  |  |
|--|--|-------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---|--|--|--|
| TEST ITEM : Betawell TEST SYSTEM : RAT, 90 SPONSOR : Cosun E | F  | INALI       | ZED :                                 | : 07-1                                | 07 JOL<br>NOV-16<br>V6.2e2            |                                       |                                       |                                       |                                       |   |  |  |  |
|  | TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT) DOSE GROUP : 04, 30000 PPM |             |                                       |                                       |                                       |                                       |                                       |                                       |                                       |   |  |  |  |
| ANIMAL NUMBER :  | 71   | 72          | 73                                    | 74                                    | 75                                    | 76                                    | 77                                    | 78                                    | 79                                    | 80                                      |  |  |  |
|  | FK0  | FK0         | FK0                                   | FK0                                   | FK0                                   | FK0                                   | FK0                                   | FK0                                   | FK0                                   | FK0                                     |  |  |  |
| LIVER - Infiltrate inflamm.                                  | -  | +<br>1.     | 1.                                    | 1.                                    | 1.                                    | 1.                                    | 1.                                    | + 1.                                  | +<br>1.                               | +<br>1.                                 |  |  |  |
| SPLEEN - Hematopoiesis incr Pigmentation, hemos.             | +<br>2.  | +           | +<br>2.                               | +                                     | +<br>2.                               | +<br>1.                               | +<br>1.                               | +<br>2.                               | +<br>1.                               | +<br>1.<br>3.                           |  |  |  |
| MESENT. LYMPH NODE - Incr. macrophages                       | · · · · · · · · · · · · · · · · · · ·                                      |             | -<br>-                                | · · · · · · · · · · · · · · · · · · · | -<br>-                                | -<br>-                                | -<br>-                                | -<br>-                                | -<br>-                                | +<br>1.                                 |  |  |  |
| PANCREAS   | -  | _           | _                                     | -                                     | -                                     | -                                     | -                                     | - · · · · · · ·                       | -<br>-                                | -                                       |  |  |  |
| MANDIB.LYMPH NODES   | -  | -           | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | -                                     | _                                       |  |  |  |
| SUBLINGUAL GLANDS  | -  | · · · · · · | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           | · · · · · ·                           |                                       | _                                     | · · · · · · · · · · · · · · · · · · ·   |  |  |  |
| MANDIBULAR GLANDS  | -  | · · · · ·   | · · · · ·                             | · · · · ·                             | · · · · ·                             | -                                     | -                                     |                                       | -                                     | -                                       |  |  |  |
| KIDNEYS - Infiltrate inflamm Casts - Mineralization          | -<br>•   |             | · · · · · · · · · · · · · · · · · · · | ( 1.<br>( 2.                          | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | -<br>-                                | · · · · · · · · · · · · · · · · · · · |   |  |  |  |
| URINARY BLADDER  | -  | · · · · ·   | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | -                                     |                                       | -                                     | -                                       |  |  |  |
| ADRENAL GLANDS   | -  | · · · · ·   | · · · · · ·                           |                                       | · · · · · ·                           |                                       | -                                     |                                       | -                                     | -                                       |  |  |  |
| BRAIN  | -  | · · · · ·   | · · · · · ·                           | -                                     | · · · · · ·                           | -                                     | -                                     |                                       | -                                     | -<br>-                                  |  |  |  |
| PITUITARY GLAND  | -  | · · · · ·   | -                                     | · · · · · ·                           | -                                     | -                                     | -                                     | • • • • • • • • • • • • • • • • • • • | · · · · · ·                           | - · · · · · · · · · · · · · · · · · · · |  |  |  |
| SCIATIC NERVE, LEFT - Demyelination                          |  |             | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +<br>1.                               | · · · · · · · · · · · · · · · · · · · | -<br>-                                | -<br>-                                | · · · · · · · · · · · · · · · · · · ·   |  |  |  |
| OVARIES  | -  | -           | -<br>-                                | -<br>-                                | -<br>-                                | · · · · · ·                           | · · · · · ·                           |                                       | -<br>-                                | -                                       |  |  |  |
| UTERUS - Cyclic dilation                                     | +G<br>P.   |             |                                       | · · · · · · · · · · · · · · · · · · · | · · · · · · · · · · · · · · · · · · · | +G<br>P.                              | · · · · · · · · · · · · · · · · · · · | +G<br>P.                              | -<br>-                                | - · · · · · · · · · · · · · · · · · · · |  |  |  |

| PATHOLOGY REPORT (FINAL INDIVIDUAL ANIMAL DATA                                 | 1)        |   |           |         |             |             | AGE<br>OX   |         |                                       | 7/ 106<br>509991 |
|--|-----------|---|-----------|---------|-------------|-------------|-------------|---------|---------------------------------------|------------------|
| TEST ITEM : Betawel TEST SYSTEM : RAT, 90 SPONSOR : Cosun E                    | F         | PATHOL. NO.: 41607 JOL<br>FINALIZED : 07-NOV-16<br>PathData®System V6.2e2 |           |         |             |             |             |         |                                       |                  |
| TABLE OF INDIVIDUAL MIC<br>DOSE GROUP : 04, 300                                |           |   | FINDI     | NGS (2  | AOFT)       |             |             |         |                                       |                  |
| ANIMAL NUMBER :  | 71<br>FK0 | 72<br>FK0   | 73<br>FK0 |         |             |             |             |         |                                       |                  |
| CERVIX   | -         | _   | _         | _       | _           | _           | _           | _       | _                                     | _                |
| VAGINA - Cycle: Proestrus - Cycle: Estrus - Cycle: Metestrus - Cycle: Diestrus | +<br>P.   | +<br>P.   | +         | +<br>P. | +<br>•<br>• | +<br>P.     | +<br>•<br>• | +<br>P. | +<br>•<br>•<br>•                      | +                |
| MAMMARY GLAND  | -         | -   | -         | -       | _           | _           | -           | _       | -                                     | -                |
| SKIN/SUBCUTIS  | _         | _   | _         | _       | _           | _           | _           | _       | _                                     | _                |
| LARYNX - Infiltrate inflamm Ectasia subm. glands                               | -         | -   | +<br>1.   | +<br>1. | _           |             | -<br>-      |         | · · · · · · · · · · · · · · · · · · · | -                |
| EYES   | -         | _   | -         | _       |             | · · · · · · |             |         | · · · · · ·                           | -                |
| OPTIC NERVES   | _         | _   | _         | _       | _           | _           | _           | _       | _                                     | _                |
| HARDERIAN GLANDS   | -         | _   | _         | _       | _           | _           | _           | _       | _                                     | -                |
| SPINAL CORD, CERVIC.   | _         | _   | _         | _       | _           | _           | _           | _       | _                                     | -                |
| - , , , , , , , , , , , , , , , , , , ,  | _         | _   | _         | _       | _           | _           | _           | _       | _                                     | _                |
|  | _         | _   | _         | _       | _           | _           | _           | _       | _                                     | -                |
| BONE, STERNUM  | _         | _   | -         | -       | _           | -           | -           | -       | -                                     | -                |
| BONE MARROW, STERNUM - Increased adipocytes                                    | +         | _   | +         | _       | _           | _           | _           | _       | _                                     | -                |

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 28/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData@System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 01, CONTROL

| ANIMAL | SEX | DEFINED  | AND FINAL | TEST | FIRST     | AND LAST  | DATE OF   |
|--------|-----|----------|-----------|------|-----------|-----------|-----------|
| NUMBER | M/F | STATE OF | NECROPSY  | DAYS | DAY UN    | DER TEST  | NECROPSY  |
|        |     |          |           |      |           |           |           |
| 1      | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 2      | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 3      | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 4      | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 5      | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 6      | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 7      | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 8      | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 9      | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 10     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
|        |     |          |           |      |           |           |           |
| 41     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 42     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 43     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 44     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 45     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 46     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 47     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 48     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 49     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 50     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
|        |     |          |           |      |           |           |           |

PATHOLOGY REPORT (FINAL) PAGE : 29/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 1

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 1 TRACHEA:

-Infiltrate inflammatory cell, lymphocytic, grade 1 THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

STOMACH:

-Cyst(s), grade 1

SPLEEN:

-Pigmentation, hemosiderin, grade 1

KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, ESOPHAGUS, PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, LIVER, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

Final Report

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 30/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 2

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

# \* MICROSCOPIC FINDINGS

#### **HEART:**

- -Infiltrate inflammatory cell, lymphocytic, grade 1 THYROID GLAND (BOTH LOBES):
- -Hypertrophy follicular cell, bilateral, grade 1 LIVER:
- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 2

MESENTERIC LYMPH NODE:

- -Increased macrophage foci, grade 2
- KIDNEYS:
  - -Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1
- -Basophilia, tubule, bilateral, grade 1
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 31/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 2

#### \* ORGANS WITHOUT ABNORMALITIES

- AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 3

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

# LUNG:

LIVER:

-Alveolar macrophage aggregation, grade 2 TRACHEA:

-Ectasia submucosal glands, grade 1

THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 2

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Pigmentation, hemosiderin, grade 2

: 32/106 : 509991 PATHOLOGY REPORT (FINAL) PAGE TOX INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, THYMUS, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO DAYS ON TEST : 92

\* ANIMAL NO. : 

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

- -Inflammation peribronchial/perivascular, grade 1
- -Vacuolation, limiting ridge, grade 1 LIVER:
  - -Infiltrate inflammatory cell, lymphocytic, grade 1

PAGE : 33/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. :

#### SPLEEN:

-Pigmentation, hemosiderin, grade 1

KIDNEYS:

-Basophilia, tubule, unilateral, grade 1

ADRENAL GLANDS:

-Vacuolation zona fasciculata, bilateral, grade 1

LARYNX:

-Ectasia submucosal glands, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS , THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 34/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 5

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 2 THYMUS:

-Hyperplasia, epithelial tubules and cords, grade 1 LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Pigmentation, hemosiderin, grade 2

PANCREAS:

-Atrophy, acinar cells, grade 1

ADRENAL GLANDS:

-Vacuolation zona fasciculata, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

Final Report

PATHOLOGY REPORT (FINAL)

INDIVIDUAL ANIMAL DATA

PAGE : 35/106

TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 6

## \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

# \* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

- -Hypertrophy follicular cell, bilateral, grade 1 LIVER:
- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 2
- -Pigmentation, hemosiderin, grade 1

MESENTERIC LYMPH NODE:

- -Increased macrophage foci, grade 1
- KIDNEYS:
- -Hyaline droplet accumulation, bilateral, grade 1 ADRENAL GLANDS:
- -Vacuolation zona fasciculata, bilateral, grade 1 EYES:
- -Atrophy retinal, unilateral, grade 2
- ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 36/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO.: 6

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 7

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

# LUNG:

- -Inflammation peribronchial/perivascular, grade 1
  LIVER:
- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 1 PROSTATE GLAND:
- -Infiltrate inflammatory cell, lymphocytic, grade 2 COAGULATING GLANDS (ANTERIOR PROSTATE):
  - Only one of paired organs examined/present

PAGE : 37/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 

#### LARYNX:

-Ectasia submucosal glands, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT) , TESTES, EPIDIDYMIDES, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO DAYS ON TEST : 93

\* ANIMAL NO. : 

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### STOMACH:

-Vacuolation, limiting ridge, grade 1 LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PAGE : 38/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO. : 

#### SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 2

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

KIDNEYS:

-Basophilia, tubule, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT) , TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO DAYS ON TEST : 93

\* ANIMAL NO. : 

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT (FINAL) PAGE : 39/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO.: 9

# \* MICROSCOPIC FINDINGS

#### T.HING •

-Inflammation peribronchial/perivascular, grade 1 THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1 PARATHYROID GLANDS:

Only one of paired organs examined/present STOMACH:

-Cyst(s), grade 1 PEYER'S PATCHES:

-Mineralization, grade 2

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-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 2

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 2

KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 2 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

Final Report

PATHOLOGY REPORT (FINAL)

INDIVIDUAL ANIMAL DATA

PAGE : 40 / 106

TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 10

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

# \* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 1 THYMUS:

-Hyperplasia, epithelial tubules and cords, grade 2 TRACHEA:

-Infiltrate inflammatory cell, lymphocytic, grade 1 THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

-Inflammation forestomach, lymphogranulocytic, grade 1 LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 1

# KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1 PITUITARY GLAND:

-Cyst(s), pars distalis, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 41/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL MALE

CONT./FF. ANIMAL NO.: 10

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, ESOPHAGUS, PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 42/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 41

#### \* NECROPSY FINDINGS

## THYMUS:

01: FOCUS/FOCI, MANY, TAN.

MANDIBULAR LYMPH NODES:

01: BOTH SIDES: DISCOLOURATION, RED-BROWN.

SKIN/SUBCUTIS:

01: SHOULDER, LEFT SIDE: SCAB FORMATION, SEVERAL.

02: CHEEK REGION, LEFT SIDE: SCAB FORMATION, SEVERAL.

03: SHOULDER, RIGHT SIDE: SCAB FORMATION, SEVERAL.

AXILLARY LYMPH NODES:

01: BOTH SIDES: ENLARGED.

02: BOTH SIDES: DISCOLOURATION, REDDISH.

NO OTHER NECROPSY OBSERVATIONS NOTED

## \* MICROSCOPIC FINDINGS

#### THYMUS:

No microscopic finding corresponding to necropsy observation no. 01. LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 1

MESENTERIC LYMPH NODE:

-Lymphangiectasis, grade 1

-Sinus histiocytosis, grade 2

MANDIBULAR LYMPH NODES:

-Erythrophagocytosis, bilateral, grade 2

This finding corresponds to necropsy observation no: 01.

# VAGINA:

-Cycle: diestrus

SKIN/SUBCUTIS:

-Inflamation exudative, grade 2

This finding corresponds to necropsy observations nos: 01,03.

-Erosion/ulcer, grade 2

PATHOLOGY REPORT (FINAL) PAGE : 43/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 41

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This finding corresponds to necropsy observation no: 02. EYES:

-Atrophy retinal, unilateral, grade 2 OPTIC NERVES:

Only one of paired organs examined/present AXILLARY LYMPH NODES:

-Hyperplasia lymphoid, bilateral, grade 2

This finding corresponds to necropsy observation no: 01.

-Congestion, bilateral

This finding corresponds to necropsy observation no: 02. ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, LARYNX, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 44/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 42

#### \* NECROPSY FINDINGS

## UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

## PARATHYROID GLANDS:

Only one of paired organs examined/present

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 3

#### UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

# VAGINA:

-Cycle: proestrus

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 45/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 42

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 43

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

# LUNG:

- -Inflammation peribronchial/perivascular, grade 1
- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 2

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

PATHOLOGY REPORT (FINAL) PAGE : 46/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 43

#### KIDNEYS:

-Mineralization, medullary, bilateral, grade 2 URINARY BLADDER:

Tissue not present for histologic examination

VAGINA:

-Cycle: estrus

LARYNX:

-Infiltrate inflammatory cell, lymphocytic, grade 1 OPTIC NERVES:

Only one of paired organs examined/present ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)

INDIVIDUAL ANIMAL DATA

PAGE : 47/ 106

TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 44

#### \* NECROPSY FINDINGS

#### UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

#### LUNG:

- -Inflammation peribronchial/perivascular, grade 1 TRACHEA:
- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 3

#### UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

# VAGINA:

-Cycle: proestrus

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 48/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 44

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, LIVER, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 45

\* NECROPSY FINDINGS

#### UTERUS:

01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

# PARATHYROID GLANDS:

Only one of paired organs examined/present

- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 3

PATHOLOGY REPORT (FINAL) PAGE : 49/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 45

## MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1 UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01. VAGINA:

-Cycle: estrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 46

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT (FINAL) PAGE : 50/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 46

## \* MICROSCOPIC FINDINGS

#### LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 1

ADRENAL GLANDS:

-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1 VAGINA:

-Cycle: diestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose
TEST SYSTEM : RAT, 90-Day, Diet
SPONSOR : Cosun Biobased Products B.V.

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

\* STATE AT NECROPSY: KO
DAYS ON TEST : 92

\* ANIMAL NO. : 47

\* NECROPSY FINDINGS

#### SPLEEN:

01: NODULE(S), D=5X4 MM, DARK RED, SOFT. NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

#### TRACHEA:

-Ectasia submucosal glands, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Pigmentation, hemosiderin, grade 1

-Hyperplasia, lymphoid, focal, grade 3

This finding corresponds to necropsy observation no: 01.

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

KIDNEYS:

-Mineralization, medullary, unilateral, grade 2

SCIATIC NERVE (LEFT):

-Demyelination, grade 1

VAGINĀ:

-Cycle: metestrus

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 52/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 47

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 48

......

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 2
- -Pigmentation, hemosiderin, grade 1

VAGINA:

-Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 53/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 48

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 49

\* NECROPSY FINDINGS

#### UTERUS:

01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

#### SPLEEN:

- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 2

#### UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01. VAGINA:

-Cycle: proestrus

PATHOLOGY REPORT (FINAL) PAGE : 54/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 49

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, LIVER, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 50

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

#### TITVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 2

PATHOLOGY REPORT (FINAL) PAGE : 55/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 01, CONTROL FEMALE

CONT./FF. ANIMAL NO.: 50

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 56/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData@System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 02, 3000 PPM

| ANIMAL   | SEX                             | DEFINED AND FI  | NAL TEST   | FIRST  | AND LAST   | DATE OF   |
|--|---------------------------------|---|--|--|--|---|
| NUMBER   | M/F                             | STATE OF NECRO  | PSY DAYS   | DAY UN   | DER TEST   | NECROPSY  |
| 11<br>12<br>13<br>14<br>15<br>16                   | M<br>M<br>M<br>M<br>M<br>M<br>M | K0 K0<br>K0 K0<br>K0 K0<br>K0 K0<br>K0 K0<br>K0 K0<br>K0 K0   | 92<br>92<br>92<br>92<br>92<br>92<br>93<br>93             | 04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15              | 03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>04-FEB-16                           | 04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>05-FEB-16  |
| 18<br>19<br>20                                     | M<br>M<br>M                     | K0       K0         K0       K0         K0       K0   | 93<br>93<br>93   | 04-NOV-15<br>04-NOV-15<br>04-NOV-15  | 04-FEB-16<br>04-FEB-16<br>04-FEB-16  | 05-FEB-16<br>05-FEB-16<br>05-FEB-16   |
| 51<br>52<br>53<br>54<br>55<br>56<br>57<br>58<br>59 | 4444444                         | K0       K0         K0       K0 | 92<br>92<br>92<br>92<br>92<br>92<br>92<br>92<br>92<br>92 | 04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15<br>04-NOV-15 | 03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16<br>03-FEB-16 | 04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16<br>04-FEB-16 |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE<br>TOX                             | : 57/ 106<br>: 509991                       |
|---|---|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | FINALIZED                               | .: 41607 JOL<br>: 07-NOV-16<br>ystem V6.2e2 |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 02, 3000 PPM  |   | MALE  |
|   |   | : 11  |
| * NECROPSY FINDINGS   |   |   |
| NO NECROPSY OBSERVATIONS NOTED.   |   |   |
| * MICROSCOPIC FINDINGS  |   |   |
| NO EXAMINATION REQUIRED.  |   |   |
| * STATE AT NECROPSY: KO   |   |   |
|   | ANIMAL NO.                              | : 12  |
|   | • | •     |
| * NECROPSY FINDINGS   |   |   |
| NO NECROPSY OBSERVATIONS NOTED.   |   |   |
| * MICROSCOPIC FINDINGS  |   |   |
| NO EXAMINATION REQUIRED.  |   |   |

| PATHOLOGY REPORT (FINAL) | PAGE | : | 58/ 106 |
|--------------------------|------|---|---------|
| INDIVIDUAL ANIMAL DATA   | TOX  | : | 509991  |
|                          |      |   |         |

PATHOL. NO.: 41607 JOL TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO. : 13 

\* NECROPSY FINDINGS

PREPUTIAL GLANDS (INGUINAL GLANDS):
01: RIGHT SIDE: FOCUS/FOCI, D=5X2 MM, TAN.
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

PREPUTIAL GLANDS (INGUINAL GLANDS):

-Dilation, unilateral, grade 3

This finding corresponds to necropsy observation no: 01.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 14 

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

| PATHOLOGY REPORT (FINAL)  | DACE                                  | <b>:</b> 59/ 106                            |
|---|---------------------------------------|---|
| INDIVIDUAL ANIMAL DATA  |                                       | : 509991                                    |
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO<br>FINALIZED<br>PathData®S | .: 41607 JOL<br>: 07-NOV-16<br>ystem V6.2e2 |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 02, 3000 PPM  |                                       | MALE  |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92 *   | ANIMAL NO.                            | : 15  |
| * NECROPSY FINDINGS   |                                       |   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                       |   |
| * MICROSCOPIC FINDINGS  |                                       |   |
| NO EXAMINATION REQUIRED.  |                                       |   |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 93 *   | ANIMAL NO.                            | : 16  |
| * NECROPSY FINDINGS   |                                       |   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                       |   |
| * MICROSCOPIC FINDINGS  |                                       |   |
| NO EXAMINATION REQUIRED.  |                                       |   |

| MECH THEM . Determine I Ameliance | DAMILOT | NO | 41.007 707 |
|-----------------------------------|---------|----|------------|
| INDIVIDUAL ANIMAL DATA            | TOX     | :  | 509991     |
| PATHOLOGY REPORT (FINAL)          | PAGE    | :  | 60/ 106    |

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 17

### \* NECROPSY FINDINGS

THYROID GLAND (BOTH LOBES):
01: BOTH SIDES: REDUCED IN SIZE.

NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

Organ examined, no pathologic findings noted
No microscopic finding corresponding to necropsy observation no. 01.

- \* ORGANS WITHOUT ABNORMALITIES
- THYROID GLAND (BOTH LOBES).

\* STATE AT NECROPSY: K0
DAYS ON TEST: 93 \* ANIMAL NO.: 18

\* NECROPSY FINDINGS

MANDIBULAR LYMPH NODES:

01: RIGHT SIDE: DISCOLOURATION, PURPLE. NO OTHER NECROPSY OBSERVATIONS NOTED

PAGE : 61/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2 TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 02, 3000 PPM MALE CONT./FF. ANIMAL NO.: 18 \* MICROSCOPIC FINDINGS MANDIBULAR LYMPH NODES: -Erythrocytes, intrasinusoidal, unilateral, grade 2 This finding corresponds to necropsy observation no: 01. \* STATE AT NECROPSY: KO DAYS ON TEST : 93 \* ANIMAL NO.: 19 \* NECROPSY FINDINGS NO NECROPSY OBSERVATIONS NOTED. \* MICROSCOPIC FINDINGS NO EXAMINATION REQUIRED. \* STATE AT NECROPSY: KO DAYS ON TEST : 93 \* ANIMAL NO. : 

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE : TOX :                                 | 62/ 106<br>509991 |
|---|--|-------------------|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO.:<br>FINALIZED :<br>PathData®Syst | 07-NOV-16         |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 02, 3000 PPM  |  | MALE              |
| CONT./FF  | `. ANIMAL NO. :                              | 20                |
| * MICROSCOPIC FINDINGS  |  |                   |
| NO EXAMINATION REQUIRED.  |  |                   |
|   |  |                   |

PATHOLOGY REPORT (FINAL) PAGE : 63/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 51

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 52

\* NECROPSY FINDINGS

THYMUS:

01: FOCUS/FOCI, MANY, REDDISH.

STOMACH:

01: GLANDULAR MUCOSA: FOCUS/FOCI, SEVERAL, REDDISH.

SKIN/SUBCUTIS:

01: DORSO-LUMBAR REGION: SCAB FORMATION, MANY.

NO OTHER NECROPSY OBSERVATIONS NOTED

: 64/ 106 PATHOLOGY REPORT (FINAL) PAGE INDIVIDUAL ANIMAL DATA TOX 509991 TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2 TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 02, 3000 PPM FEMALE 52 CONT./FF. ANIMAL NO. : \* MICROSCOPIC FINDINGS THYMUS: -Congestion This finding corresponds to necropsy observation no: 01. STOMACH: -Inflammation, glandular stomach, lymphogranulocytic, grade 1 -Hemorrhage, mucosal, focal, grade 2 This finding corresponds to necropsy observation no: 01. SKIN/SUBCUTIS: -Inflammation adnexal, grade 2 -Erosion/ulcer, grade 2 This finding corresponds to necropsy observation no: 01. \* STATE AT NECROPSY: KO DAYS ON TEST : 92 \* ANIMAL NO. : 53 \* NECROPSY FINDINGS UTERUS: 01: CONTAINS FLUID. NO OTHER NECROPSY OBSERVATIONS NOTED \* MICROSCOPIC FINDINGS UTERUS: -Cyclic dilation This finding corresponds to necropsy observation no: 01. VAGINA: -Cycle: estrus

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 65/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 54

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

\_\_\_\_\_

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 55

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

PATHOLOGY REPORT (FINAL) PAGE : 66/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 56

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 57

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 67/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM FEMALE

CONT./FF. ANIMAL NO.: 57

VAGINA:

-Cycle: estrus

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

PATHOLOGY REPORT (FINAL) PAGE : 68/106
INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 02, 3000 PPM FEMALE

CONT./FF. ANIMAL NO.: 59

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 60

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 69/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData@System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 03, 10000 PPM

| 2377427 | 27.1 |          |            |      |           |           |           |
|---------|------|----------|------------|------|-----------|-----------|-----------|
| ANIMAL  | SEX  |          | AND FINAL  | TEST | _         | AND LAST  | DATE OF   |
| NUMBER  | M/F  | STATE OF | ' NECROPSY | DAYS | DAY UN    | DER TEST  | NECROPSY  |
| 21      | M    | ко       | к0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 22      | M    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 23      | M    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 24      | M    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 25      | M    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 26      | M    | K0       | K0         | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 27      | M    | K0       | K0         | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 28      | M    | K0       | K0         | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 29      | M    | K0       | K0         | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 30      | M    | K0       | K0         | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
|         |      |          |            |      |           |           |           |
| 61      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 62      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 63      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 64      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 65      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 66      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 67      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 68      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 69      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 70      | F    | K0       | K0         | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE : TOX :                                | 70/ 106<br>509991   |
|---|---|---------------------|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO.:<br>FINALIZED :<br>PathData®Sys | 07-NOV-16           |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM                                       |   | MALE                |
| * STATE AT NECROPSY: KO DAYS ON TEST : 92 *   | ANIMAL NO.:                                 |                     |
| * NECROPSY FINDINGS   |   |                     |
| NO NECROPSY OBSERVATIONS NOTED.   |   |                     |
| * MICROSCOPIC FINDINGS  |   |                     |
| NO EXAMINATION REQUIRED.  |   |                     |
|   |   |                     |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92 *   | ANIMAL NO. :                                | 22                  |
| * NECROPSY FINDINGS   | • • • • • • • • • • • • •                   | • • • • • • • • • • |
|   |   |                     |
| NO NECROPSY OBSERVATIONS NOTED.   |   |                     |
| * MICROSCOPIC FINDINGS  |   |                     |
| NO EXAMINATION REQUIRED.  |   |                     |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE<br>TOX | : 71/106<br>: 509991                        |
|---|-------------|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. |             | .: 41607 JOL<br>: 07-NOV-16<br>ystem V6.2e2 |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM                                       |             | MALE  |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92 *   | ANIMAL NO.  | : 23  |
| * NECROPSY FINDINGS   |             |   |
| NO NECROPSY OBSERVATIONS NOTED.   |             |   |
| * MICROSCOPIC FINDINGS  |             |   |
| NO EXAMINATION REQUIRED.  |             |   |
|   |             |   |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92 *   | ANIMAL NO.  | : 24  |
| * NECROPSY FINDINGS   |             |   |
| NO NECROPSY OBSERVATIONS NOTED.   |             |   |
| * MICROSCOPIC FINDINGS  |             |   |
| NO EXAMINATION REQUIRED.  |             |   |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  |                                 | : 72/106<br>: 509991                        |
|---|---------------------------------|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO FINALIZED PathData®S | .: 41607 JOL<br>: 07-NOV-16<br>ystem V6.2e2 |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM                                       |                                 | MALE  |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92 *   | ANIMAL NO.                      | : 25  |
| * NECROPSY FINDINGS   |                                 |   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                 |   |
| * MICROSCOPIC FINDINGS  |                                 |   |
| NO EXAMINATION REQUIRED.  |                                 |   |
|   |                                 | <del> </del>                                |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 93 *   | ANIMAL NO.                      | : 26  |
| * NECROPSY FINDINGS   |                                 |   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                 |   |
| * MICROSCOPIC FINDINGS  |                                 |   |
| NO EXAMINATION REQUIRED.  |                                 |   |

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE<br>TOX                             | : 73/106<br>: 509991                        |
|---|---|---|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | FINALIZED                               | .: 41607 JOL<br>: 07-NOV-16<br>ystem V6.2e2 |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM                                       |   | MALE  |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 93 *   |   | : 27  |
| * NECROPSY FINDINGS   |   |   |
| NO NECROPSY OBSERVATIONS NOTED.   |   |   |
| * MICROSCOPIC FINDINGS  |   |   |
| NO EXAMINATION REQUIRED.  |   |   |
|   |   |   |
| * STATE AT NECROPSY: KO DAYS ON TEST : 93 *   | ANIMAL NO.                              | : 28  |
| * NECROPSY FINDINGS   | • | • • • • • • • • • • • • •                   |
| NO NECROPSY OBSERVATIONS NOTED.   |   |   |
| * MICROSCOPIC FINDINGS  |   |   |
| NO EXAMINATION REQUIRED.  |   |   |

PAGE : 74/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2 TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM MALE \* STATE AT NECROPSY: KO DAYS ON TEST : 93 \* ANIMAL NO. : 29 \* NECROPSY FINDINGS NO NECROPSY OBSERVATIONS NOTED. \* MICROSCOPIC FINDINGS NO EXAMINATION REQUIRED. \* STATE AT NECROPSY: KO DAYS ON TEST : 93 \* ANIMAL NO. : \* NECROPSY FINDINGS NO NECROPSY OBSERVATIONS NOTED. \* MICROSCOPIC FINDINGS NO EXAMINATION REQUIRED.

PAGE : 75/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 10000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO. : 61 

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

\* STATE AT NECROPSY: KO DAYS ON TEST : 92 \* ANIMAL NO. :

62 

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

| PATHOLOGY REPORT (FINAL)<br>INDIVIDUAL ANIMAL DATA  | PAGE<br>TOX                    | :       | 76/ 106<br>509991 |
|---|--------------------------------|---------|-------------------|
| TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet SPONSOR : Cosun Biobased Products B.V. | PATHOL. NO FINALIZED PathData® | :       | 07-NOV-16         |
| TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 03, 10000 PPM                                       |                                |         | FEMALE            |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92   | * ANIMAL NO                    | . :<br> | 63                |
| * NECROPSY FINDINGS   |                                |         |                   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                |         |                   |
| * MICROSCOPIC FINDINGS NO EXAMINATION REQUIRED.   |                                |         |                   |
|   |                                |         |                   |
| * STATE AT NECROPSY: K0 DAYS ON TEST : 92   | * ANIMAL NO                    | . :<br> | 64                |
| * NECROPSY FINDINGS   |                                |         |                   |
| NO NECROPSY OBSERVATIONS NOTED.   |                                |         |                   |
| * MICROSCOPIC FINDINGS NO EXAMINATION REQUIRED.   |                                |         |                   |

PATHOLOGY REPORT (FINAL) PAGE : 77/ 106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 10000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 65

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 66

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE: 78/106
TOX: 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 10000 PPM FEMALE

CONT./FF. ANIMAL NO.: 66

VAGINA:

-Cycle: estrus

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 67

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

PATHOLOGY REPORT (FINAL) PAGE : 79/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 10000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 68

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

\_\_\_\_\_

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 69

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

PATHOLOGY REPORT (FINAL) PAGE : 80/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 03, 10000 PPM FEMALE

\* STATE AT NECROPSY: K0

DAYS ON TEST : 92 \* ANIMAL NO.: 70

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 81/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData@System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 04, 30000 PPM

| ANIMAL | SEX | DEFINED  | AND FINAL | TEST | FIRST     | AND LAST  | DATE OF   |
|--------|-----|----------|-----------|------|-----------|-----------|-----------|
| NUMBER | M/F | STATE OF | NECROPSY  | DAYS | DAY UN    | DER TEST  | NECROPSY  |
|        |     |          |           |      |           |           |           |
| 31     | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 32     | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 33     | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 34     | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 35     | M   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 36     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 37     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 38     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 39     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
| 40     | M   | K0       | K0        | 93   | 04-NOV-15 | 04-FEB-16 | 05-FEB-16 |
|        |     |          |           |      |           |           |           |
| 71     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 72     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 73     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 74     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 75     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 76     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 77     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 78     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 79     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
| 80     | F   | K0       | K0        | 92   | 04-NOV-15 | 03-FEB-16 | 04-FEB-16 |
|        |     |          |           |      |           |           |           |

PATHOLOGY REPORT (FINAL) PAGE : 82/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 31

#### \* NECROPSY FINDINGS

### BONE:

01: STERNUM MALALIGNED.

NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

#### LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
  - -Hematopoiesis, extramedullary, increased, grade 1
  - -Pigmentation, hemosiderin, grade 2

#### KIDNEYS:

- -Hyaline droplet accumulation, bilateral, grade 1 PITUITARY GLAND:
- -Cyst(s), pars distalis, grade 1

# BONE (STERNUM):

- -Developmental artifact
- This finding corresponds to necropsy observation no.: 01 in the BONE.

# BONE:

For diagnosis of necropsy observation no. 01 see under: BONE (STERNUM).

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 83/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 31

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE MARROW (STERNUM), BONE.

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 32

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 1 PARATHYROID GLANDS:

Only one of paired organs examined/present LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Pigmentation, hemosiderin, grade 2

PATHOLOGY REPORT (FINAL) PAGE : 84/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 32

### ADRENAL GLANDS:

-Vacuolation zona fasciculata, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: K0
DAYS ON TEST : 92

DAYS ON TEST : 92 \* ANIMAL NO.: 33

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

# LUNG:

- -Inflammation peribronchial/perivascular, grade 1
- -Osseus metaplasia, grade 2

PATHOLOGY REPORT (FINAL) PAGE : 85/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 33

THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Pigmentation, hemosiderin, grade 1

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1 KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 86/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 34

\* NECROPSY FINDINGS

THYMUS:

01: FOCUS/FOCI, MANY, REDDISH.
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

THYMUS:

-Congestion

This finding corresponds to necropsy observation no: 01.

TRACHEA:

-Infiltrate inflammatory cell, lymphocytic, grade 1

THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

STOMACH:

-Vacuolation, limiting ridge, grade 1

PEYER'S PATCHES:

-Mineralization, grade 2

with fibrosis

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 2

KIDNEYS:

-Nephrogenic rest, unilateral

-Hyaline droplet accumulation, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 87/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 34

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, ESOPHAGUS, PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: K0
DAYS ON TEST : 92

\* ANIMAL NO.: 35

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

# LUNG:

-Alveolar macrophage aggregation, grade 1 TRACHEA:

-Infiltrate inflammatory cell, lymphocytic, grade 1 THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 2 PARATHYROID GLANDS:

Only one of paired organs examined/present LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL) PAGE : 88/106
INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 35

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#### SPLEEN:

-Pigmentation, hemosiderin, grade 1 PITUITARY GLAND:

-Cyst(s), pars distalis, grade 1

PROSTATE GLAND:

-Infiltrate inflammatory cell, lymphocytic, grade 1 OPTIC NERVES:

Only one of paired organs examined/present BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

PAGE : 89/106 TOX : 509991 PATHOLOGY REPORT (FINAL) INDIVIDUAL ANIMAL DATA

TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO. : 36 

### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

# \* MICROSCOPIC FINDINGS

-Inflammation peribronchial/perivascular, grade 1 THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1 PARATHYROID GLANDS:

Only one of paired organs examined/present

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Single cell necrosis (apoptosis), grade 1

-Pigmentation, hemosiderin, grade 1

KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS. PATHOLOGY REPORT (FINAL) PAGE : 90/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData@System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 36

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 37

# \* NECROPSY FINDINGS

#### TESTES:

01: BOTH SIDES: REDUCED IN SIZE.

EPIDIDYMIDES:

01: BOTH SIDES: REDUCED IN SIZE.
NO OTHER NECROPSY OBSERVATIONS NOTED

# \* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 2

-Osseus metaplasia, grade 1

#### LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 91/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 37

#### SPLEEN:

-Pigmentation, hemosiderin, grade 1 MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

#### KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1

-Basophilia, tubule, unilateral, grade 1

ADRENAL GLANDS:

-Vacuolation zona fasciculata, bilateral, grade 1 TESTES:

-Atrophy, tubular, bilateral, grade 3

This finding corresponds to necropsy observation no: 01. EPIDIDYMIDES:

-Cell debris, luminal, bilateral, grade 2

This finding corresponds to necropsy observation no: 01. PROSTATE GLAND:

-Infiltrate inflammatory cell, lymphocytic, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 92/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 38

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1 LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 1

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

SCIATIC NERVE (LEFT):

-Demyelination, grade 1

OPTIC NERVES:

Only one of paired organs examined/present ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 93/106
INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 39

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

SPLEEN:

-Pigmentation, hemosiderin, grade 1

PANCREAS:

-Atrophy, acinar cells, grade 1

ADRENAL GLANDS:

-Vacuolation zona fasciculata, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

TOX: 509991

TEST ITEM: Betawell L-Arabinose
TEST SYSTEM: RAT, 90-Day, Diet
SPONSOR: Cosun Biobased Products B.V.

PAGE: 94/106
TOX: 509991

PATHOL. NO.: 41607 JOL
FINALIZED: 07-NOV-16
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 93 \* ANIMAL NO.: 40

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

# \* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):

-Hypertrophy follicular cell, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Fibrosis, focal, grade 1

SPLEEN:

-Pigmentation, hemosiderin, grade 2

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 1 ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA
PAGE : 95/106
TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM MALE

CONT./FF. ANIMAL NO.: 40

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), TESTES, EPIDIDYMIDES, PROSTATE GLAND, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 96/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 71

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

#### SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 2

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, LIVER, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 97/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 72

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivascular, grade 1

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Pigmentation, hemosiderin, grade 2

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: estrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 98/106
INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 73

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

## \* MICROSCOPIC FINDINGS

#### LUNG:

-Inflammation peribronchial/perivascular, grade 1

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Hematopoiesis, extramedullary, increased, grade 2

-Pigmentation, hemosiderin, grade 2

VAGINA:

-Cycle: diestrus

LARYNX:

-Infiltrate inflammatory cell, lymphocytic, grade 1 BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 99/ 106 TOX INDIVIDUAL ANIMAL DATA 509991 TEST ITEM : Betawell L-Arabinose TEST SYSTEM : RAT, 90-Day, Diet PATHOL. NO.: 41607 JOL FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2 TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP : 04, 30000 PPM FEMALE \* STATE AT NECROPSY: KO DAYS ON TEST : 92 \* ANIMAL NO. : 74 \* NECROPSY FINDINGS NO NECROPSY OBSERVATIONS NOTED. \* MICROSCOPIC FINDINGS LUNG: -Alveolar macrophage aggregation, grade 1 -Osseus metaplasia, grade 2 THYROID GLAND (BOTH LOBES): -Thymus, ectopic, unilateral STOMACH: -Cyst(s), glandular stomach, grade 1 -Infiltrate inflammatory cell, lymphocytic, grade 1 -Pigmentation, hemosiderin, grade 1 KIDNEYS: -Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1

-Casts, unilateral, grade 2

-Ectasia submucosal glands, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

-Cycle: metestrus

VAGINA:

LARYNX:

PATHOLOGY REPORT (FINAL) PAGE : 100/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

CONT./FF. ANIMAL NO.: 74

\* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 75

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### STOMACH:

-Cyst(s), glandular stomach, grade 1

LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 2
- -Pigmentation, hemosiderin, grade 1

VAGINA:

-Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL) PAGE : 101/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

CONT./FF. ANIMAL NO.: 75

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 76

\* NECROPSY FINDINGS

#### UTERUS:

01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

#### LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 2
- SCIATIC NERVE (LEFT):
- -Demyelination, grade 1

PATHOLOGY REPORT (FINAL) PAGE : 102/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

CONT./FF. ANIMAL NO.: 76

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 77

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT (FINAL) PAGE : 103/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

CONT./FF. ANIMAL NO.: 77

#### \* MICROSCOPIC FINDINGS

#### LUNG:

-Alveolar macrophage aggregation, grade 1

#### LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 3

VAGINA:

-Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL)

INDIVIDUAL ANIMAL DATA

PAGE : 104/ 106

TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 78

\* NECROPSY FINDINGS

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

\* MICROSCOPIC FINDINGS

#### LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:
- -Hematopoiesis, extramedullary, increased, grade 2
- -Pigmentation, hemosiderin, grade 2

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

-Cycle: proestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

- \* ORGANS WITHOUT ABNORMALITIES
- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 105/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 79

\* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

\* MICROSCOPIC FINDINGS

#### LIVER:

- -Infiltrate inflammatory cell, lymphocytic, grade 1
- -Hematopoiesis, extramedullary, increased, grade 1
- -Pigmentation, hemosiderin, grade 3

VAGINA:

-Cycle: diestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

#### \* ORGANS WITHOUT ABNORMALITIES

- HEART, AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, KIDNEYS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

PATHOLOGY REPORT (FINAL) PAGE : 106/106 INDIVIDUAL ANIMAL DATA TOX : 509991

TEST ITEM : Betawell L-Arabinose PATHOL. NO.: 41607 JOL TEST SYSTEM : RAT, 90-Day, Diet FINALIZED : 07-NOV-16 SPONSOR : Cosun Biobased Products B.V. PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS

DOSE GROUP : 04, 30000 PPM FEMALE

\* STATE AT NECROPSY: KO

DAYS ON TEST : 92 \* ANIMAL NO.: 80

#### \* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

## \* MICROSCOPIC FINDINGS

#### HEART:

-Myxomatous change valvular, aortic valve, grade 2 LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1 SPLEEN:

-Hematopoiesis, extramedullary, increased, grade 1

-Pigmentation, hemosiderin, grade 3

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

KIDNEYS:

-Mineralization, medullary, unilateral, grade 1

VAGINA:

-Cycle: diestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

# \* ORGANS WITHOUT ABNORMALITIES

- AORTA, LUNG, THYMUS, TRACHEA, ESOPHAGUS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, PANCREAS, MANDIBULAR LYMPH NODES, SUBLINGUAL GLANDS, MANDIBULAR (SUBMANDIBULAR/SUBMAXILLARY) GLANDS, URINARY BLADDER, ADRENAL GLANDS, BRAIN, PITUITARY GLAND, SCIATIC NERVE (LEFT), OVARIES, UTERUS, CERVIX, MAMMARY GLAND, SKIN/SUBCUTIS, LARYNX, EYES, OPTIC NERVES, HARDERIAN GLANDS, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), BONE (STERNUM), BONE MARROW (STERNUM).

Betawell L-Arabinose Project 509991

# APPENDIX 6 SUMMARY OF DOSE RANGE FINDING STUDY

Final Report - Page 1 -

- Page 248 of 249 -

# **Summary of Dose Range Finding Study**

Study Plan Treatment: 09 October to 23 October 2015

Necropsy: 23 October 2015

### Aim of the study

In order to set the dose levels for the main study (Project 509991) a dose range finding study was performed (Project 509992).

#### Guidelines

No guidelines were applicable as this study was intended for dose level selection purposes only.

#### Materials and methods

If not mentioned otherwise, test system, procedures and techniques were identical to those used during the main study.

#### **Test System/Animal husbandry**

Number of rats/group 3 females (group-housed, allocated at random and identified by

ear- and tailmark).

Age at start of treatment Approximately 7 weeks.

Room number A 0.59

Housing 3 animals/cage.

**Treatment** 

Duration of treatment 14 days.

Dose levels 50000 and 75000 ppm.

Dose levels were based on information provided by and at request of the

Sponsor.

No chemical analyses of diet preparations were conducted.

**Observations** 

Clinical signs: At least once daily. Mortality: At least twice daily.

Body weights: Weekly and on the day of necropsy.

Food consumption: Weekly. Test article intake: Weekly.

**Pathology** 

Necropsy: All animals were subjected to an external, thoracic and abdominal

examination on Day 15 after the last observation of clinical signs

(scheduled necropsy). No organs were fixed. Animals were not deprived

of food prior to necropsy.

#### Results

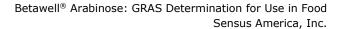
No signs of toxicity were noted at any dose level.

# Conclusion

Based on the results of this range finding study and the consideration that a high % test item would affect energy intake due to replacing nutrients by test item , dose levels for the main study were 3000, 10000 and 30000 ppm.

Final Report - Page 2 -

- Page 249 of 249 -





APPENDIX C2
EVALUATION OF THE MUTAGENIC ACTIVITY
OF BETAWELL L-ARABINOSE IN THE
SALMONELLA TYPHIMURIUM REVERSE
MUTATION ASSAY AND THE ESCHERICHIA
COLI REVERSE MUTATION ASSAY
(PLATE INCORPORATION AND
PRE-INCUBATION METHODS)



# **FINAL REPORT**

# Study Title

# EVALUATION OF THE MUTAGENIC ACTIVITY OF BETAWELL L-ARABINOSE IN THE SALMONELLA TYPHIMURIUM REVERSE MUTATION ASSAY AND THE ESCHERICHIA COLI REVERSE MUTATION ASSAY (PLATE INCORPORATION AND PRE-INCUBATION METHODS)

Study Director

C.M. Verspeek-Rip.

### **Test Facility**

WIL Research Europe B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

# Sponsor

Cosun Biobased Products B.V. As part of Royal Cosun Postbus 3411 4800 MG Breda Netherlands

**Laboratory Project Identification** 

WIL Research Project 509988 Test item 206781/A

- Page 1 of 42-

# 1. CONTENTS

| 1.   | CONTENTS  |          |
|------|---|----------|
| 2.   | STATEMENT OF GLP COMPLIANCE   | 4        |
| 3.   | TEST FACILITY QUALITY ASSURANCE STATEMENT                                       | 5        |
| 4.   | SUMMARY   |          |
| 5.   | INTRODUCTION  |          |
| ٥.   | 5.1. Study schedule   |          |
|      | 5.2. Purpose  |          |
|      |   |          |
|      | 5.3. Guidelines   | <u>/</u> |
|      | 5.4. Retention of records and materials   |          |
|      | 5.5. Responsible personnel  |          |
|      | 5.5.1. Test facility  |          |
|      | 5.5.2. Sponsor Representative   | 7        |
| 6.   | MATERIALS AND METHODS   | 8        |
|      | 6.1. Test item  | 8        |
|      | 6.1.1. Test item information  | 8        |
|      | 6.1.2. Study specific test item information                                     |          |
|      | 6.2. Vehicle information  |          |
|      | 6.3. Reference item   |          |
|      | 6.3.1. Negative control   |          |
|      | 6.3.2. Positive controls  |          |
|      |   |          |
|      | 6.4. Test Item preparation  |          |
|      | 6.5. Chemical analysis of dose preparations                                     | ٠١       |
|      | 6.6. Test System  |          |
|      | 6.7. Cell culture   |          |
|      | 6.8. Metabolic activation system  |          |
|      | 6.8.1. S9-fraction  | 11       |
|      | 6.8.2. Preparation of S9-mix  | 11       |
|      | 6.9. Study design   |          |
|      | 6.9.1. Dose range finding test  |          |
|      | 6.9.2. First experiment: direct plate assay                                     |          |
|      | 6.9.3. Second experiment: pre-incubation assay                                  |          |
|      | 6.9.4. Colony counting  | 11       |
|      |   |          |
|      | 6.10. Interpretation  |          |
|      | 6.10.1. Acceptability of the assay  |          |
|      | 6.10.2. Data evaluation and statistical procedures                              |          |
|      | 6.11. List of deviations  |          |
|      | 6.11.1. List of study plan deviations   |          |
|      | 6.11.2. List of standard operating procedures deviations                        |          |
| 7.   |   |          |
| 8.   | RESULTS   | 13       |
|      | 8.1. First experiment: Direct plate assay                                       | 13       |
|      | 8.2. Second experiment: Pre-incubation assay                                    |          |
|      | 8.3. Formulation analysis   |          |
| 9.   | DISCUSSION AND CONCLUSION   | 12       |
|      | REFERENCES  |          |
| 10.  | REFERENCES  | 14       |
|      |   |          |
| TAF  | BLES  |          |
| Tab  |   |          |
| . 40 | typhimurium reverse mutation assay and in the Escherichia coli reverse mutation |          |
|      | assayassay  | 4.5      |
| Tek  |   | 10       |
| Tab  |   |          |
|      | reverse mutation assay  | 16       |
| Tab  |   |          |
|      | reverse mutation assay and in the Escherichia coli reverse mutation assay       | 17       |

| <b>APPENDICES</b> |   |    |
|-------------------|---|----|
| APPENDIX 1        | SUMMARY TABLES  | 15 |
| APPENDIX 2        | SUPPORTING MATERIALS AND METHOD                       | 18 |
| APPENDIX 3        | DETAILED TABLES                                       | 19 |
| APPENDIX 4        | HISTORICAL CONTROL DATA OF THE SOLVENT CONTROL        | 30 |
| APPENDIX 5        | HISTORICAL CONTROL DATA OF THE POSITIVE CONTROL ITEMS | 31 |
| APPENDIX 6        | CERTIFICATE OF ANALYSIS                               | 32 |
|                   | EODMIII ATION ANALYSIS                                |    |

# 2. STATEMENT OF GLP COMPLIANCE

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with the following GLP regulations:

- OECD Principles of Good Laboratory Practice concerning Mutual Acceptance of Data in the Assessment of Chemicals, 26 November 1997 (C(97) 186 Final);
- EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).

Except for the following:

- The characterisation of the test item was conducted in an ISO 9001 environment.

The data generated and reported are considered to be valid.

| WIL Research Europe B.V. |                   |  |  |  |  |  |  |
|--------------------------|-------------------|--|--|--|--|--|--|
|                          | (b) (6)           |  |  |  |  |  |  |
|                          |                   |  |  |  |  |  |  |
| Signature:               |                   |  |  |  |  |  |  |
| Name:                    | C.M. Verspeek-Rip |  |  |  |  |  |  |
| Title:                   | Study Director    |  |  |  |  |  |  |
| Date:                    | 11 Jana 24 2016   |  |  |  |  |  |  |

## 3. TEST FACILITY QUALITY ASSURANCE STATEMENT

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands.

Study title: Evaluation of the mutagenic activity of Betawell L-Arabinose in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (plate incorporation and preincubation methods)

This report was inspected by the WIL Research Europe Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s). The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected.

The dates of Quality Assurance inspections are given below.

| Project                | 509988   |   |   |   |
|------------------------|--|---|---|---|
| Type of<br>Inspections | Phase/Process  | Start<br>Inspection<br>date               | End<br>Inspection<br>date                 | Reporting date                            |
| Study                  | Study Plan<br>Study Plan Amendment 01<br>Report  | 17-Aug-2015<br>15-Dec-2015<br>24-Dec-2015 | 17-Aug-2015<br>15-Dec-2015<br>24-Dec-2015 | 17-Aug-2015<br>15-Dec-2015<br>24-Dec-2015 |
| Process                | Analytical and physical chemistry Test Substance Handling Exposure Observations/Measurements Specimen Handling | 12-Sep-2015                               | 24-Sep-2015                               | 28-Sep-2015                               |
|                        | Genetic and In Vitro Toxicology Test Substance Handling Exposure Observations/Measurements Specimen Handling   | 23-Sep-2015                               | 30-Sep-2015                               | 01-Oct-2015                               |
|                        | <b>Test Substance Receipt</b> Test Substance Handling  | 09-Nov-2015                               | 20-Nov-2015                               | 20-Nov-2015                               |

The facility inspection program is conducted in accordance with Standard Operating Procedure.

The review of the final report was completed on the date of signing this QA statement.

WIL Research Europe B.V.

|            | (b) (6)      |  |
|------------|--------------|--|
| Signature: |              |  |
| Name:      | C. N<br>Head | litchell B.Sc., FRQA<br>of Quality Assurance |
| Date:      | 7 Jan &      | 216  |

#### 4. SUMMARY

Evaluation of the mutagenic activity of Betawell L-Arabinose in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (plate incorporation and preincubation methods)

Betawell L-Arabinose was tested in the *Salmonella typhimurium* reverse mutation assay with four histidine-requiring strains of *Salmonella typhimurium* (TA1535, TA1537, TA100 and TA98) and in the *Escherichia coli* reverse mutation assay with a tryptophan-requiring strain of *Escherichia coli* (WP<sub>2</sub>uvrA). The test was performed in two independent experiments, at first a direct plate assay was performed and secondly a pre-incubation assay both in the absence and presence of S9-mix (rat liver S9-mix induced Aroclor 1254).

The study procedures described in this report were based on the most recent OECD and EC guidelines.

Batch C32-1 of the test item was a white powder. The test item was dissolved in Milli-Q water.

The concentrations analysed in the samples prepared for use during the second mutation experiment were in agreement with the nominal concentrations (i.e. mean accuracies between 98% and 102%).

In the dose range finding study, the test item was initially tested up to concentrations of 5000  $\mu$ g/plate in the strains TA100 and WP<sub>2</sub>uvrA in the direct plate assay. Betawell L-Arabinose did not precipitate on the plates at this dose level. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed. In the first mutation experiment, Betawell L-Arabinose was tested up to concentrations of 5000  $\mu$ g/plate in the strains TA1535, TA1537 and TA98. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed.

In the second mutation experiment, the test item was tested up to concentrations of 5000  $\mu$ g/plate in the tester strains TA1535, TA1537, TA98, TA100 and WP<sub>2</sub>uvrA in the pre-incubation assay. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed.

In this study, acceptable responses were obtained for the negative and strain-specific positive control items indicating that the test conditions were adequate and that the metabolic activation system functioned properly.

Betawell L-Arabinose did not induce a significant dose-related increase in the number of revertant (His<sup>+</sup>) colonies in each of the four tester strains (TA1535, TA1537, TA98 and TA100) and in the number of revertant (Trp<sup>+</sup>) colonies in tester strain WP<sub>2</sub>uvrA both in the absence and presence of S9-metabolic activation. These results were confirmed in an independently repeated experiment.

Based on the results of this study it is concluded that Betawell L-Arabinose is not mutagenic in the *Salmonella typhimurium* reverse mutation assay and in the *Escherichia coli* reverse mutation assay.

#### 5. INTRODUCTION

# 5.1. Study schedule

Experimental starting date : 08 October 2015 Experimental completion date : 30 November 2015

#### 5.2. Purpose

The objective of this study was to evaluate the test item for its ability to induce reverse mutations in a gene of histidine-requiring *Salmonella typhimurium* bacterial strains resulting in histidine-independent strains, and in a gene of tryptophan-requiring *Escherichia coli* bacterial strain resulting in a tryptophan-independent strain.

#### Background of the test system

The Salmonella typhimurium reverse mutation assay and the Escherichia coli reverse mutation assay have shown to be rapid and adequate indicators for the mutagenic activity of a wide range of chemical compounds.

The assay was conducted in the absence and presence of a metabolizing system (S9-mix).

The Salmonella typhimurium strains used in this study were TA98, TA100, TA1535 and TA1537. The Escherichia coli strain used was WP<sub>2</sub>uvrA.

The strains TA98 and TA1537 are capable of detecting frameshift mutagens, strains TA100, TA1535 and WP₂uvrA are capable of detecting base-pair substitution mutagens (1-5).

#### 5.3. Guidelines

The study procedures described in this report are in compliance with the following guidelines:

- Organisation for Economic Co-operation and Development (OECD), OECD Guidelines for Testing of Chemicals; Guideline no. 471: "Genetic Toxicology: Bacterial Reverse Mutation Test". (adopted July 21, 1997)
- European Community (EC). Commission regulation (EC) No. 440/2008, Part B: Methods for the Determination of Toxicity and other health effects, Guideline B.13/14: "Mutagenicity: Reverse Mutation Test using Bacteria". Official Journal of the European Union No. L142, 31 May 2008.

#### 5.4. Retention of records and materials

Records and material pertaining to the study, which include study plan and amendments, raw data and the final report will be retained in the archives of the test facility for a minimum of 5 years after the finalization of the report. After this period, the sponsor will be contacted to determine how the records and materials should be handled. The test facility will retain information concerning decisions made.

A sample of the test item will be retained until expiry date or applicable retest date. After this period the sample(s) will be destroyed.

#### 5.5. Responsible personnel

#### 5.5.1. Test facility

Study Director C.M. Verspeek-Rip

Principal Scientist (analytical chemistry) J. Ciric, PhD.

## 5.5.2. Sponsor Representative

Study Monitor Alex Benschop and Diederick Meyer

Final Report - Page 7 -

#### 6. MATERIALS AND METHODS

#### 6.1. Test item

#### 6.1.1. Test item information

Identification Betawell L-Arabinose

Appearance White powder

Batch C32-1

Purity/Composition See Certificate of Analysis
Test item storage At room temperature
Stable under storage conditions until 15 May 2017 (expiry date)

See APPENDIX 6; Certificate of Analysis

# 6.1.2. Study specific test item information

Purity/composition correction factor No correction factor required

Test item handling No specific handling conditions required

Stability at higher temperatures Stable, maximum temperature: 50°C, maximum duration: 48

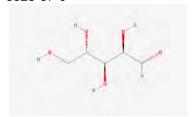
hours

Chemical name (IUPAC), synonym or

trade name CAS Number

Molecular structure

5328-37-0



(2R,3S,4S)-2,3,4,5-Tetrahydroxypentanal, arabinose

Molecular formula  $C_5H_{10}O_5$  Molecular weight 150.13

# 6.2. Vehicle information

Stability in vehicle Water: Stable

Solubility in vehicle Water: Approximately 50% (w/w)

### 6.3. Reference item

#### 6.3.1. Negative control

The vehicle of the test item, being Milli-Q water (Millipore Corp., Bedford, MA., USA).

#### 6.3.2. Positive controls

#### (WITHOUT METABOLIC ACTIVATION)

| Strain | Chemical   | Solvent | Concentration/plate | Concentration/plate  |
|--------|--|---------|---------------------|----------------------|
|        |  |         | Direct plate assay  | Pre-incubation assay |
| TA1535 | sodium azide (SA)<br>(Sigma Aldrich Chemie,<br>Steinheim, Germany) | Saline  | 5 μg                | 5 μg                 |
| TA1537 | ICR-191 (Sigma)  | DMSO    | 2.5 µg              |                      |
| TA1537 | 2-nitrofluorene (NF)<br>(Sigma)                                    | DMSO    |                     | 15 µg                |
| TA98   | 2-nitrofluorene (NF)   | DMSO    | 10 μg               | 10 µg                |

| TA100                | methylmethanesulfonate<br>(MMS) (Sigma)  | DMSO | 650 µg | 650 µg |
|----------------------|--|------|--------|--------|
| WP <sub>2</sub> uvrA | 4-nitroquinoline N-oxide (4-NQO) (Sigma) | DMSO | 10 µg  | 10 µg  |

(WITH METABOLIC ACTIVATION)

| Strain               | Chemical                           | Solvent | Concentration/plate Direct plate assay | Concentration/plate<br>Pre-incubation assay |
|----------------------|------------------------------------|---------|--|---|
| TA1535               | 2-aminoanthracene (2AA)<br>(Sigma) | DMSO    | 2.5 µg                                 | 2.5 µg                                      |
| TA1537               | 2-aminoanthracene (2AA)            | DMSO    | 2.5 µg                                 | 2.5 µg                                      |
| TA98                 | 2-aminoanthracene (2AA)            | DMSO    | 1 μg                                   | 1 µg  |
| TA100                | 2-aminoanthracene (2AA)            | DMSO    | 1 μg                                   | 5 μg  |
| WP <sub>2</sub> uvrA | 2-aminoanthracene (2AA)            | DMSO    | 15 µg                                  | 15 µg                                       |

#### Solvents for reference items

Saline = physiological saline (Eurovet Animal Health, Bladel, The Netherlands) DMSO = dimethyl sulfoxide (SeccoSolv, Merck, Darmstadt, Germany)

# 6.4. Test Item preparation

No correction was made for the purity/composition of the test compound.

A solubility test was performed in project 509989. The test item was dissolved in Milli-Q water. All preparations were used within 3 hours after adding vehicle to the test item.

# 6.5. Chemical analysis of dose preparations

Analyses was conducted on a single occasion during the treatment phase on samples as specified below, according to a validated method (Project 509990).

| Dose                                   | Analysis (type of sample)       |
|--|---------------------------------|
| Vehicle<br>Low<br>Intermediate<br>High | acc (R) acc (R) acc (R) acc (R) |

Duplicate samples were analysed.

acc=accuracy,

R=random position of container

The accuracy of preparation is considered acceptable if the mean measured concentrations are 85-115%.

# 6.6. Test System

Test System Salmonella typhimurium bacteria and Escherichia coli bacteria

Rationale Recommended test system in international guidelines (e.g. OECD, EC).

Source Trinova Biochem GmbH, Germany [Master culture from Dr. Bruce N. Ames

(TA1535: 2006, TA1537: 2009, TA98: 2006, TA100: 2006; and Master culture from The National Collections of Industrial and Marine Bacteria, Aberdeen, UK

(WP2uvrA: 2008)]

The characteristics of the different Salmonella typhimurium strains were as follows:

StrainHistidine mutationMutation typeTA1537hisC3076FrameshiftTA98hisD3052/R-factor\*Frameshift

TA1535 *his*G46 Base-pair substitutions TA100 *his*G46/R-factor\* Base-pair substitutions

Each tester strain contained the following additional mutations:

<u>rfa</u>: deep rough (defective lipopolysaccharide cellcoat)

gal : mutation in the galactose metabolism

<u>chl</u> : mutation in nitrate reductasebio : defective biotin synthesis

<u>uvrB</u>: loss of the excision repair system (deletion of the ultraviolet-repair B gene)

The Salmonella typhimurium strains were regularly checked to confirm their histidine-requirement, crystal violet sensitivity, ampicillin resistance (TA98 and TA100), UV-sensitivity and the number of spontaneous revertants.

The Escherichia coli WP<sub>2</sub>uvrA strain detects base-pair substitutions. The strain lacks an excision repair system and is sensitive to agents such as UV. The sensitivity of the strain to a wide variety of mutagens has been enhanced by permeabilization of the strain using Tris-EDTA treatment (Ref.1). The strain was regularly checked to confirm the tryptophan-requirement, UV-sensitivity and the number of spontaneous revertants.

Stock cultures of the five strains were stored in liquid nitrogen (-196°C).

#### 6.7. Cell culture

#### Preparation of bacterial cultures

Samples of frozen stock cultures of bacteria were transferred into enriched nutrient broth (Oxoid LTD, Hampshire, England) and incubated in a shaking incubator (37  $\pm$  1°C, 150 rpm), until the cultures reached an optical density of 1.0  $\pm$  0.1 at 700 nm (10<sup>9</sup> cells/ml). Freshly grown cultures of each strain were used for a test.

### Agar plates

Agar plates ( $\emptyset$  9 cm) contained 25 ml glucose agar medium. Glucose agar medium contained per liter: 18 g purified agar (Merck) in Vogel-Bonner Medium E, 20 g glucose (Fresenius Kabi). The agar plates for the test with the *Salmonella typhimurium* strains also contained 12.5 µg/plate biotin (Merck) and 15 µg/plate histidine (Sigma) and the agar plates for the test with the *Escherichia coli* strain contained 15 µg/plate tryptophan (Sigma).

# Top agar

Milli-Q water containing 0.6% (w/v) bacteriological agar (Oxoid LTD) and 0.5% (w/v) sodium chloride (Merck) was heated to dissolve the agar. Samples of 3 ml top agar were transferred into 10 ml glass tubes with metal caps. Top agar tubes were autoclaved for 20 min at  $121 \pm 3$ °C.

# **Environmental conditions**

All incubations were carried out in a controlled environment at a temperature of  $37.0 \pm 1.0^{\circ}$ C (actual range  $35.7 - 38.8^{\circ}$ C). The temperature was continuously monitored throughout the experiment. Due to addition of plates (which were at room temperature) to the incubator or due to opening and closing the incubator door, temporary deviations from the temperature may occur. Based on laboratory historical data these deviations are considered not to affect the study integrity.

<sup>\*:</sup> R-factor = plasmid pKM101 (increases error-prone DNA repair)

# 6.8. Metabolic activation system

#### 6.8.1. **S9-fraction**

Rat liver microsomal enzymes (S9 homogenate) were obtained from Trinova Biochem GmbH, Giessen, Germany and were prepared from male Sprague Dawley rats that had been injected intraperitoneally with Aroclor 1254 (500 mg/kg).

Before use, all S9 batches were characterised with the mutagens benzo-(a)-pyrene (Sigma) and 2-aminoanthracene, which require metabolic activation, in tester strain TA100 at concentrations of  $5 \mu g/plate$  and  $2.5 \mu g/plate$ , respectively.

#### 6.8.2. Preparation of S9-mix

S9-mix was prepared immediately before use and kept on ice. S9-mix contained per 10 ml: 30 mg NADP and 15.2 mg glucose-6-phosphate in 5.5 ml Milli-Q water; 2 ml 0.5 M sodium phosphate buffer pH 7.4; 1 ml 0.08 M MgCl<sub>2</sub> solution; 1 ml 0.33 M KCl solution. The above solution was filter (0.22  $\mu$ m)-sterilized. To 9.5 ml of S9-mix components 0.5 ml S9-fraction was added (5% (v/v) S9-fraction) to complete the S9-mix.

# 6.9. Study design

#### 6.9.1. Dose range finding test

Selection of an adequate range of doses was based on a dose range finding test with the strains TA100 and the WP<sub>2</sub>uvrA, both with and without S9-mix. Eight concentrations, 1.7, 5.4, 17, 52, 164, 512, 1600 and 5000 µg/plate were tested in triplicate.

The highest concentration of the test item used in the subsequent mutation assays was 5000 µg/plate. At least five different doses (increasing with approximately half-log steps) of the test item were tested in triplicate in each strain in the absence and presence of S9-mix. The first experiment was a direct plate assay and the second experiment was a pre-incubation assay.

The negative control (vehicle) and relevant positive controls were concurrently tested in each strain in the presence and absence of S9-mix.

#### 6.9.2. First experiment: direct plate assay

The above mentioned dose range finding study with two tester strains is reported as a part of the direct plate assay. In the second part of this experiment, the test item was tested both in the absence and presence of S9-mix in the tester strains TA1535, TA1537 and TA98. Top agar in top agar tubes was melted by heating to  $45 \pm 2^{\circ}$ C. The following solutions were successively added to 3 ml molten top agar: 0.1 ml of a fresh bacterial culture ( $10^{\circ}$  cells/ml) of one of the tester strains, 0.1 ml of a dilution of the test item in Milli-Q water and either 0.5 ml S9-mix (in case of activation assays) or 0.5 ml 0.1 M phosphate buffer (in case of non-activation assays). The ingredients were mixed on a Vortex and the content of the top agar tube was poured onto a selective agar plate. After solidification of the top agar, the plates were inverted and incubated in the dark at  $37.0 \pm 1.0^{\circ}$ C for  $48 \pm 4$  h. After this period revertant colonies (histidine independent (His<sup>†</sup>) for *Salmonella typhimurium* bacteria and tryptophan independent (Trp<sup>†</sup>) for *Escherichia coli*) were counted.

# 6.9.3. Second experiment: pre-incubation assay

The test item was tested both in the absence and presence of S9-mix in all tester strains. Top agar in top agar tubes was melted by heating to  $45 \pm 2^{\circ}$ C. The following solutions were pre-incubated for 30 minutes by 70 rpm at 37°C, either 0.5 ml S9-mix (in case of activation assays) or 0.5 ml 0.1 M phosphate buffer (in case of non-activation assays), 0.1 ml of a fresh bacterial culture ( $10^{9}$  cells/ml) of one of the tester strains, 0.1 ml of a dilution of the test item in Milli-Q water.

After the pre-incubation period the solutions were added to 3 ml molten top agar. The ingredients were mixed on a Vortex and the content of the top agar tube was poured onto a selective agar plate. After solidification of the top agar, the plates were inverted and incubated in the dark at  $37.0 \pm 1.0^{\circ}$ C for  $48 \pm 4$  h. After this period revertant colonies (histidine independent (His<sup>+</sup>) for *Salmonella typhimurium* bacteria and tryptophan independent (Trp<sup>+</sup>) for *Escherichia coli*) were counted.

# 6.9.4. Colony counting

The revertant colonies were counted automatically with the Sorcerer Colony Counter. Plates with sufficient test item precipitate to interfere with automated colony counting were counted manually. Evidence of test item precipitate on the plates and the condition of the bacterial background lawn were evaluated when considered necessary, macroscopically and/or microscopically by using a dissecting microscope.

#### 6.10. Interpretation

# 6.10.1. Acceptability of the assay

A Salmonella typhimurium reverse mutation assay and/or Escherichia coli reverse mutation assay is considered acceptable if it meets the following criteria:

- a) The vehicle control and positive control plates from each tester strain (with or without S9-mix) must exhibit a characteristic number of revertant colonies when compared against relevant historical control data generated at WIL Research Europe.
- b) The selected dose range should include a clearly toxic concentration or should exhibit limited solubility as demonstrated by the preliminary toxicity range-finding test or should extend to 5 mg/plate.
- c) No more than 5% of the plates are lost through contamination or some other unforeseen event. If the results are considered invalid due to contamination, the experiment will be repeated.

# 6.10.2. Data evaluation and statistical procedures

No formal hypothesis testing was done.

In addition to the criteria stated below, any increase in the total number of revertants should be evaluated for its biological relevance including a comparison of the results with the historical control data range.

A test item is considered negative (not mutagenic) in the test if:

- a) The total number of revertants in tester strain TA100 or WP<sub>2</sub>uvrA is not greater than two (2) times the concurrent control, and the total number of revertants in tester strains TA1535, TA1537 or TA98 is not greater than three (3) times the concurrent control.
- b) The negative response should be reproducible in at least one follow up experiment.

A test item is considered positive (mutagenic) in the test if:

- a) The total number of revertants in tester strain TA100 or WP<sub>2</sub>uvrA is greater than two (2) times the concurrent control, or the total number of revertants in tester strains TA1535, TA1537 or TA98 is greater than three (3) times the concurrent control.
- b) In case a repeat experiment is performed when a positive response is observed in one of the tester strains, the positive response should be reproducible in at least one follow up experiment.

# 6.11. List of deviations

#### 6.11.1. List of study plan deviations

There were no deviations from the study plan.

# 6.11.2. List of standard operating procedures deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

#### 7. ELECTRONIC SYSTEMS FOR DATA ACQUISITION

The following electronic systems were used for data acquisition:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA).
- Ames study Manager version 1.23 (Perceptive Instruments Ltd., St Edmunds, Suffolk, United Kingdom).

#### 8. RESULTS

#### 8.1. First experiment: Direct plate assay

Betawell L-Arabinose was initially tested in the tester strains TA100 and WP<sub>2</sub>uvrA as a dose range finding test with concentrations of 1.7, 5.4, 17, 52, 164, 512, 1600 and 5000  $\mu$ g/plate in the absence and presence of S9-mix. Based on the results of the dose range finding test, the following dose range was selected for the mutation assay with the tester strains, TA1535, TA1537 and TA98 in the absence and presence of S9-mix: 52, 164, 512, 1600 and 5000  $\mu$ g/plate. The results are shown in Table 1 and Table 2. The individual data are presented in APPENDIX 3.

#### Precipitate

Precipitation of Betawell L-Arabinose on the plates was not observed at the start or at the end of the incubation period.

#### Toxicity

To determine the toxicity of Betawell L-Arabinose, the reduction of the bacterial background lawn, the increase in the size of the microcolonies and the reduction of the revertant colonies were observed. The definitions are stated in APPENDIX 2.

No reduction of the bacterial background lawn and no biologically significant decrease in the number of revertants were observed.

# Mutagenicity

In the direct plate test, no increase in the number of revertants was observed upon treatment with Betawell L-Arabinose under all conditions tested.

#### 8.2. Second experiment: Pre-incubation assay

To obtain more information about the possible mutagenicity of Betawell L-Arabinose, a pre-incubation experiment was performed in the absence and presence of S9-mix. Based on the results of the first mutation assay, Betawell L-Arabinose was tested up to the dose level of 5000  $\mu$ g/plate in the tester strains TA1535, TA1537, TA98, TA100 and WP<sub>2</sub>uvrA. The results are shown in Table 3, the individual data are presented in APPENDIX 3.

#### Precipitate

Precipitation of Betawell L-Arabinose on the plates was not observed at the start or at the end of the incubation period.

# **Toxicity**

There was no reduction in the bacterial background lawn and no biologically relevant decrease in the number of revertants at any of the concentrations tested in all tester strains in the absence and presence of S9-mix.

#### Mutagenicity

In the pre-incubation test, no increase in the number of revertants was observed upon treatment with Betawell L-Arabinose under all conditions tested.

#### 8.3. Formulation analysis

The concentrations analysed in the second mutation experiment in the low, intermediate and high formulations were in agreement with target concentrations (i.e. mean accuracies were 102%, 101% and 98%, respectively).

The formulation analysis report is presented in APPENDIX 7.

#### 9. DISCUSSION AND CONCLUSION

All bacterial strains showed negative responses over the entire dose range, i.e. no significant dose-related increase in the number of revertants in two independently repeated experiments.

The negative control values were within the laboratory historical control data ranges.

The strain-specific positive control values were within the laboratory historical control data ranges indicating that the test conditions were adequate and that the metabolic activation system functioned properly, except the response for TA1537 in the second experiment, absence of S9-mix. The purpose of the positive control is as a reference for the test system, where a positive response is required to check if the test system functions correctly. Since the value was more than 3 times greater than the concurrent solvent control values, this deviation in the mean plate count of the positive control had no effect on the results of the study.

Based on the results of this study it is concluded that Betawell L-Arabinose is not mutagenic in the *Salmonella typhimurium* reverse mutation assay and in the *Escherichia coli* reverse mutation assay.

# 10. REFERENCES

- 1 Leonardo, J.M., Dornfeld, S.S. and Peak, M.J., 1984, Evaluation of E. coli K12 343 \ 113 and derived strains for microbial mutagenicity assays. Mutation Res., 130, 87-95.
- Ames, B.N., McCann, J. and Yamasaki, E., 1975, Methods for detecting carcinogens and mutagens with the *Salmonella/mammalian* microsome mutagenicity test, Mutation Res., <u>31</u>, 347-364.
- 3 Maron, D.M. and Ames, B.N., 1983, Revised methods for the *Salmonella* mutagenicity test, Mutation Res., 113, 173-215. Erratum, 1983, Mutation Res., 113, 533.
- 4 Green, M.H.L. and Muriel, W.J., 1976, Mutagen testing using Trp<sup>+</sup> reversion in *Escherichia coli*, Mutation Res., <u>38</u>, 3-32.
- Vogel, H.J. and Bonner, D.M., 1956, Acetylornithinase of *Escherichia coli*: partial purification and some properties. J. Biol. Chem., 218, 97-106.

# APPENDIX 1 SUMMARY TABLES

Table 1 Dose range finding test: Mutagenic response of the test item in the Salmonella typhimurium reverse mutation assay and in the Escherichia coli reverse mutation assay

| Direct plate assa  | ау     |                    |              |          |   |
|--------------------|--------|--------------------|--------------|----------|---|
| Dose<br>(µg/plate) |        |                    |              |          | e plates (± S.D.) with<br>e <i>Escherichia coli</i> strain. |
|                    | TA1    | 00                 | W            | P2uvr    | rA  |
|                    |        |                    | Without S9-m | ıix      |   |
| Positive control   | 610 ±  | 30                 | 1110 ±       | 150      |   |
| Solvent control    | 74 ±   | 1                  | 27 ±         | 4        |   |
| 1.7                | 87 ±   | 7                  | 26 ±         | 4        |   |
| 5.4                | 81 ±   | 12                 | 27 ±         | 3        |   |
| 17                 | 90 ±   | 12                 | 27 ±         | 4        |   |
| 52                 | 94 ±   | 4                  | 27 ±         | 6        |   |
| 164                | 79 ±   | 11                 | 29 ±         | 5        |   |
| 512                | 77 ±   | 12                 | 26 ±         | 13       |   |
| 1600               | 76 ±   | 10                 | 25 ±         | 3        |   |
| 5000               | 81 ±   | 10 <sup>n NP</sup> | 21 ±         | 4        | n NP  |
|                    |        |                    | With S9-mix  | <u>(</u> |   |
| Positive control   | 1219 ± | 49                 | 164 ±        | 25       |   |
| Solvent control    | 96 ±   | 6                  | 26 ±         | 4        |   |
| 1.7                | 104 ±  | 10                 | 29 ±         | 6        |   |
| 5.4                | 90 ±   | 20                 | 30 ±         | 4        |   |
| 17                 | 93 ±   | 23                 | 22 ±         | 4        |   |
| 52                 | 98 ±   | 17                 | 26 ±         | 5        |   |
| 164                | 78 ±   | 4                  | 33 ±         | 3        |   |
| 512                | 97 ±   | 13                 | 26 ±         | 4        |   |
| 1600               | 70 ±   | 8                  | 24 ±         | 5        |   |
| 5000               | 76 ±   | 10 <sup>n NP</sup> | 29 ±         | 10       | n NP  |

NP No precipitate

n Normal bacterial background lawn

# APPENDIX 1 — continued —

Table 2 Experiment 1: Mutagenic response of the test item in the *Salmonella typhimurium* reverse mutation assay

| Direct plate assa  | ау    |                   |                                       |                   |               |                    |
|--------------------|-------|-------------------|---------------------------------------|-------------------|---------------|--------------------|
| Dose<br>(μg/plate) |       |                   | nt colonies/3 rep<br>onella typhimuri |                   | (± S.D.) with |                    |
|                    | TA15  | 35                | T.                                    | A1537             |               | TA98               |
|                    |       |                   | Without S9-m                          | <u>ix</u>         |               |                    |
| Positive control   | 822 ± | 95                | 743 ±                                 | 87                | 801 ±         | 153                |
| Solvent control    | 14 ±  | 3                 | 6 ±                                   | 3                 | 13 ±          | 1                  |
| 52                 | 11 ±  | 4                 | 8 ±                                   | 1                 | 21 ±          | 2                  |
| 164                | 15 ±  | 5                 | 8 ±                                   | 4                 | 14 ±          | 3                  |
| 512                | 13 ±  | 2                 | 4 ±                                   | 4                 | 23 ±          | 6                  |
| 1600               | 15 ±  | 2                 | 4 ±                                   | 4                 | 13 ±          | 3                  |
| 5000               | 13 ±  | 4 <sup>n NP</sup> | 5 ±                                   | 3 <sup>n NP</sup> | 23 ±          | 4 <sup>n NP</sup>  |
|                    |       |                   | With S9-mix                           |                   |               |                    |
| Positive control   | 246 ± | 7                 | 340 ±                                 | 15                | 870 ±         | 100                |
| Solvent control    | 18 ±  | 5                 | 8 ±                                   | 2                 | 33 ±          | 5                  |
| 52                 | 17 ±  | 3                 | 11 ±                                  | 1                 | 30 ±          | 2                  |
| 164                | 22 ±  | 4                 | 15 ±                                  | 1                 | 30 ±          | 6                  |
| 512                | 13 ±  | 4                 | 14 ±                                  | 8                 | 28 ±          | 4                  |
| 1600               | 15 ±  | 2                 | 8 ±                                   | 3                 | 28 ±          | 4                  |
| 5000               | 13 ±  | 3 n NP            | 8 ±                                   | 2 n NP            | 29 ±          | 12 <sup>n NP</sup> |

NP No precipitate

n Normal bacterial background lawn

# APPENDIX 1 - continued -

Table 3 Experiment 2: Mutagenic response of the test item in the *Salmonella typhimurium* reverse mutation assay and in the *Escherichia coli* reverse mutation assay

Pre-incubation assay

| Dose<br>(μg/plate) |       |                   |        |                   | replicate plates (± S.D.) with urium and one Escherichia coli strain. |                   |        |                   |         |                   |  |  |
|--------------------|-------|-------------------|--------|-------------------|---|-------------------|--------|-------------------|---------|-------------------|--|--|
|                    | TA    | 1535              | TA1537 |                   | 37 TA98   |                   | TA100  |                   | WP2uvrA |                   |  |  |
| Without S9-mix     |       |                   |        |                   |   |                   |        |                   |         |                   |  |  |
| Positive control   | 901 ± | 51                | 55 ±   | 3                 | 410 ±   | 51                | 631 ±  | 24                | 195 ±   | 17                |  |  |
| Solvent control    | 7 ±   | 1                 | 7 ±    | 3                 | 16 ±  | 5                 | 74 ±   | 14                | 20 ±    | 6                 |  |  |
| 52                 | 15 ±  | 1                 | 5 ±    | 2                 | 10 ±  | 6                 | 83 ±   | 14                | 15 ±    | 4                 |  |  |
| 164                | 5 ±   | 4                 | 6 ±    | 3                 | 10 ±  | 3                 | 75 ±   | 13                | 19 ±    | 4                 |  |  |
| 512                | 9 ±   | 3                 | 5 ±    | 2                 | 13 ±  | 5                 | 69 ±   | 6                 | 15 ±    | 4                 |  |  |
| 1600               | 10 ±  | 2                 | 6 ±    | 5                 | 10 ±  | 7                 | 79 ±   | 14                | 24 ±    | 7                 |  |  |
| 5000               | 9 ±   | 1 <sup>n NP</sup> | 4 ±    | 1 <sup>n NP</sup> | 10 ±  | 6 <sup>n NP</sup> | 73 ±   | 5 <sup>n NP</sup> | 19 ±    | 2 <sup>n NP</sup> |  |  |
|                    |       |                   |        | With              | S9-mix  |                   |        |                   |         |                   |  |  |
| Positive control   | 128 ± | 8                 | 235 ±  | 13                | 1178 ±  | 98                | 2494 ± | 103               | 525 ±   | 59                |  |  |
| Solvent control    | 10 ±  | 4                 | 7 ±    | 2                 | 11 ±  | 6                 | 80 ±   | 13                | 20 ±    | 3                 |  |  |
| 52                 | 13 ±  | 6                 | 7 ±    | 4                 | 21 ±  | 3                 | 80 ±   | 13                | 27 ±    | 4                 |  |  |
| 164                | 7 ±   | 2                 | 7 ±    | 2                 | 23 ±  | 6                 | 81 ±   | 2                 | 25 ±    | 3                 |  |  |
| 512                | 10 ±  | 2                 | 8 ±    | 3                 | 21 ±  | 2                 | 86 ±   | 11                | 28 ±    | 4                 |  |  |
| 1600               | 13 ±  | 3                 | 6 ±    | 5                 | 19 ±  | 4                 | 85 ±   | 9                 | 21 ±    | 5                 |  |  |
| 5000               | 11 ±  | 3 <sup>n NP</sup> | 4 ±    | 1 <sup>n NP</sup> | 22 ±  | 5 <sup>n NP</sup> | 85 ±   | 3 <sup>n NP</sup> | 26 ±    | 7 n NP            |  |  |

NP No precipitate

n Normal bacterial background lawn

#### APPENDIX 2 SUPPORTING MATERIALS AND METHOD

#### Bacterial background lawn evaluation

The condition of the bacterial background lawn is evaluated (if indicated), both macroscopically and microscopically by using a dissecting microscope (results are normal unless indicated in tables).

| Definition         | Characteristics  |
|--------------------|--|
| Normal             | Distinguished by a healthy microcolony lawn.   |
| Slightly reduced   | Distinguished by a slight thinning of the microcolony lawn.  |
| Moderately reduced | Distinguished by a moderate thinning of the microcolony lawn.  |
| Extremely reduced  | Distinguished by an extreme thinning of the microcolony lawn and an increase in the size of the microcolonies compared to the solvent control plate. |
| Absent             | Distinguished by a complete lack of any microcolony background lawn.   |

#### Precipitation evaluation

Evidence of test article precipitate on the plates is recorded by addition of the following precipitation definition.

| Definition            | Characteristics   |
|-----------------------|---|
| Slight Precipitate    | Distinguished by noticeable precipitate on the plate.   |
| Moderate Precipitate  | However, the precipitate does not influence automated counting of the plate.  Distinguished by a marked amount of precipitate on the plate, requiring the |
| Woderate i recipitate | plate to be hand counted.   |
| Heavy Precipitate     | Distinguished by a large amount of precipitate on the plate, making the required hand count difficult.  |

# Evaluation of the reduction in the number of revertants

The reduction in the number of revertant colonies compared to number of revertants in the solvent control is evaluated as follows:

A reduction of 21-40%: slight reduction.

A reduction of 41-60%: moderate reduction.

A reduction of 61-99%: extreme reduction.

If the size of the microcolonies was increased to small colonies due to an extremely reduced background lawn the reduction is evaluated as microcolonies. If no revertant colonies are observed on the plates the reduction is evaluated as a complete lack of revertants.

However, any mean plate count equal to the minimal value of the historical control data range should be considered not toxic.

# **APPENDIX 3 DETAILED TABLES**

Individual plate counts; (following pages)

# LIST OF ABBREVIATIONS

n Normal bacterial background lawn

NP No precipitate

Dose range finding Strain TA100

| ml d             |      |      | MITHOU | T S9-MI |      |      |         | _ | CD. |
|------------------|------|------|--------|---------|------|------|---------|---|-----|
| plate            | 1    |      | 2      |         | 3    |      | MEAN    |   | SD  |
| dose (µg/plate)  |      |      |        |         |      |      |         |   |     |
| positive control | 627  |      | 575    |         | 628  |      | 610     | ± | 30  |
| solvent control  | 73   |      | 73     |         | 75   |      | 74      | ± | 1   |
| 1.7              | 80   |      | 88     |         | 93   |      | 87      | ± | 7   |
| 5.4              | 75   |      | 94     |         | 73   |      | 81      | ± | 12  |
| 17               | 76   |      | 95     |         | 98   |      | 90      | ± | 12  |
| 52               | 98   |      | 90     |         | 95   |      | 94      | ± | 4   |
| 164              | 88   |      | 83     |         | 67   |      | 79      | ± | 11  |
| 512              | 90   |      | 73     |         | 68   |      | 77      | ± | 12  |
| 1600             | 73   |      | 87     |         | 68   |      | 76      | ± | 10  |
| 5000             | 87   | n NP | 86     | n NP    | 69   | n NP | 81      | ± | 10  |
|                  |      |      |        |         |      |      |         |   |     |
|                  |      |      |        |         |      |      |         |   |     |
| plate            | 1    |      | WITH 9 | S9-MIX  | 3    |      | MEAN    |   | SD  |
| plate            |      |      | 2      |         | 3    |      | IVIEAIN |   | SD  |
| dose (µg/plate)  |      |      |        |         |      |      |         |   |     |
| positive control | 1252 |      | 1242   |         | 1163 |      | 1219    | ± | 49  |
| solvent control  | 90   |      | 97     |         | 101  |      | 96      | ± | 6   |
| 1.7              | 94   |      | 106    |         | 113  |      | 104     | ± | 10  |
| 5.4              | 82   |      | 75     |         | 112  |      | 90      | ± | 20  |
| 17               | 90   |      | 117    |         | 72   |      | 93      | ± | 23  |
| 52               | 113  |      | 80     |         | 102  |      | 98      | ± | 17  |
| 164              | 75   |      | 76     |         | 83   |      | 78      | ± | 4   |
| 512              | 82   |      | 103    |         | 107  |      | 97      | ± | 13  |
| 1600             | 67   |      | 65     |         | 79   |      | 70      | ± | 8   |
| 5000             | 69   | n NP | 72     | n NP    | 87   | n NP | 76      | ± | 10  |
|                  |      |      |        |         |      |      |         |   |     |

Dose range finding Strain WP2uvrA

|                  |      |      | WITHOU | T S9-M |      |      |      |   |     |
|------------------|------|------|--------|--------|------|------|------|---|-----|
| plate            | 1    |      | 2      |        | 3    |      | MEAN |   | SD  |
| dose (µg/plate)  |      |      |        |        |      |      |      |   |     |
| positive control | 1275 |      | 981    |        | 1073 |      | 1110 | ± | 150 |
| solvent control  | 24   |      | 27     |        | 31   |      | 27   | ± | 4   |
| 1.7              | 24   |      | 30     |        | 23   |      | 26   | ± | 4   |
| 5.4              | 29   |      | 29     |        | 23   |      | 27   | ± | 3   |
| 17               | 30   |      | 29     |        | 23   |      | 27   | ± | 4   |
| 52               | 27   |      | 33     |        | 22   |      | 27   | ± | 6   |
| 164              | 34   |      | 29     |        | 24   |      | 29   | ± | 5   |
| 512              | 33   |      | 34     |        | 11   |      | 26   | ± | 13  |
| 1600             | 29   |      | 23     |        | 23   |      | 25   | ± | 3   |
| 5000             | 26   | n NP | 19     | n NP   | 18   | n NP | 21   | ± | 4   |
|                  |      |      | WITH   | S9-MIX |      |      |      |   |     |
| plate            | 1    |      | 2      |        | 3    |      | MEAN |   | SD  |
| dose (µg/plate)  |      |      |        |        |      |      |      |   |     |
| positive control | 135  |      | 177    |        | 180  |      | 164  | ± | 25  |
| solvent control  | 24   |      | 24     |        | 31   |      | 26   | ± | 4   |
| 1.7              | 30   |      | 23     |        | 35   |      | 29   | ± | 6   |
| 5.4              | 26   |      | 30     |        | 34   |      | 30   | ± | 4   |
| 17               | 19   |      | 22     |        | 26   |      | 22   | ± | 4   |
| 52               | 29   |      | 20     |        | 29   |      | 26   | ± | 5   |
| 164              | 30   |      | 35     |        | 33   |      | 33   | ± | 3   |
| 512              | 23   |      | 24     |        | 30   |      | 26   | ± | 4   |
| 1600             | 22   |      | 20     |        | 30   |      | 24   | ± | 5   |
| 5000             | 18   | n NP | 37     | n NP   | 31   | n NP | 29   | ± | 10  |
|                  |      |      |        |        |      |      |      |   |     |

|                  |     |      | WITHOU | T S9-MI |     |      |      |   |    |
|------------------|-----|------|--------|---------|-----|------|------|---|----|
| plate            | 1   |      | 2      |         | 3   |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |        |         |     |      |      |   |    |
| positive control | 928 |      | 744    |         | 793 |      | 822  | ± | 95 |
| solvent control  | 16  |      | 15     |         | 10  |      | 14   | ± | 3  |
| 52               | 10  |      | 15     |         | 8   |      | 11   | ± | 4  |
| 164              | 14  |      | 20     |         | 11  |      | 15   | ± | 5  |
| 512              | 12  |      | 11     |         | 15  |      | 13   | ± | 2  |
| 1600             | 18  |      | 14     |         | 14  |      | 15   | ± | 2  |
| 5000             | 16  | n NP | 8      | n NP    | 15  | n NP | 13   | ± | 4  |
|                  |     |      |        |         |     |      |      |   |    |
|                  |     |      | WITH S | S9-MIX  |     |      |      |   |    |
| plate            | 1   |      | 2      |         | 3   |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |        |         |     |      |      |   |    |
| positive control | 252 |      | 248    |         | 238 |      | 246  | ± | 7  |
| solvent control  | 20  |      | 12     |         | 22  |      | 18   | ± | 5  |
| 52               | 14  |      | 19     |         | 19  |      | 17   | ± | 3  |
| 164              | 20  |      | 26     |         | 19  |      | 22   | ± | 4  |
| 512              | 8   |      | 15     |         | 16  |      | 13   | ± | 4  |
| 1600             | 16  |      | 16     |         | 12  |      | 15   | ± | 2  |
| 5000             | 12  | n NP | 10     | n NP    | 16  | n NP | 13   | ± | 3  |
|                  |     |      |        |         |     |      |      |   |    |

|                  |     |      | UT S9-MIX |        |   |    |
|------------------|-----|------|-----------|--------|---|----|
| plate            | 1   |      | 2 3       | MEAN   |   | SD |
| dose (µg/plate)  |     |      |           |        |   |    |
| positive control | 762 | 81   | 8 648     | 743    | ± | 87 |
| solvent control  | 4   |      | 4 10      | 6      | ± | 3  |
| 52               | 7   |      | 8 8       | 8      | ± | 1  |
| 164              | 11  |      | 4 8       | 8      | ± | 4  |
| 512              | 7   | :    | 5 0       | 4      | ± | 4  |
| 1600             | 4   |      | 8 1       | 4      | ± | 4  |
| 5000             | 4   | n NP | 3 n NP 8  | n NP 5 | ± | 3  |
|                  |     |      |           |        |   |    |
|                  |     | WITH | I S9-MIX  |        |   |    |
| plate            | 1   | :    | 2 3       | MEAN   |   | SD |
| dose (µg/plate)  |     |      |           |        |   |    |
| positive control | 332 | 35   | 331       | 340    | ± | 15 |
| solvent control  | 7   | •    | 7 11      | 8      | ± | 2  |
| 52               | 10  | 1:   | 2 12      | 11     | ± | 1  |
| 164              | 16  | 1:   | 5 15      | 15     | ± | 1  |
| 512              | 19  | ;    | 5 18      | 14     | ± | 8  |
| 1600             | 11  |      | 8 5       | 8      | ± | 3  |
| 5000             | 10  | n NP | 7 n NP 7  | n NP 8 | ± | 2  |
|                  |     |      |           |        |   |    |

| plate            | 1   | WITHOU<br>2 | T S9-MIX | MEAN    | SD    |
|------------------|-----|-------------|----------|---------|-------|
| dose (µg/plate)  |     |             |          |         |       |
| positive control | 901 | 877         | 624      | 801     | ± 153 |
| solvent control  | 12  | 12          | 14       | 13      | ± 1   |
| 52               | 22  | 23          | 19       | 21      | ± 2   |
| 164              | 14  | 11          | 16       | 14      | ± 3   |
| 512              | 20  | 18          | 30       | 23      | ± 6   |
| 1600             | 10  | 14          | 15       | 13      | ± 3   |
| 5000             | 23  | n NP 19     | n NP 26  | n NP 23 | ± 4   |
|                  |     |             |          |         |       |
|                  |     | WITH        | S9-MIX   |         |       |
| plate            | 1   | 2           | 3        | MEAN    | SD    |
| dose (µg/plate)  |     |             |          |         |       |
| positive control | 952 | 899         | 758      | 870     | ± 100 |
| solvent control  | 38  | 29          | 33       | 33      | ± 5   |
| 52               | 33  | 29          | 29       | 30      | ± 2   |
| 164              | 34  | 23          | 33       | 30      | ± 6   |
| 512              | 31  | 23          | 30       | 28      | ± 4   |
| 1600             | 29  | 24          | 31       | 28      | ± 4   |
| 5000             | 34  | n NP 16     | n NP 38  | n NP 29 | ± 12  |
|                  |     |             |          |         |       |

| plate            | 1   | V    | VITHOU<br>2 | T S9-MIX | <b>(</b> 3 |      | MEAN |   | SD |
|------------------|-----|------|-------------|----------|------------|------|------|---|----|
| dose (µg/plate)  |     |      |             |          |            |      |      |   |    |
| positive control | 911 |      | 846         |          | 947        |      | 901  | ± | 51 |
| solvent control  | 7   |      | 8           |          | 7          |      | 7    | ± | 1  |
| 52               | 16  |      | 15          |          | 14         |      | 15   | ± | 1  |
| 164              | 7   |      | 8           |          | 1          |      | 5    | ± | 4  |
| 512              | 9   |      | 7           |          | 12         |      | 9    | ± | 3  |
| 1600             | 8   |      | 10          |          | 11         |      | 10   | ± | 2  |
| 5000             | 8   | n NP | 10          | n NP     | 10         | n NP | 9    | ± | 1  |
|                  |     |      |             |          |            |      |      |   |    |
|                  |     |      | WITH:       | S9-MIX   |            |      |      |   |    |
| plate            | 1   |      | 2           |          | 3          |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |             |          |            |      |      |   |    |
| positive control | 122 |      | 125         |          | 137        |      | 128  | ± | 8  |
| solvent control  | 7   |      | 14          |          | 10         |      | 10   | ± | 4  |
| 52               | 8   |      | 20          |          | 12         |      | 13   | ± | 6  |
| 164              | 7   |      | 8           |          | 5          |      | 7    | ± | 2  |
| 512              | 11  |      | 8           |          | 11         |      | 10   | ± | 2  |
| 1600             | 15  |      | 15          |          | 10         |      | 13   | ± | 3  |
| 5000             | 8   | n NP | 14          | n NP     | 11         | n NP | 11   | ± | 3  |
|                  |     |      |             |          |            |      |      |   |    |

|                  |     | V    | VITHOUT S9-MI | IX  |      |      |   |    |
|------------------|-----|------|---------------|-----|------|------|---|----|
| plate            | 1   |      | 2             | 3   |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |               |     |      |      |   |    |
| positive control | 54  |      | 53            | 58  |      | 55   | ± | 3  |
| solvent control  | 4   |      | 10            | 7   |      | 7    | ± | 3  |
| 52               | 4   |      | 7             | 5   |      | 5    | ± | 2  |
| 164              | 3   |      | 8             | 8   |      | 6    | ± | 3  |
| 512              | 5   |      | 4             | 7   |      | 5    | ± | 2  |
| 1600             | 7   |      | 10            | 0   |      | 6    | ± | 5  |
| 5000             | 3   | n NP | 4 n NP        | 4   | n NP | 4    | ± | 1  |
|                  |     |      | WITH S9-MIX   |     |      |      |   |    |
| plate            | 1   |      | 2             | 3   |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |               |     |      |      |   |    |
| positive control | 220 |      | 245           | 239 |      | 235  | ± | 13 |
| solvent control  | 5   |      | 9             | 8   |      | 7    | ± | 2  |
| 52               | 3   |      | 7             | 10  |      | 7    | ± | 4  |
| 164              | 7   |      | 8             | 5   |      | 7    | ± | 2  |
| 512              | 5   |      | 11            | 8   |      | 8    | ± | 3  |
| 1600             | 10  |      | 1             | 7   |      | 6    | ± | 5  |
|                  | 3   | n NP |               |     | n NP |      | ± | 1  |

| plate            | 1    | ,    | WITHOU<br>2 | T S9-MI | X<br>3 |      | MEAN |   | SD |
|------------------|------|------|-------------|---------|--------|------|------|---|----|
| dose (µg/plate)  |      |      |             |         |        |      |      |   |    |
| positive control | 412  |      | 359         |         | 460    |      | 410  | ± | 51 |
| solvent control  | 22   |      | 14          |         | 12     |      | 16   | ± | 5  |
| 52               | 10   |      | 15          |         | 4      |      | 10   | ± | 6  |
| 164              | 8    |      | 8           |         | 14     |      | 10   | ± | 3  |
| 512              | 18   |      | 10          |         | 10     |      | 13   | ± | 5  |
| 1600             | 18   |      | 7           |         | 5      |      | 10   | ± | 7  |
| 5000             | 16   | n NP | 5           | n NP    | 8      | n NP | 10   | ± | 6  |
|                  |      |      |             |         |        |      |      |   |    |
|                  |      |      |             |         |        |      |      |   |    |
|                  |      |      | WITH S      | S9-MIX  |        |      |      |   |    |
| plate            | 1    |      | 2           |         | 3      |      | MEAN |   | SD |
| dose (µg/plate)  |      |      |             |         |        |      |      |   |    |
| positive control | 1207 |      | 1069        |         | 1258   |      | 1178 | ± | 98 |
| solvent control  | 18   |      | 8           |         | 8      |      | 11   | ± | 6  |
| 52               | 22   |      | 24          |         | 18     |      | 21   | ± | 3  |
| 164              | 30   |      | 20          |         | 20     |      | 23   | ± | 6  |
| 512              | 22   |      | 22          |         | 18     |      | 21   | ± | 2  |
| 1600             | 15   |      | 20          |         | 22     |      | 19   | ± | 4  |
| 5000             | 24   | n NP | 16          | n NP    | 25     | n NP | 22   | ± | 5  |
|                  |      |      |             |         |        |      |      |   |    |

| plate            | 1    |      | WITHOU<br>2 | T S9-M | IX<br>3 |      | MEAN |   | SD  |
|------------------|------|------|-------------|--------|---------|------|------|---|-----|
| dose (µg/plate)  |      |      |             |        |         |      |      |   |     |
| positive control | 603  |      | 642         |        | 648     |      | 631  | ± | 24  |
| solvent control  | 72   |      | 88          |        | 61      |      | 74   | ± | 14  |
| 52               | 75   |      | 99          |        | 75      |      | 83   | ± | 14  |
| 164              | 75   |      | 63          |        | 88      |      | 75   | ± | 13  |
| 512              | 68   |      | 75          |        | 64      |      | 69   | ± | 6   |
| 1600             | 69   |      | 72          |        | 95      |      | 79   | ± | 14  |
| 5000             | 78   | n NP | 68          | n NP   | 73      | n NP | 73   | ± | 5   |
|                  |      |      |             |        |         |      |      |   |     |
|                  |      |      | WITH S      | S9-MIX |         |      |      |   |     |
| plate            | 1    |      | 2           |        | 3       |      | MEAN |   | SD  |
| dose (µg/plate)  |      |      |             |        |         |      |      |   |     |
| positive control | 2612 |      | 2424        |        | 2445    |      | 2494 | ± | 103 |
| solvent control  | 71   |      | 73          |        | 95      |      | 80   | ± | 13  |
| 52               | 93   |      | 79          |        | 67      |      | 80   | ± | 13  |
| 164              | 82   |      | 78          |        | 82      |      | 81   | ± | 2   |
| 512              | 80   |      | 80          |        | 99      |      | 86   | ± | 11  |
| 1600             | 79   |      | 82          |        | 95      |      | 85   | ± | 9   |
| 5000             | 82   | n NP | 88          | n NP   | 86      | n NP | 85   | ± | 3   |
|                  |      |      |             |        |         |      |      |   |     |

Experiment 2 Strain WP2uvrA

| plate            | 1   |      | WITHOU<br>2 | T S9-MI | X<br>3 |      | MEAN |   | SD |
|------------------|-----|------|-------------|---------|--------|------|------|---|----|
| dose (µg/plate)  |     |      |             |         |        |      |      |   |    |
| positive control | 177 |      | 209         |         | 200    |      | 195  | ± | 17 |
| solvent control  | 14  |      | 20          |         | 26     |      | 20   | ± | 6  |
| 52               | 11  |      | 14          |         | 19     |      | 15   | ± | 4  |
| 164              | 19  |      | 15          |         | 22     |      | 19   | ± | 4  |
| 512              | 12  |      | 19          |         | 15     |      | 15   | ± | 4  |
| 1600             | 31  |      | 18          |         | 22     |      | 24   | ± | 7  |
| 5000             | 18  | n NP | 18          | n NP    | 22     | n NP | 19   | ± | 2  |
|                  |     |      |             |         |        |      |      |   |    |
|                  |     |      |             |         |        |      |      |   |    |
|                  |     |      | WITH        | S9-MIX  |        |      |      |   |    |
| plate            | 1   |      | 2           |         | 3      |      | MEAN |   | SD |
| dose (µg/plate)  |     |      |             |         |        |      |      |   |    |
| positive control | 585 |      | 521         |         | 468    |      | 525  | ± | 59 |
| solvent control  | 24  |      | 18          |         | 19     |      | 20   | ± | 3  |
| 52               | 30  |      | 29          |         | 22     |      | 27   | ± | 4  |
| 164              | 22  |      | 27          |         | 27     |      | 25   | ± | 3  |
| 512              | 24  |      | 30          |         | 31     |      | 28   | ± | 4  |
| 1600             | 19  |      | 27          |         | 18     |      | 21   | ± | 5  |
| 5000             | 24  | n NP | 20          | n NP    | 34     | n NP | 26   | ± | 7  |
|                  |     |      |             |         |        |      |      |   |    |

APPENDIX 4 HISTORICAL CONTROL DATA OF THE SOLVENT CONTROL

|        | TA1    | 535    | TA1    | 537    | TA98    |         | TA100    |          | WP2uvrA |         |
|--------|--------|--------|--------|--------|---------|---------|----------|----------|---------|---------|
| S9-mix | -      | +      | -      | +      | -       | +       | -        | +        | 1       | +       |
| Range  | 5 - 36 | 3 - 34 | 3 – 25 | 3 - 28 | 10 - 50 | 10 - 57 | 64 - 153 | 66 - 156 | 13 – 68 | 12 - 70 |
| Mean   | 18     | 14     | 7      | 10     | 19      | 27      | 106      | 106      | 28      | 34      |
| SD     | 6      | 5      | 3      | 4      | 6       | 7       | 17       | 17       | 7       | 7       |
| n      | 1422   | 148    | 1224   | 1251   | 1494    | 1523    | 1500     | 1500     | 1194    | 1224    |

SD = Standard deviation n = Number of observations

Historical control data from experiments performed between November 2013 and November 2015.

APPENDIX 5 HISTORICAL CONTROL DATA OF THE POSITIVE CONTROL ITEMS

|        | TA1535    |           | TA1       | 537       | TA98       |            |  |
|--------|-----------|-----------|-----------|-----------|------------|------------|--|
| S9-mix | -         | +         | -         | +         | -          | +          |  |
| Range  | 78 - 1932 | 81 - 1332 | 62 – 1565 | 55 – 1112 | 347 – 1764 | 261 - 1885 |  |
| Mean   | 781       | 236       | 635       | 407       | 918        | 812        |  |
| SD     | 269       | 94        | 190       | 128       | 171        | 290        |  |
| n      | 1510      | 1515      | 1214      | 1233      | 1517       | 1539       |  |

|        | TA         | 100        | WP2uvrA    |           |  |
|--------|------------|------------|------------|-----------|--|
| S9-mix | -          | +          | -          | +         |  |
| Range  | 549 – 1798 | 640 - 2760 | 123 – 1958 | 85 - 1390 |  |
| Mean   | 918        | 1402       | 1371       | 261       |  |
| SD     | 147        | 331        | 274        | 155       |  |
| n      | 1491       | 1494       | 1202       | 1230      |  |

SD = Standard deviation n = Number of observations

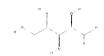
Historical control data from experiments performed between November 2013 and November 2015.

#### APPENDIX 6 CERTIFICATE OF ANALYSIS

Certificate of analysis Specification date: 15.06.2015

# Certificate of analysis

: Betawell<sup>®</sup> Ara-P Product name



| Component                            | Value           |
|--------------------------------------|-----------------|
| Arabinose                            | 99.9 wt%        |
| Glucose                              | <0.01 wt%       |
| Mannose                              | <0.01 wt%       |
| Rhamnose                             | 0.01 wt%        |
| Xylose                               | 0.03 wt%        |
| Fucose                               | <0.01 wt%       |
| Galactose                            | 0.04 wt%        |
| Galacturonic acid                    | <0.01 wt%       |
| Beet pectin derived oligosaccharides | 0.02 wt%        |
| Water content                        | 0.1 wt%         |
| Solubility ( 10% in water)           | < 20 Hazen      |
| Clarity                              | 0.85 – 0.90 FNU |

CAS-Nr.

: 5328-37-0 (for L-Arabinose)

Origin

: Sugar beet : C32-1

Batch number Batch size

Product number

: total 40 kg.

: 7000 (Cosun internal number)

Appearance (color) : Whitish to white

Appearance (form)

: Powder

Smell

: Neutral

Infrared spectrum

: Conforms to structure

Minimum purity

: > 99 wt% of Dry Solids (L-arabinose, method: HPLC (C18-aq), PDA)

Functionality

: food ingredient (USA, Asia), flavor ingredient (for EU see Regulation 872/2012),

cosmetic ingredient.

Storage conditions

: Dry, keep out of sunshine.

Shelf life

: The expiry date of this product is 24 months after the production date indicated

on this certificate of analysis when properly stored and maintained.

Production date

: 15.05.2015

Betawell Ara-P, powder of arabinose page 1 of 2

#### APPENDIX 6 - continued -



Certificate of analysis Specification date: 15.06.2015

#### Additional specifications:

| Test                          | Method              | Maximum      |
|-------------------------------|---------------------|--------------|
| Total Viable Count / g (30°C) | ISO 4833:2003       | 1000 CFU / g |
| Yeasts / g                    | ISO 7954:1987       | 20 CFU / g   |
| Moulds / g                    | ISO 7954:1987       | 20 CFU / g   |
| Staph. aureus / g             | ISO 6888-3 :2003    | Absent       |
| Salmonella / 50g              | ISO 6579:2002       | Absent       |
| E. coli / g                   | ISO 16649-2:2001    | Absent       |
| Bacillus cereus / g           | ISO 7932:2004       | 100 CFU / g  |
| Coliforms / g                 | ISO 4832:2006       | Absent       |
| Enterobacteria / g            | ISO 21528-1:2004    | Absent       |
| Listeria / g                  | ISO 11290-1:1997    | Absent       |
| Clostridium perfringens/g     | ISO 7937:2004       | Absent       |
| Faecal Streps/g               | External laboratory | Absent       |
| Aflatoxins                    | External laboratory | < 0.1 µg/kg  |

| Metals  | Value (ppm) |
|---------|-------------|
| Arsenic | <0.01       |
| Lead    | <0.01       |
| Mercury | <0.0001     |
| Cadmium | <0.005      |
| Tin     | <0.01       |
| Copper  | <0.01       |
| Silver  | <0.05       |
| Bismuth | <0.2        |

This powder is produced from sugar beet grown in the Netherlands and Germany. This material has been checked for compliance with international pesticide tolerance legislation, does not contain and/or has not been in contact with genetically modified organisms, does not contain any ingredient with an animal origin and does not contain any known allergen.

Cosun Biobased Products B.V.
P.O. Box 3411, 4800 MG Breda, The Netherlands
Tel +31 76 530 33 33, Fax +31 76 530 32 06

The information and recommendations in this leaflet are to the best of our knowledge, information and belief accurate at the date of publication. Nothing herein is to be construed as warranty expressed or implied. In all cases it is the responsibility of users to determine the applicability of such information or the suitability of any products for their own particular purpose.

Betawell Ara-P, powder of arabinose page 2 of 2

# APPENDIX 7 FORMULATION ANALYSIS

# DETERMINATION OF THE CONCENTRATIONS

# **ANALYTICAL REPORT**

<u>Author</u>

J.Ciric, PhD.

# 1. CONTENTS

| CONTENTS            |  |
|---------------------|--|
| REPORT APPROVAL     | 36   |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
| ·                   |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
|                     |  |
| BLES                |  |
|                     |  |
| ble 1 QC samples    | 42   |
| ble 2 Accuracy test |  |
| b                   | REPORT APPROVAL SUMMARY INTRODUCTION 4.1. Study schedule analytical phase 4.2. Purpose of the study MATERIALS AND METHODS 5.1. Reagents 5.2. Study samples 5.3. Analytical method 5.3.1. Analytical conditions 5.3.2. Preparation of solutions 5.3.3. Sample injections 5.4. Electronic systems for data acquisition 5.5. Formulas 5.6. Specifications RESULTS 6.1. Calibration curves 6.2. Samples 6.2.1. QC samples 6.2.2. Study samples |

# 2. REPORT APPROVAL

WIL Research Europe B.V.

(b) (6)

Signature

Name:

J. Ciric, PhD.

Title: Principal Scientist
Analytical Chemistry

Date: 06 January 2016

# 3. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation of the test item in stock solutions used for spiking in the mutation assay.

# Accuracy of preparation

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

In the vehicle, no test tem was detected.

#### 4. INTRODUCTION

#### 4.1. Study schedule analytical phase

Experimental starting date : 24 November 2015 Experimental completion date : 24 November 2015

#### 4.2. Purpose of the study

The purpose of the analytical phase was to determine the accuracy of preparation of the test item in formulations.

#### 5. MATERIALS AND METHODS

#### 5.1. Reagents

Water Tap water purified by a Milli-Q water purification system

(Millipore, Bedford, MA, USA)

Acetonitrile Biosolve, Valkenswaard, The Netherlands

All reagents were of analytical grade, unless specified otherwise.

#### 5.2. Study samples

Accuracy were determined for stock solutions used for spiking in mutation assay.

Samples of  $500 \, \mu l$  were taken from the stock solutions and transferred into glass vials or  $5 \, or \, 10 \, m l$  volumetric flasks. The samples were taken at random positions. The samples in glass vials were directly analysed. The volumetric flasks were filled up to the mark with water. The solutions were further diluted to obtain an end solution of water and concentrations within the calibration range.

#### 5.3. Analytical method

#### 5.3.1. Analytical conditions

Analysis was based on the analytical method validated for the test item in project 509990.

Analytical conditions:

Instrument Acquity UPLC system (Waters, Milford, MA, USA)

Detector Acquity ELSD system (Waters)

Column Asahipak NH2P-50 4E, 250 mm  $\times$  4.6 mm i.d., dp = 5  $\mu$ m

(Shodex, New York, NY, USA)

Column temperature 40°C Injection volume 10 µl

Mobile phase 20/80 (v/v) acetonitrile/water

Flow 1 ml/min

**ELSD** detection

Temperature 40°C
Nebuliser gas nitrogen
Gas 25.0 psi
Nebulizer Cooling
Gain 500

# 5.3.2. Preparation of solutions

#### Stock solutions

Stock solutions of the test item were prepared in water at a concentration of 2000 mg/l.

#### Calibration solutions

Calibration solutions in the concentration range of 25 – 100 mg/l were prepared from two stock solutions. The end solution of the calibration solutions was water.

#### QC samples

QC samples of 5 ml were prepared with the test item in water at a target concentration of 0.52 and 50 mg/ml. Samples of 500  $\mu$ l were taken and treated similarly as the study samples (see paragraph 5.2 'Study samples').

#### 5.3.3. Sample injections

Calibration solutions were injected in duplicate. Test samples and QC samples were analysed by single injection.

#### 5.4. Electronic systems for data acquisition

System control, data acquisition and data processing were performed using the following program:

- Empower 3 database version 7.21 (Waters, Milford, MA, USA).

Temperature, relative humidity and/or atmospheric pressure during sample storage and/or performance of the studies was monitored continuously using the following program:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA).

#### 5.5. Formulas

Response (R) Peak area test item [units]

Calibration curve  $R = a\,C_{\,N}^{\,2} \,\,+\,b\,C_{\,N}^{\,} \,+\,c$ 

where:

a = quadratic regression factor [units  $\times$  (l/mg)<sup>2</sup>] b = linear regression factor [units  $\times$  l/mg]

c = intercept [units]

Analysed concentration (C<sub>A</sub>)  $C_A = \frac{-b + \sqrt{b^2 - 4 \, a \times (c - R)}}{2 \, a} \times \frac{d}{1000} \quad [mg/ml]$ 

where:

d = dilution factor

Accuracy  $\frac{C_A}{C_N} \times 100 \text{ [\%]}$ 

QC samples

where:

 $C_N$  = nominal concentration [mg/ml]

Accuracy  $\frac{C_A}{C_T} \times 100 \text{ [\%]}$ 

Study samples

where:

 $C_T$  = target concentration [mg/ml]

# 5.6. Specifications

Preparation of stock solution was considered acceptable if the mean accuracy was in the range 85 – 115% of the target concentration.

#### 6. RESULTS

#### 6.1. Calibration curves

A calibration curve was constructed using five concentrations. For each concentration, two responses were used. Quadratic regression analysis was performed using the least squares method with a 1/concentration<sup>2</sup> weighting factor. The coefficient of correlation (r) was > 0.99.

#### 6.2. Samples

#### 6.2.1. QC samples

The results for the QC samples are given in Table 1

The mean accuracies of the QC samples were within the criterion range of 85 – 115%. It demonstrated that the analytical method was adequate for the determination of the test item in the study samples.

#### 6.2.2. Study samples

The results for the study samples are given in Table 2.

#### Accuracy of preparation

In the vehicle, no test item was detected.

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

# **TABLES**

Table 1 QC samples

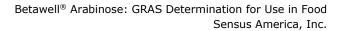
| Date of preparation | Date of analysis | Target concentration | Nominal concentration | Analysed concentration | Accuracy  | Mean<br>accuracy |
|---------------------|------------------|----------------------|-----------------------|------------------------|-----------|------------------|
| proparation         | analysis         | [mg/ml]              | [mg/ml]               | [mg/ml]                | [%]       | [%]              |
| 24-Nov-2015         | 24-Nov-2015      | 0.52                 | 0.521<br>0.521        | 0.528<br>0.506         | 101<br>97 | 99               |
| 24-Nov-2015         | 24-Nov-2015      | 50                   | 50.1<br>50.1          | 55.9<br>48.3           | 111<br>96 | 104              |

Table 2 Accuracy test

| Group        | Date of analysis | Sample position |              | Concentration<br>[mg/ml] |              | uracy<br>%] |
|--------------|------------------|-----------------|--------------|--------------------------|--------------|-------------|
|              |                  |                 | Target       | Analysed                 | Individual   | Mean        |
| Vehicle      | 24-Nov-2015      | Random          | 0.00<br>0.00 | n.d.<br>n.d.             | n.a.<br>n.a. | n.a.        |
| Low          | 24-Nov-2015      | Random          | 0.52<br>0.52 | 0.506<br>0.552           | 97<br>106    | 102         |
| Intermediate | 24-Nov-2015      | Random          | 5.12<br>5.12 | 4.70<br>5.67             | 92<br>111    | 101         |
| High         | 24-Nov-2015      | Random          | 50<br>50     | 49.3<br>48.5             | 99<br>97     | 98          |

n.d. Not detected.

n.a. Not applicable.





APPENDIX C3
AN IN VITRO MICRONUCLEUS ASSAY WITH
BETAWELL L-ARABINOSE IN CULTURED
PERIPHERAL HUMAN LYMPHOCYTES



# **FINAL REPORT**

# Study Title

# AN IN VITRO MICRONUCLEUS ASSAY WITH BETAWELL L-ARABINOSE IN CULTURED PERIPHERAL HUMAN LYMPHOCYTES

# Study Director

I.A.J. Verbaan, PhD.

# **Test Facility**

WIL Research Europe B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

#### Sponsor

Cosun Biobased Products B.V. As part of Royal Cosun Postbus 3411 4800 MG Breda Netherlands

**Laboratory Project Identification** 

WIL Research Project 509989 Test item 206781/A

- Page 1 of 37 -

# 1. CONTENTS

| 1.       | CONTENTS   |     |
|----------|--|-----|
| 2.       | STATEMENT OF GLP COMPLIANCE                              | 4   |
| 3.       | TEST FACILITY QUALITY ASSURANCE STATEMENT                | 5   |
| 4.       | SUMMARY  |     |
| 5.       | INTRODUCTION   |     |
| 0.       | 5.1. Study schedule                                      |     |
|          | 5.2. Purpose   |     |
|          | 5.3. Guidelines  |     |
|          |  |     |
|          | 5.4. Retention of records and materials                  |     |
|          | 5.5. Responsible personnel                               |     |
|          | 5.5.1. Test facility                                     |     |
| _        | 5.5.2. Sponsor Representative                            | 8   |
| 6.       | MATERIALS AND METHODS                                    |     |
|          | 6.1. Test item   |     |
|          | 6.1.1. Test item information                             |     |
|          | 6.1.2. Study specific test item information              | 8   |
|          | 6.2. Vehicle information                                 | 9   |
|          | 6.3. Reference item                                      | 9   |
|          | 6.3.1. Negative control                                  | 9   |
|          | 6.3.2. Positive controls                                 |     |
|          | 6.4. Test item preparation                               |     |
|          | 6.4.1. Chemical analysis of dose preparations            | .10 |
|          | 6.5. Test system   |     |
|          | 6.6. Cell culture  |     |
|          | 6.7. Metabolic activation system                         |     |
|          | 6.7.1. Preparation of S9-mix                             | 11  |
|          | 6.8. Study design  |     |
|          | 6.8.1. Dose range finding test                           |     |
|          |  |     |
|          | 6.8.2. First cytogenetic assay                           |     |
|          | 6.8.3. Second cytogenetic assay                          |     |
|          | 6.8.4. Preparation of slides                             |     |
|          | 6.8.5. Cytotoxicity assessment                           |     |
|          | 6.8.6. Cytogenetic assessment/scoring of micronuclei     | .13 |
|          | 6.9. Interpretation                                      |     |
|          | 6.9.1. Acceptability of the assay                        |     |
|          | 6.9.2. Data evaluation and statistical procedures        | 13  |
|          | 6.10. List of deviations                                 |     |
|          | 6.10.1. List of study plan deviations                    |     |
|          | 6.10.2. List of standard operating procedures deviations | .14 |
| 7.       | ELECTRONIC SYSTEMS FOR DATA ACQUISITION                  | .14 |
| 8.       | RESULTS  | 14  |
|          | 8.1. Dose range finding test                             |     |
|          | 8.2. First cytogenetic assay                             |     |
|          | 8.3. Second cytogenetic assay                            |     |
|          | 8.4. Formulation analysis                                |     |
|          | 8.5. Evaluation of the results                           |     |
| 9.       | CONCLUSION   |     |
| a.<br>1∩ |  | 16  |

| IABLES     |  |    |
|------------|--|----|
| Table 1    | Cytokinesis-block proliferation index of human lymphocyte cultures treated with Betawell L-Arabinose in the dose range finding test                          | 17 |
| Table 2    | Cytokinesis-block proliferation index of human lymphocytes cultures treated with Betawell L-Arabinose in the first cytogenetic assay                         | 18 |
| Table 3    | Number of mononucleated or binucleated cells with micronuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the first cytogenetic assay  | 19 |
| Table 4    | Cytokinesis-block proliferation index of human lymphocyte cultures treated with Betawell L-Arabinose in the second cytogenetic assay                         | 20 |
| Table 5    | Number of mononucleated or binucleated cells with micronuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the second cytogenetic assay | 21 |
| Table 6    | Scoring of cells with one, two or more nuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the first cytogenetic assay                  | 22 |
| Table 7    | Scoring of cells with one, two or more nuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the second cytogenetic assay                 | 23 |
| APPENDICES |  |    |
| APPENDIX 1 | TABLES   | 17 |
| APPENDIX 2 | INDIVIDUAL DATA  | 22 |
| APPENDIX 3 | STATISTICAL EVALUATION OF THE TEST RESULTS   | 24 |
| APPENDIX 4 | HISTORICAL CONTROL DATA FOR <i>IN VITRO</i> MICRONUCLEUS STUDIES OF THE SOLVENT CONTROL  | 25 |
| APPENDIX 5 | HISTORICAL CONTROL DATA FOR <i>IN VITRO</i> MICRONUCLEUS STUDIES OF THE POSITIVE CONTROL SUBSTANCES  | 26 |
| APPENDIX 6 | CERTIFICATE OF ANALYSIS  |    |
| APPENDIX 7 | ANALYTICAL REPORT  |    |

# 2. STATEMENT OF GLP COMPLIANCE

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with the following GLP regulations:

- OECD Principles of Good Laboratory Practice concerning Mutual Acceptance of Data in the Assessment of Chemicals, 26 November 1997 (C(97) 186 Final);
- EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).

Except for the following:

The characterisation of the test item was conducted in an ISO 9001 environment.

The data generated and reported are considered to be valid.

| WIL Research Europe B.V. |                      |  |  |  |
|--------------------------|----------------------|--|--|--|
| (b) (6                   | 6)                   |  |  |  |
|                          |                      |  |  |  |
| Signature:               |                      |  |  |  |
| Name:                    | I.A.J. Verbaan, PhD. |  |  |  |
| Title:                   | Study Director       |  |  |  |
| Date:                    | 18 February 2016     |  |  |  |
|                          |                      |  |  |  |

#### 3. TEST FACILITY QUALITY ASSURANCE STATEMENT

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands.

Study title: An *in vitro* micronucleus assay with Betawell L-Arabinose in cultured peripheral human lymphocytes

This report was inspected by the WIL Research Europe Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s).

The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected. The dates of Quality Assurance inspections are given below.

Project 509989

| Type of Inspections | Phase/Process  | Start<br>Inspection<br>date               | End<br>Inspection<br>date                 | Reporting date                            |
|---------------------|--|---|---|---|
| Study               | Study Plan<br>Study Plan Amendment 01<br>Report  | 02-Sep-2015<br>16-Sep-2015<br>05-Feb-2016 | 02-Sep-2015<br>16-Sep-2015<br>05-Feb-2016 | 02-Sep-2015<br>16-Sep-2015<br>05-Feb-2016 |
| Process             | Test Substance Receipt Test Substance Handling   | 09-Nov-2015                               | 20-Nov-2015                               | 20-Nov-2015                               |
|                     | Analytical and physical chemistry Test Substance Handling Exposure Observations/Measurements Specimen Handling | 30-Nov-2015                               | 14-Dec-2015                               | 17-Dec-2015                               |
|                     | Genetic and In Vitro Toxicology Test Substance Handling Exposure Observations/Measurements Specimen Handling   | 14-Dec-2015                               | 21-Dec-2015                               | 22-Dec-2015                               |

The facility inspection program is conducted in accordance with Standard Operating Procedure.

The review of the final report was completed on the date of signing this QA statement.

WIL Research Europe B.V.

(b) (6

Name: Ali Bouhuijzen M. Sc. Compliance Specialist III

Date: 17-Feb-2016

Final Report

Signature:

#### 4. SUMMARY

An in vitro micronucleus assay with Betawell L-Arabinose in cultured peripheral human lymphocytes.

This report describes the effect of Betawell L-Arabinose on the number of micronuclei formed in cultured peripheral human lymphocytes in the presence and absence of a metabolic activation system (phenobarbital and \(\mathbb{B}\)-naphthoflavone induced rat liver S9-mix). The possible clastogenicity and aneugenicity of Betawell L-Arabinose was tested in two independent experiments.

The study procedures described in this report are in compliance with the most recent OECD and EC guidelines.

Batch C32-1 of Betawell L-Arabinose was a white powder. The test item was dissolved in Milli-Q water.

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%). In the vehicle, no test tem was detected. Stock solutions at the entire range were stable when stored at room temperature under normal laboratory light conditions for at least 4 hours.

In the first cytogenetic assay, Betawell L-Arabinose was tested up to 1501  $\mu$ g/ml for a 3 hours exposure time with a 27 hours harvest time in the absence and presence of S9-fraction.

In the second cytogenetic assay, Betawell L-Arabinose was also tested up to 1501  $\mu$ g/ml for a 24 hours exposure time with a 24 hours harvest time in the absence of S9-mix.

The number of mono- and binucleated cells with micronuclei found in the solvent control cultures was within the 95% control limits of the distribution of the historical negative control database. The positive control chemicals, mitomycin C and cyclophosphamide both produced a statistically significant increase in the number of binucleated cells with micronuclei. The positive control chemical colchicine produced a statistically significant increase in the number of mononucleated cells with micronuclei. In addition, the number of mono- and binucleated cells with micronuclei found in the positive control cultures was within the 95% control limits of the distribution of the historical positive control database. It was therefore concluded that the test conditions were adequate and that the metabolic activation system (S9-mix) functioned properly.

Betawell L-Arabinose did not induce a statistically significant or biologically relevant increase in the number of mono- and binucleated cells with micronuclei in the absence and presence of S9-mix, in either of the two experiments.

Finally, it is concluded that this test is valid and that Betawell L-Arabinose is not clastogenic or aneugenic in human lymphocytes under the experimental conditions described in this report.

#### 5. INTRODUCTION

#### 5.1. Study schedule

Experimental starting date : 07 October 2015 Experimental completion date : 14 December 2015

#### 5.2. Purpose

The objective of this study was to evaluate Betawell L-Arabinose for its ability to induce micronuclei in cultured human lymphocytes, either in the presence or absence of a metabolic activation system (S9-mix).

#### Background of the test system

Whole blood samples obtained from young healthy subjects were treated with an anti-coagulant (heparin) and cultured in the presence of a mitogen (phytohaemagglutinin). These stimulated human lymphocytes were used because they are sensitive indicators of clastogenic and aneugenic activity of a broad range of chemicals (1 - 5).

The stimulated lymphocytes were exposed to the test item both in the presence and absence of a metabolic activation system (S9-mix). In combination with this metabolic activation system indirect chemical mutagens, i.e. those requiring metabolic transformation into reactive intermediates, can be tested for possible clastogenic effects *in vitro*.

During or after exposure of the stimulated human lymphocytes to the test item, cells were cultured to allow chromosome or spindle damage to lead to the formation of micronuclei in interphase cells. Micronuclei are small particles consisting of acentric chromosome fragments (clastogenic event) or whole chromosomes (aneugenic event leading to chromosome loss), which are unable to migrate to the poles during the anaphase stage of cell division. After telophase, these fragments may not be included in the nuclei of daughter cells and form single or multiple micronuclei in the cytoplasm.

Prior to the mitosis (during or after exposure of the test item) the chemical cytochalasin B was added to the cultures. Cytochalasin B arrests the formation of actin filaments. Consequently, the cell is not able to divide, but nuclear division still continues. In this way, cytochalasin B allows discrimination between cells that have undergone nuclear division (binucleated) and cells that have not (mononucleated).

Cells were harvested, stained and interphase cells (mono and bi-nucleated cells) were analysed microscopically for the presence of micronuclei. Results from cultures treated with the test item were compared with control (vehicle) treated cultures.

Micronuclei were evaluated in the first post-exposure mitosis (i.e. 24 hours after exposure).

A test item that induces a positive response in this assay is presumed to be a potential clastogenic or aneugenic agent.

#### 5.3. Guidelines

The study procedures described in this report are in compliance with the following guidelines:

- Organisation for Economic Co-operation and Development (OECD), OECD Guideline for the Testing of Chemicals, Guideline no. 487: *In Vitro* Mammalian Cell Micronucleus Test (adopted 26 September 2014).
- European Community (EC). Commission regulation (EC) No. 440/2008, Part B: Methods for the Determination of Toxicity and other health effects, Guideline B.49 "InVitro Mammalian Cell Micronucleus Test". Official Journal of the European Union No. L142; Amended by EC No. 640/2012 OJ No. L193, 20 July 2012.

#### 5.4. Retention of records and materials

Records and material pertaining to the study, which include study plan and amendments, raw data, specimens, except perishable specimens, and the final report will be retained in the archives of the test facility for a minimum of 5 years after the finalization of the report. After this period, the sponsor will be contacted to determine how the records and materials should be handled. The test facility will retain information concerning decisions made.

Perishable specimens (e.g. requiring refrigeration or freezing) will be discarded following evaluation in the study without further notice to the study sponsor.

A sample of the test item will be retained until expiry date or applicable retest date. After this period the sample(s) will be destroyed.

#### 5.5. Responsible personnel

# 5.5.1. Test facility

Study Director I.A.J. Verbaan, PhD.

Principal Scientist (analytical J. Ciric, PhD.

chemistry)

#### 5.5.2. Sponsor Representative

Study Monitor Alex Benschop and Diederick Meyer

#### 6. MATERIALS AND METHODS

#### 6.1. Test item

#### 6.1.1. Test item information

IdentificationBetawell L-ArabinoseAppearanceWhite powder

Batch C32-1

Purity/Composition See Certificate of Analysis
Test substance storage At room temperature

Test substance storage At room temperature
Stable under storage conditions until 15 May 2017 (expiry date)

See APPENDIX 6; Certificate of Analysis

#### 6.1.2. Study specific test item information

Purity/composition correction factor No correction factor required

Test substance handling No specific handling conditions required

Stability at higher temperatures Stable, maximum temperature: 50°C, maximum duration: 48

hours

Chemical name (IUPAC), synonym or (2R,3S,4S)-2,3,4,5-Tetrahydroxypentanal, arabinose

5328-37-0

trade name
CAS Number
Molecular structure

Molecular formula  $C_5H_{10}O_5$  Molecular weight 150.13

pH 5-7 at concentration of < 20%

#### 6.2. Vehicle information

Solubility in vehicle Water: Approximately 50% (w/w)

Stability in vehicle Water: Stable

#### 6.3. Reference item

#### 6.3.1. Negative control

The vehicle for the test item was Milli-Q water.

#### 6.3.2. Positive controls

#### Without metabolic activation (-S9-mix):

Mitomycin C (MMC-C; CAS no. 50-07-7, Sigma, Zwijndrecht, The Netherlands) was used as a direct acting clastogen at a final concentration of 0.25 and 0.38  $\mu$ g/ml for a 3 hour exposure period and 0.15 and 0.23  $\mu$ g/ml for a 24 hour exposure period.

Colchicine (Colch; CAS no. 64-86-8, Acros Organics, Geel, Belgium) was used as a direct acting aneugen at a final concentration of 0.1  $\mu$ g/ml for a 3 hour exposure period and 0.05  $\mu$ g/ml for a 24 hour exposure period.

#### With metabolic activation (+S9-mix):

Cyclophosphamide (CP; CAS no. 50-18-0, Baxter B.V., Utrecht, The Netherlands) was used as an indirect acting clastogen, requiring metabolic activation, at a final concentration of 15 and 17.5  $\mu$ g/ml for a 3 hour exposure period.

#### Solvent for positive controls

Hanks' Balanced Salt Solution (HBSS) (Life Technologies, Bleiswijk, The Netherlands), without calcium and magnesium.

All reference stock solutions were stored in aliquots at ≤-15°C in the dark. These solutions were thawed immediately before use.

#### 6.4. Test item preparation

No correction was made for the purity/composition of the test item.

A solubility test was performed in RPMI 1640 medium (Life Technologies, Bleiswijk, The Netherlands). Betawell L-Arabinose was dissolved in Milli-Q water for the assays performed in this study. Betawell L-Arabinose concentrations were used within 1 hour after preparation.

The pH and the osmolarity of the culture medium containing the highest tested concentration were recorded.

#### 6.4.1. Chemical analysis of dose preparations

Analyses was conducted on a single occasion during the treatment phase on samples as specified below, according to a validated method (Project 509990).

Dose Analysis (type of sample)

Vehicle acc(R)Low  $acc + stab_{t=0}(R)$ ,  $stab_{t=4, RT, light}(R)$ Intermediate acc(R)High  $acc + stab_{t=0}(R)$ ,  $stab_{t=4, RT, light}(R)$ 

Duplicate samples were analysed.

acc=accuracy, stab=stability (hours)

R=random position of container

RT=room temperature, light=normal laboratory light conditions

The accuracy of preparation is considered acceptable if the mean measured concentrations are 85-115%. Formulations are considered stable if the relative difference before and after storage is  $\leq 10\%$ .

#### 6.5. Test system

Cultured peripheral human lymphocytes were used as test system. Peripheral human lymphocytes are recommended in the international OECD guideline.

Blood was collected from healthy adult, non-smoking volunteers (aged 18 to 35 years). The Average Generation Time (AGT) of the cells and the age of the donor at the time the AGT was determined (December 2014) are presented below:

Dose range finding study: age 32, AGT = 12.8 h First cytogenetic assay: age 27, AGT = 12.6 h Second cytogenetic assay: age 23, AGT = 12.8 h

#### 6.6. Cell culture

# **Blood samples**

Blood samples were collected by venipuncture using the Venoject multiple sample blood collecting system with a suitable size sterile vessel containing sodium heparin (Vacuette, Greiner Bio-One, Alphen aan den Rijn, The Netherlands). Immediately after blood collection lymphocyte cultures were started.

#### Culture medium

Culture medium consisted of RPMI 1640 medium (Life Technologies), supplemented with 20% (v/v) heat-inactivated (56°C; 30 min) foetal calf serum (Life Technologies), L-glutamine (2 mM) (Life Technologies), penicillin/streptomycin (50 U/ml and 50 µg/ml respectively) (Life Technologies) and 30 U/ml heparin (Sigma, Zwijndrecht, The Netherlands).

#### Lymphocyte cultures

Whole blood (0.4 ml) treated with heparin was added to 5 ml or 4.8 ml culture medium (in the absence and presence of S9-mix, respectively). Per culture 0.1 ml (9 mg/ml) phytohaemagglutinin (Remel Europe Ltd., Dartford, United Kingdom) was added.

#### **Environmental conditions**

All incubations were carried out in a controlled environment, in which optimal conditions were a humid atmosphere of 80 - 100% (actual range 59 - 91%), containing  $5.0 \pm 0.5\%$  CO<sub>2</sub> in air in the dark at  $37.0 \pm 1.0$ °C (actual range 35.7 - 37.3°C). Temperature and humidity were continuously monitored throughout the experiment. The CO<sub>2</sub> percentage was monitored once on each working day. Temporary deviations from the temperature, humidity and CO<sub>2</sub> percentage may occur due to opening and closing of the incubator door. Based on laboratory historical data these deviations are considered not to affect the study integrity.

#### 6.7. Metabolic activation system

Rat S9 homogenate was obtained from Trinova Biochem GmbH, Giessen, Germany and is prepared from male Sprague Dawley rats that have been dosed orally with a suspension of phenobarbital (80 mg/kg body weight) and \(\mathbb{G}\)-naphthoflavone (100 mg/kg).

#### 6.7.1. Preparation of S9-mix

S9-mix was prepared immediately before use and kept on ice. S9-mix components contained per ml physiological saline: 1.63 mg MgCl $_2$ .6H $_2$ O (Merck); 2.46 mg KCl (Merck); 1.7 mg glucose-6-phosphate (Roche, Mannheim, Germany); 3.4 mg NADP (Randox); 4  $\mu$ mol HEPES (Life Technologies). The above solution was filter (0.22  $\mu$ m)-sterilized. To 0.5 ml S9-mix components 0.5 ml S9-fraction was added (50% (v/v) S9-fraction) to complete the S9-mix.

Metabolic activation was achieved by adding 0.2 ml S9-mix to 5.3 ml of a lymphocyte culture (containing 4.8 ml culture medium, 0.4 ml blood and 0.1 ml (9 mg/ml) phytohaemagglutinin). The concentration of the S9-fraction in the exposure medium was 1.8% (v/v).

#### 6.8. Study design

#### 6.8.1. Dose range finding test

In order to select the appropriate dose levels for the *in vitro* micronucleus test cytotoxicity data was obtained in a dose range finding test. Betawell L-Arabinose was tested in the absence and presence of S9-mix.

Lymphocytes (0.4 ml blood of a healthy donor was added to 5 ml or 4.8 ml culture medium, without and with metabolic activation respectively and 0.1 ml (9 mg/ml) Phytohaemagglutinin) were cultured for  $46 \pm 2$  hours and thereafter exposed to selected doses of Betawell L-Arabinose for 3 hours and 24 hours in the absence of S9-mix or for 3 hours in the presence of S9-mix. Cytochalasine B (Sigma) was added to the cells simultaneously with the test item at the 24 hours exposure time. A vehicle control was included at each exposure time.

The highest tested concentration was the recommended dose of 1501  $\mu$ g/ml (= 0.01 M).

After 3 hours exposure to Betawell L-Arabinose in the absence or presence of S9-mix, the cells were separated from the exposure medium by centrifugation (5 min, 365 g). The supernatant was removed and cells were rinsed with 5 ml HBSS. After a second centrifugation step, HBSS was removed and cells were resuspended in 5 ml culture medium with Cytochalasine B (5  $\mu$ g/ml) and incubated for another 24 hours (1.5 times normal cell cycle). The cells that were exposed for 24 hours in the absence of S9-mix were not rinsed after exposure but were fixed immediately.

Cytotoxicity of Betawell L-Arabinose in the lymphocyte cultures was determined using the cytokinesis-block proliferation index (CBPI index).

Based on the results of the dose range finding test an appropriate range of dose levels was chosen for the cytogenetic assays considering the highest dose level was the recommended 0.01 M.

#### 6.8.2. First cytogenetic assay

Lymphocytes were cultured for  $46 \pm 2$  hours and thereafter exposed in duplicate to selected doses of Betawell L-Arabinose for 3 hours in the absence and presence of S9-mix. After 3 hours exposure, the cells were separated from the exposure medium by centrifugation (5 min, 365 g). The supernatant was removed and the cells were rinsed once with 5 ml HBSS. After a second centrifugation step, HBSS was removed and cells were resuspended in 5 ml culture medium with Cytochalasin B (5  $\mu$ g/ml) and incubated for another 24 hours. Appropriate vehicle and positive controls were included in the first cytogenetic assay.

# 6.8.3. Second cytogenetic assay

To confirm the results of the first cytogenetic assay a second cytogenetic assay was performed with an extended exposure time of the cells in the absence of S9-mix.

Lymphocytes were cultured for  $46 \pm 2$  hours and thereafter exposed in duplicate to selected doses of Betawell L-Arabinose with cytochalasin B (5  $\mu$ g/ml) for 24 hours in the absence of S9-mix. Appropriate vehicle and positive controls were included in the second cytogenetic assay.

#### 6.8.4. Preparation of slides

To harvest the cells, cell cultures were centrifuged (5 min, 365 g) and the supernatant was removed. Cells in the remaining cell pellet were resuspended in 1% Pluronic F68 (Applichem, Darmstadt, Germany). After centrifugation (5 min, 250 g), the cells in the remaining pellet were swollen by hypotonic 0.56% (w/v) potassium chloride (Merck) solution. Immediately after, ethanol (Merck): acetic acid (Merck) fixative (3:1 v/v) was added. Cells were collected by centrifugation (5 min, 250 g) and cells in the pellet were fixated carefully with 3 changes of ethanol: acetic acid fixative (3:1 v/v).

Fixed cells were dropped onto cleaned slides, which were immersed in a 1:1 mixture of 96% (v/v) ethanol (Merck)/ether (Merck) and cleaned with a tissue. The slides were marked with the WIL Research Europe study identification number and group number. At least two slides were prepared per culture. Slides were allowed to dry and thereafter stained for 10 - 30 min with 5% (v/v) Giemsa (Merck) solution in Sörensenbuffer pH 6.8. Thereafter slides were rinsed in water and allowed to dry. The dry slides were automatically embedded in a 1:10 mixture of xylene (Klinipath, Duiven, The Netherlands)/pertex (Histolab, Gothenburg, Sweden) and mounted with a coverslip in an automated coverslipper (Leica Microsystems B.V., Rijswijk, The Netherlands).

# 6.8.5. Cytotoxicity assessment

A minimum of 500 cells per culture was counted, scoring cells with one, two or more nuclei (multinucleated cells). The cytostasis / cytotoxicity was determined by calculating the Cytokinesis-Block Proliferation Index (CBPI).

 $Cytostasis = 100-100{(CBPI_t - 1)/(CBPI_c - 1)}$ 

- t = test item or control treatment culture
- c = vehicle control culture

Three analysable concentrations were scored for micronuclei. The number of micronuclei per cell was not recorded. Since Betawell L-Arabinose was not cytotoxic, the highest concentration analysed was the recommended dose of 0.01 M.

## 6.8.6. Cytogenetic assessment/scoring of micronuclei

To prevent bias, all slides were randomly coded before examination of micronuclei and scored. An adhesive label with WIL Research Europe study identification number and code was stuck over the marked slide. At least 1000 (with a maximum deviation of 5%) binucleated cells per culture were examined by light microscopy for micronuclei. In addition, at least 1000 (with a maximum deviation of 5%) mononucleated cells per culture were scored for micronuclei separately. Since the lowest concentration of MMC-C and CP resulted in a positive response the highest concentration was not examined for the presence of micronuclei. Due to cytotoxicity the number of examined bi- or mononucleated cells in the positive control groups might be <1000. However, when an expected statistical significant increase is observed, this has no effect on the study integrity.

The following criteria for scoring of binucleated cells were used (1 - 2, 6):

- Main nuclei that were separate and of approximately equal size.
- Main nuclei that touch and even overlap as long as nuclear boundaries are able to be distinguished.
- Main nuclei that were linked by nucleoplasmic bridges.

The following cells were not scored:

- Trinucleated, quadranucleated, or multinucleated cells.
- Cells where main nuclei were undergoing apoptosis (because micronuclei may be gone already or may be caused by apoptotic process).

The following criteria for scoring micronuclei were adapted from Fenech, 1996 (1):

- The diameter of micronuclei should be less than one-third of the main nucleus.
- Micronuclei should be separate from or marginally overlap with the main nucleus as long as there is clear identification of the nuclear boundary.
- Micronuclei should have similar staining as the main nucleus.

# 6.9. Interpretation

#### 6.9.1. Acceptability of the assay

An in vitro micronucleus test is considered acceptable if it meets the following criteria:

- a) The concurrent negative control data are considered acceptable when they are within the 95% control limits of the distribution of the historical negative control database.
- b) The concurrent positive controls should induce responses that are compatible with those generated in the historical positive control database.
- c) The positive control item colchicine induces a statistically significant increase in the number of mononucleated cells with micronuclei and the positive control items MMC-C and CP induces a statistically significant increase in the number of binucleated cells with micronuclei. The positive control data will be analysed by the Chi-square test (one-sided, p < 0.05).</p>

# 6.9.2. Data evaluation and statistical procedures

GraphPad PRISM version 4.03 was used for statistical analysis of the data.

A test item is considered positive (clastogenic or aneugenic) in the *in vitro* micronucleus test if all of the following criteria are met:

- a) At least one of the test concentrations exhibits a statistically significant (Chi-square test, one-sided, p < 0.05) increase compared with the concurrent negative control.
- b) Any of the results are outside the 95% control limits of the historical control data range.

A test item is considered negative (not clastogenic or aneugenic) in the in vitro micronucleus test if:

- a) None of the test concentrations exhibits a statistically significant (Chi-square test, one-sided, p < 0.05) increase compared with the concurrent negative control.
- b) All results are inside the 95% control limits of the negative historical control data range.

#### 6.10. List of deviations

#### 6.10.1. List of study plan deviations

There were no deviations from the study plan.

#### 6.10.2. List of standard operating procedures deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

#### 7. ELECTRONIC SYSTEMS FOR DATA ACQUISITION

The following electronic systems were used for data acquisition:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA): temperature and humidity.

#### 8. RESULTS

#### 8.1. Dose range finding test

A concentration of 1501  $\mu$ g/ml (= 0.01 M) showed no precipitation in the culture medium and was used as the highest concentration of Betawell L-Arabinose.

The pH and osmolarity of a concentration of 1501  $\mu$ g/ml were 7.45 and 310 mOsm/kg respectively (compared to 7.34 and 297 mOsm/kg in culture medium).

In the dose range finding test blood cultures were treated with 17, 52, 164, 512 and 1501  $\mu$ g Betawell L-Arabinose/ml culture medium and exposed for 3 and 24 hours in the absence of S9-mix and for 3 hours in the presence of S9-mix.

Table 1 shows the cytokinesis-block proliferation index of cultures treated with various Betawell L-Arabinose concentrations or with the negative control item.

#### 8.2. First cytogenetic assay

Based on the results of the dose range finding test the following dose levels were selected for the cytogenetic assay:

Without & With S9-mix: 171, 512 and 1501  $\mu$ g/ml culture medium (3 hours exposure time, 27 hours harvest time).

Table 2 shows the cytokinesis-block proliferation index of cultures treated with various Betawell L-Arabinose concentrations or with the positive or negative control items.

All dose levels were selected for scoring of micronuclei.

Both in the absence and presence of S9-mix, Betawell L-Arabinose did not induce a statistically significant or biologically relevant increase in the number of mono- and binucleated cells with micronuclei (APPENDIX 1, Table 3).

#### 8.3. Second cytogenetic assay

To obtain more information about the possible clastogenicity and aneugenicity of Betawell L-Arabinose, a second cytogenetic assay was performed in which human lymphocytes were exposed for 24 hours in the absence of S9-mix. The following dose levels were selected for the second cytogenetic assay:

Without S9-mix : 164, 512 and 1501 μg Betawell L-Arabinose/ml culture medium (24 hours exposure time, 24 hours harvest time).

Table 4 shows the cytokinesis-block proliferation index of cultures treated with various Betawell L-Arabinose concentrations or with the positive or negative control items.

All dose levels were selected for the scoring of micronuclei.

Betawell L-Arabinose did not induce a statistically significant or biologically relevant increase in the number of mono- and binucleated cells with micronuclei (APPENDIX 1, Table 5).

# 8.4. Formulation analysis

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%). In the vehicle, no test tem was detected. Stock solutions at the entire range were stable when stored at room temperature under normal laboratory light conditions for at least 4 hours.

The formulation analysis report is presented in APPENDIX 6.

#### 8.5. Evaluation of the results

The ability of Betawell L-Arabinose to induce micronuclei in human peripheral lymphocytes was investigated in two independent experiments. The highest concentration analysed was selected based on the recommended dose of 0.01 M.

The cytokinesis-block proliferation indices of cultures treated with various Betawell L-Arabinose concentrations or with the negative control items are presented in Table 1, Table 2 and Table 4 (APPENDIX 1). The scores for the number of mono- and binucleated cells with micronuclei are presented in Table 3 and Table 5 (APPENDIX 1). Duplicate cultures are indicated by A and B. The individual data are described in Table 6 and Table 7 (APPENDIX 2). APPENDIX 3 presents the statistical evaluations of the test results.

The number of mono- and binucleated cells with micronuclei found in the solvent control was within the 95% control limits of the distribution of the historical negative control database (Table 3 and Table 5; APPENDIX 4).

The positive control chemicals, mitomycin C and cyclophosphamide both produced a statistically significant increase in the number of binucleated cells with micronuclei. The positive control chemical colchicine produced a statistically significant increase in the number of mononucleated cells with micronuclei. Furthermore, colchicine also showed a statistically significant increase in the number of binucleated cells with micronuclei, in the second cytogenetic assay. In addition, the number of monoand binucleated cells with micronuclei found in the positive control cultures was within the 95% control limits of the distribution of the historical positive control database. Although in the absence of S9-mix the response of MMC-C was just above the upper control limits, these limits are 95% control limits and a slightly higher response is within the expected response ranges. It was therefore concluded that the test conditions were adequate and that the metabolic activation system (S9-mix) functioned properly.

Betawell L-Arabinose did not induce a statistically significant or biologically relevant increase in the number of mono- and binucleated cells with micronuclei in the absence and presence of S9-mix, in either of the two experiments.

#### 9. CONCLUSION

Finally, it is concluded that this test is valid and that Betawell L-Arabinose is not clastogenic or aneugenic in human lymphocytes under the experimental conditions described in this report.

#### 10. REFERENCES

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#### **APPENDIX 1 TABLES**

Table 1 Cytokinesis-block proliferation index of human lymphocyte cultures treated with Betawell L-Arabinose in the dose range finding test

Without metabolic activation (-S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration | Number o | Number of cells withnuclei |           |      |            |  |
|---------------|----------|----------------------------|-----------|------|------------|--|
| μg/ml         | 1        | 2                          | 3 or more | CBPI | cytostasis |  |
| 0             | 212      | 267                        | 21        | 1.62 | 0          |  |
| 17            | 208      | 270                        | 22        | 1.63 | -2         |  |
| 52            | 243      | 228                        | 37        | 1.59 | 4          |  |
| 164           | 210      | 271                        | 19        | 1.62 | 0          |  |
| 512           | 222      | 256                        | 22        | 1.60 | 3          |  |
| 1501          | 221      | 259                        | 30        | 1.63 | -1         |  |

# Without metabolic activation (-S9-mix)

24 hours exposure time, 24 hours harvest time

| Concentration | Number o | Number of cells withnuclei |           |      |            |  |
|---------------|----------|----------------------------|-----------|------|------------|--|
| μg/ml         | 1        | 2                          | 3 or more | CBPI | cytostasis |  |
| 0             | 190      | 254                        | 56        | 1.73 | 0          |  |
| 17            | 189      | 248                        | 63        | 1.75 | -2         |  |
| 52            | 204      | 244                        | 52        | 1.70 | 5          |  |
| 164           | 177      | 260                        | 63        | 1.77 | -5         |  |
| 512           | 193      | 258                        | 49        | 1.71 | 3          |  |
| 1501          | 203      | 239                        | 58        | 1.71 | 3          |  |

# With metabolic activation (+S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration | Number o | Number of cells withnuclei |           |      |            |  |  |
|---------------|----------|----------------------------|-----------|------|------------|--|--|
| μg/ml         | 1        | 2                          | 3 or more | CBPI | cytostasis |  |  |
| 0             | 210      | 267                        | 23        | 1.63 | 0          |  |  |
| 17            | 218      | 257                        | 25        | 1.61 | 2          |  |  |
| 52            | 202      | 276                        | 22        | 1.64 | -2         |  |  |
| 164           | 201      | 274                        | 25        | 1.65 | -4         |  |  |
| 512           | 197      | 276                        | 27        | 1.66 | -5         |  |  |
| 1501          | 207      | 263                        | 30        | 1.65 | -3         |  |  |

Note: All calculations were performed without rounding off.

# APPENDIX 1 TABLES - continued -

Table 2 Cytokinesis-block proliferation index of human lymphocytes cultures treated with Betawell L-Arabinose in the first cytogenetic assay

Without metabolic activation (-S9-mix)

3 hours exposure time, 27 hours harvest time

|                     |             |           | %          |
|---------------------|-------------|-----------|------------|
| Concentration µg/ml | CBPI        | Mean CBPI | cytostasis |
| 0                   | 1.58 - 1.60 | 1.59      | 0          |
| 171                 | 1.51 - 1.53 | 1.52      | 11         |
| 512                 | 1.45 - 1.51 | 1.48      | 18         |
| 1501                | 1.46 - 1.46 | 1.46      | 22         |
| 0.25 MMC-C          | 1.38 - 1.41 | 1.40      | 33         |
| 0.38 MMC-C          | 1.26 - 1.29 | 1.28      | 53         |
| 0.1 Colchicine      | 1.04 - 1.07 | 1.06      | 91         |

# With metabolic activation (+S9-mix)

3 hours exposure time, 27 hours harvest time

|                     |             |           | %          |
|---------------------|-------------|-----------|------------|
| Concentration µg/ml | CBPI        | Mean CBPI | cytostasis |
| 0                   | 1.58 - 1.62 | 1.60      | 0          |
| 171                 | 1.56 - 1.57 | 1.56      | 6          |
| 512                 | 1.46 - 1.50 | 1.48      | 20         |
| 1501                | 1.46 - 1.49 | 1.48      | 21         |
| 15 CP               | 1.16 - 1.20 | 1.18      | 70         |
| 17.5 CP             | 1.08 - 1.14 | 1.11      | 82         |

Note: All calculations were performed without rounding off.

#### **APPENDIX 1** TABLES - continued -

Table 3 Number of mononucleated or binucleated cells with micronuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the first cytogenetic

# Without metabolic activation (-S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration | Cytostasis | Number of mononucleated cells with micronuclei 1) |      |       | Number of binucleated cells with micronuclei 1) |      |       |
|---------------|------------|---|------|-------|---|------|-------|
| (µg/ml)       | (%)        | 1000  | 1000 | 2000  | 1000  | 1000 | 2000  |
|               |            | Α   | В    | A+B   | Α   | В    | A+B   |
| 0             | 0          | 1   | 1    | 2     | 3   | 3    | 6     |
| 171           | 11         | 0   | 2    | 2     | 2   | 4    | 6     |
| 512           | 18         | 0   | 0    | 0     | 1   | 3    | 4     |
| 1501          | 22         | 0   | 1    | 1     | 2   | 2    | 4     |
| 0.25 MMC-C    | 33         | 2   | 2    | 4     | 21  | 23   | 44*** |
| 0.1 Colch     | 91         | 24  | 32   | 56*** | 9   | 4    | 13    |

# With metabolic activation (+S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration Cytostasis | Number of mononucleated cells with micronuclei 1) |      |      | Number of binucleated cells with micronuclei 1) |      |      |       |
|--------------------------|---|------|------|---|------|------|-------|
| (µg/ml)                  | (%)   | 1000 | 1000 | 2000  | 1000 | 1000 | 2000  |
|                          |   | Α    | В    | A+B   | Α    | В    | A+B   |
| 0                        | 0   | 0    | 0    | 0   | 1    | 3    | 4     |
| 171                      | 6   | 1    | 0    | 1   | 3    | 1    | 4     |
| 512                      | 20  | 1    | 0    | 1   | 3    | 2    | 5     |
| 1501                     | 21  | 1    | 0    | 1   | 2    | 2    | 4     |
| 15 CP                    | 70  | 0    | 2    | 2   | 19   | 15   | 34*** |

Significantly different from control group (Chi-square test), \* P < 0.05, \*\* P < 0.01 or \*\*\* P < 0.001.

<sup>\*)</sup> 1) 1000 bi- and mononucleated cells were scored for the presence of micronuclei. Duplicate cultures are indicated by A and B.

# APPENDIX 1 TABLES - continued -

Table 4 Cytokinesis-block proliferation index of human lymphocyte cultures treated with Betawell L-Arabinose in the second cytogenetic assay

Without metabolic activation (-S9-mix)

24 hours exposure time, 24 hours harvest time

|                     |             |           | %          |
|---------------------|-------------|-----------|------------|
| Concentration µg/ml | CBPI        | Mean CBPI | Cytostasis |
| 0                   | 1.64 - 1.69 | 1.66      | 0          |
| 164                 | 1.64 - 1.66 | 1.65      | 1          |
| 512                 | 1.66 - 1.67 | 1.67      | -1         |
| 1501                | 1.64 - 1.71 | 1.68      | -2         |
| 0.15 MMC-C          | 1.38 - 1.46 | 1.42      | 37         |
| 0.23 MMC-C          | 1.29 - 1.33 | 1.31      | 53         |
| 0.05 Colchicine     | 1.01 - 1.04 | 1.03      | 96         |

Note: All calculations were performed without rounding off.

#### **APPENDIX 1** TABLES - continued -

Table 5 Number of mononucleated or binucleated cells with micronuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the second

cytogenetic assay

Without metabolic activation (-S9-mix)

24 hours exposure time, 24 hours harvest time

| Concentration | Cytostasis |      | f mononucle<br>h micronucle |        | Number of binucleated cells with micronuclei 1) |                |       |
|---------------|------------|------|-----------------------------|--------|---|----------------|-------|
| (µg/ml)       | (%)        | 1000 | 1000                        | 2000   | 1000  | 1000           | 2000  |
|               |            | Α    | В                           | A+B    | Α   | В              | A+B   |
| 0             | 0          | 0    | 2                           | 2      | 3   | 7              | 10    |
| 164           | 1          | 1    | 0                           | 1      | 4   | 6              | 10    |
| 512           | -1         | 0    | 2                           | 2      | 6   | 7              | 13    |
| 1501          | -2         | 2    | 0                           | 2      | 8   | 2              | 10    |
| 0.15 MMC-C    | 37         | 4    | 1                           | 5      | 25  | 35             | 60*** |
| 0.05 Colch    | 96         | 39   | 62                          | 101*** | 3 <sup>2</sup>                                  | 4 <sup>2</sup> | 7***  |

Significantly different from control group (Chi-square test), \* P < 0.05, \*\* P < 0.01 or \*\*\* P < 0.001. 1000 bi- and mononucleated cells were scored for the presence of micronuclei.

<sup>\*)</sup> 1) Duplicate cultures are indicated by A and B.

<sup>2)</sup> 72 and 57 binucleated cells, respectively were counted for the presence of micronuclei.

# **APPENDIX 2 INDIVIDUAL DATA**

Table 6 Scoring of cells with one, two or more nuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the first cytogenetic assay

# Without metabolic activation (-S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration  |         | Number o | of cells with | nuclei    |      |
|----------------|---------|----------|---------------|-----------|------|
| μg/ml          | Culture | 1        | 2             | 3 or more | CBPI |
|                | Α       | 224      | 266           | 12        | 1.58 |
| 0              | В       | 211      | 280           | 11        | 1.60 |
|                | Α       | 246      | 241           | 13        | 1.53 |
| 171            | В       | 256      | 231           | 13        | 1.51 |
|                | Α       | 257      | 231           | 12        | 1.51 |
| 512            | В       | 280      | 214           | 6         | 1.45 |
|                | Α       | 291      | 213           | 11        | 1.46 |
| 1501           | В       | 279      | 213           | 8         | 1.46 |
|                | Α       | 309      | 190           | 1         | 1.38 |
| 0.25 MMC-C     | В       | 298      | 206           | 0         | 1.41 |
|                | Α       | 353      | 147           | 0         | 1.29 |
| 0.38 MMC-C     | В       | 372      | 128           | 0         | 1.26 |
|                | Α       | 465      | 35            | 0         | 1.07 |
| 0.1 Colchicine | В       | 479      | 21            | 0         | 1.04 |

# With metabolic activation (+S9-mix)

3 hours exposure time, 27 hours harvest time

| Concentration |         | Number of cells withnuclei |     |           |      |  |
|---------------|---------|----------------------------|-----|-----------|------|--|
| μg/ml         | Culture | 1                          | 2   | 3 or more | CBPI |  |
|               | Α       | 212                        | 266 | 22        | 1.62 |  |
| 0             | В       | 228                        | 253 | 19        | 1.58 |  |
|               | Α       | 238                        | 244 | 18        | 1.56 |  |
| 171           | В       | 235                        | 247 | 18        | 1.57 |  |
|               | Α       | 291                        | 217 | 12        | 1.46 |  |
| 512           | В       | 264                        | 224 | 12        | 1.50 |  |
|               | Α       | 265                        | 227 | 8         | 1.49 |  |
| 1501          | В       | 285                        | 198 | 17        | 1.46 |  |
|               | Α       | 402                        | 98  | 0         | 1.20 |  |
| 15 CP         | В       | 418                        | 82  | 0         | 1.16 |  |
|               | Α       | 431                        | 69  | 0         | 1.14 |  |
| 17.5 CP       | В       | 466                        | 42  | 0         | 1.08 |  |

# APPENDIX 2 INDIVIDUAL DATA - continued -

Table 7 Scoring of cells with one, two or more nuclei of human lymphocyte cultures treated with Betawell L-Arabinose in the second cytogenetic assay

Without metabolic activation (-S9-mix)
24 hours exposure time, 24 hours harvest time

|                 | 1       |           |               |           | 1    |
|-----------------|---------|-----------|---------------|-----------|------|
| Concentration   |         | Number of | of cells with | nuclei    |      |
| μg/ml           | Culture | 1         | 2             | 3 or more | CBPI |
|                 | Α       | 201       | 255           | 44        | 1.69 |
| 0               | В       | 212       | 257           | 31        | 1.64 |
|                 | Α       | 210       | 248           | 42        | 1.66 |
| 164             | В       | 211       | 257           | 32        | 1.64 |
|                 | Α       | 203       | 257           | 40        | 1.67 |
| 512             | В       | 193       | 284           | 23        | 1.66 |
|                 | Α       | 184       | 275           | 41        | 1.71 |
| 1501            | В       | 219       | 242           | 39        | 1.64 |
|                 | Α       | 314       | 183           | 3         | 1.38 |
| 0.15 MMC-C      | В       | 272       | 227           | 1         | 1.46 |
|                 | Α       | 338       | 159           | 3         | 1.33 |
| 0.23 MMC-C      | В       | 356       | 143           | 1         | 1.29 |
|                 | Α       | 482       | 18            | 0         | 1.04 |
| 0.05 Colchicine | В       | 493       | 7             | 0         | 1.01 |

# APPENDIX 3 STATISTICAL EVALUATION OF THE TEST RESULTS

Chi-square Test

TOTAL NUMBER OF CELLS WITH MICRONUCLEI; TREATMENT/CONTROL COMPARISON, (MONONUCLEATED/BINUCLEATED CELLS)  $^{1)}$ .

| EXPOSURE<br>DOSE (μg/ml)   | S9-MIX                   | NUCLEATED        | P-VALUE<br>one-sided          | DECISION AT 95%<br>CONFIDENCE LEVEL       |  |  |  |
|--|--------------------------|------------------|-------------------------------|---|--|--|--|
| First cytogenetic assay  |                          |                  |                               |   |  |  |  |
| 3 hours exposure tim<br>Positive controls<br>MMC-C (0.25)<br>Colch (0.1)<br>CP (15)        | <u>e</u><br>-<br>-<br>+  | bi<br>mono<br>bi | ≤0.0001<br>≤0.0001<br>≤0.0001 | significant<br>significant<br>significant |  |  |  |
| Second cytogenetic   | assay                    |                  |                               |   |  |  |  |
| 24 hours exposure tin<br>Positive controls<br>MMC-C (0.15)<br>Colch (0.05)<br>Colch (0.05) | <u>ne</u><br>-<br>-<br>- | bi<br>mono<br>bi | ≤0.0001<br>≤0.0001<br>≤0.0001 | significant<br>significant<br>significant |  |  |  |

<sup>1)</sup> Only statistically significant results are presented.

APPENDIX 4 HISTORICAL CONTROL DATA FOR *IN VITRO* MICRONUCLEUS STUDIES OF THE SOLVENT CONTROL

|  | М               | ononucleated                     |       | В                  | inucleated      |                  |
|--|-----------------|----------------------------------|-------|--------------------|-----------------|------------------|
|  | + S9-mix        | - S9-mix                         |       | + S9-mix - S9-mix  |                 | 9-mix            |
|  | 3 hour exposure | 3 hour 24 hour exposure exposure |       | 3 hour<br>exposure | 3 hour exposure | 24 hour exposure |
| Mean number of micronucleated cells (per 1000 cells) | 0.85            | 0.93                             | 0.85  | 3.26               | 3.80            | 4.06             |
| SD   | 0.88            | 0.97                             | 1.13  | 2.17               | 2.63            | 2.47             |
| n  | 54              | 56                               | 55    | 54                 | 56              | 55               |
| Upper control limit<br>(95% control<br>limits)       | 3.36            | 3.35                             | 3.17  | 8.58               | 10.53           | 10.85            |
| Lower control limit<br>(95% control<br>limits)       | -1.66           | -1.49                            | -1.46 | -2.06              | -2.92           | -2.74            |

SD = Standard deviation n = Number of observations

Distribution historical negative control data from experiments performed between January 2012 and June 2015.

APPENDIX 5 HISTORICAL CONTROL DATA FOR *IN VITRO* MICRONUCLEUS STUDIES OF THE POSITIVE CONTROL SUBSTANCES

|  | Monon                            | ucleated | Binucleated     |                 |                     |
|--|----------------------------------|----------|-----------------|-----------------|---------------------|
|  | - S9-mix                         |          | + S9-mix        | - S9            | 9-mix               |
|  | 3 hour 24 hour exposure exposure |          | 3 hour exposure | 3 hour exposure | 24 hour<br>exposure |
| Mean number of micronucleated cells (per 1000 cells) | 46.2                             | 52.1     | 29.3            | 30.4            | 30.0                |
| SD   | 28.1                             | 25.0     | 14.9            | 16.4            | 10.1                |
| n  | 54                               | 56       | 58              | 60              | 60                  |
| Upper control limit (95% control limits)             | 93.1                             | 92.7     | 57.8            | 56.48           | 54.7                |
| Lower control limit (95% control limits)             | -0.58                            | 11.5     | 0.70            | 4.28            | 5.31                |

SD = Standard deviation n = Number of observations

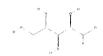
Distribution historical positive control data from experiments performed between January 2012 and June 2015.

#### APPENDIX 6 CERTIFICATE OF ANALYSIS

Certificate of analysis Specification date: 15.06.2015

# Certificate of analysis

: Betawell<sup>®</sup> Ara-P Product name



| Component                            | Value           |
|--------------------------------------|-----------------|
| Arabinose                            | 99.9 wt%        |
| Glucose                              | <0.01 wt%       |
| Mannose                              | <0.01 wt%       |
| Rhamnose                             | 0.01 wt%        |
| Xylose                               | 0.03 wt%        |
| Fucose                               | <0.01 wt%       |
| Galactose                            | 0.04 wt%        |
| Galacturonic acid                    | <0.01 wt%       |
| Beet pectin derived oligosaccharides | 0.02 wt%        |
| Water content                        | 0.1 wt%         |
| Solubility ( 10% in water)           | < 20 Hazen      |
| Clarity                              | 0.85 - 0.90 FNU |

CAS-Nr.

: 5328-37-0 (for L-Arabinose)

Origin

: Sugar beet : C32-1

Batch number Batch size

: total 40 kg.

Product number

: 7000 (Cosun internal number)

Appearance (form)

Appearance (color) : Whitish to white

Smell

: Powder

: Neutral

Infrared spectrum

: Conforms to structure

Minimum purity

: > 99 wt% of Dry Solids (L-arabinose, method: HPLC (C18-aq), PDA)

Functionality

: food ingredient (USA, Asia), flavor ingredient (for EU see Regulation 872/2012),

cosmetic ingredient.

Storage conditions

Shelf life

: Dry, keep out of sunshine.

: The expiry date of this product is 24 months after the production date indicated

on this certificate of analysis when properly stored and maintained.

Production date

: 15.05.2015

Betawell Ara-P, powder of arabinose page 1 of 2

#### APPENDIX 6 - continued -



Certificate of analysis Specification date: 15.06.2015

#### Additional specifications:

| Test                          | Method              | Maximum      |
|-------------------------------|---------------------|--------------|
| Total Viable Count / g (30°C) | ISO 4833:2003       | 1000 CFU / g |
| Yeasts / g                    | ISO 7954:1987       | 20 CFU / g   |
| Moulds / g                    | ISO 7954:1987       | 20 CFU / g   |
| Staph. aureus / g             | ISO 6888-3 :2003    | Absent       |
| Salmonella / 50g              | ISO 6579:2002       | Absent       |
| E. coli / g                   | ISO 16649-2:2001    | Absent       |
| Bacillus cereus / g           | ISO 7932:2004       | 100 CFU / g  |
| Coliforms / g                 | ISO 4832:2006       | Absent       |
| Enterobacteria / g            | ISO 21528-1:2004    | Absent       |
| Listeria / g                  | ISO 11290-1:1997    | Absent       |
| Clostridium perfringens/g     | ISO 7937:2004       | Absent       |
| Faecal Streps/g               | External laboratory | Absent       |
| Aflatoxins                    | External laboratory | < 0.1 µg/kg  |

| Metals  | Value (ppm) |
|---------|-------------|
| Arsenic | <0.01       |
| Lead    | <0.01       |
| Mercury | <0.0001     |
| Cadmium | <0.005      |
| Tin     | <0.01       |
| Copper  | <0.01       |
| Silver  | <0.05       |
| Bismuth | <0.2        |

This powder is produced from sugar beet grown in the Netherlands and Germany. This material has been checked for compliance with international pesticide tolerance legislation, does not contain and/or has not been in contact with genetically modified organisms, does not contain any ingredient with an animal origin and does not contain any known allergen.

Cosun Biobased Products B.V.
P.O. Box 3411, 4800 MG Breda, The Netherlands
Tel +31 76 530 33 33, Fax +31 76 530 32 06

The information and recommendations in this leaflet are to the best of our knowledge, information and belief accurate at the date of publication. Nothing herein is to be construed as warranty expressed or implied. In all cases it is the responsibility of users to determine the applicability of such information or the suitability of any products for their own particular purpose.

Betawell Ara-P, powder of arabinose page 2 of 2

# APPENDIX 7 ANALYTICAL REPORT

# DETERMINATION OF THE CONCENTRATIONS

**ANALYTICAL REPORT** 

<u>Author</u>

J. Ciric, PhD.

# 1. CONTENTS

| 1.  | CONTENTS                                     | 30 |
|-----|--|----|
| 2.  | REPORT APPROVAL                              | 31 |
| 3.  | SUMMARY                                      |    |
| 4.  | INTRODUCTION                                 |    |
|     | 4.1. Study schedule analytical phase         |    |
|     | 4.2. Purpose of the study                    |    |
| 5.  | MATERIALS AND METHODS                        |    |
|     | 5.1. Reagents                                |    |
|     | 5.2. Study samples                           |    |
|     | 5.3. Analytical method                       |    |
|     | 5.3.1. Analytical conditions                 |    |
|     | 5.3.2. Preparation of solutions              |    |
|     | 5.3.3. Sample injections                     |    |
|     | 5.4. Electronic systems for data acquisition |    |
|     | 5.5. Formulas                                |    |
|     | 5.6. Specifications                          |    |
| 6.  | RESULTS                                      |    |
|     | 6.1. Calibration curves                      |    |
|     | 6.2. Samples                                 |    |
|     | 6.2.1. QC samples                            |    |
|     | 6.2.2. Study samples                         |    |
| TAF | BLES   |    |
| .,  |  |    |
| Tah | ole 1 QC samples                             | 37 |
|     | ble 2 Accuracy test                          |    |
|     | ole 3 Stability test                         |    |
|     |  |    |

# **REPORT APPROVAL**

WIL Research Europe B.V.

(b) (6)

Signature

Name:

J. Ciric, PhD.

Title: **Principal Scientist Analytical Chemistry** 

16 February 2016 Date:

# 3. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation and stability of the test item in stock solutions used for spiking in the cytogenetic assay.

#### Accuracy of preparation

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

In the vehicle, no test tem was detected.

#### Stability

Stock solutions at the entire range were stable when stored at room temperature under normal laboratory light conditions for at least 4 hours.

#### 4. INTRODUCTION

#### 4.1. Study schedule analytical phase

Experimental starting date : 25 November 2015 Experimental completion date : 25 November 2015

#### 4.2. Purpose of the study

The purpose of the analytical phase was to determine the accuracy of preparation and stability of the test item in formulations.

#### 5. MATERIALS AND METHODS

#### 5.1. Reagents

Water Tap water purified by a Milli-Q water purification system

(Millipore, Bedford, MA, USA)

Acetonitrile Biosolve, Valkenswaard, The Netherlands

All reagents were of analytical grade, unless specified otherwise.

#### 5.2. Study samples

Accuracy and stability were determined for stock solutions used for spiking in cytogenetic assay.

Samples of 500  $\mu$ l were taken from the stock solutions and transferred into glass vials or 5 or 10 ml volumetric flasks. The samples were taken at random positions. The samples in glass vials were analysed. The volumetric flasks were filled up to the mark with water. The solutions were further diluted to obtain an end solution of water and concentrations within the calibration range.

# 5.3. Analytical method

#### 5.3.1. Analytical conditions

Analysis was based on the analytical method validated for the test item in project 509990.

Analytical conditions:

Instrument Acquity UPLC system (Waters, Milford, MA, USA)

Detector Acquity ELSD system (Waters)

Column Asahipak NH2P-50 4E, 250 mm  $\times$  4.6 mm i.d., dp = 5  $\mu$ m

(Shodex, New York, NY, USA)

Column temperature 40°C Injection volume 10 µl

Mobile phase 20/80 (v/v) acetonitrile/water

Flow 1 ml/min

ELSD detection

Temperature 40°C
Nebuliser gas nitrogen
Gas 25.0 psi
Nebulizer Cooling
Gain 500

# 5.3.2. Preparation of solutions

#### Stock solutions

Stock solutions of the test item were prepared in water at a concentration of 2000 mg/l.

# Calibration solutions

Calibration solutions in the concentration range of 25 – 100 mg/l were prepared from two stock solutions. The end solution of the calibration solutions was water.

#### QC samples

QC samples of 5 ml were prepared with the test item in water at a target concentration of 16.4 and 150 mg/ml. Samples of 500 µl were taken and treated similarly as the study samples (see paragraph 5.2 'Study samples').

# 5.3.3. Sample injections

Calibration solutions were injected in duplicate. Test samples and QC samples were analysed by single injection.

# 5.4. Electronic systems for data acquisition

System control, data acquisition and data processing were performed using the following program:

- Empower 3 database version 7.21 (Waters, Milford, MA, USA).

Temperature, relative humidity and/or atmospheric pressure during sample storage and/or performance of the studies was monitored continuously using the following program:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA).

#### 5.5. Formulas

Response (R) Peak area test item [units]

Calibration curve  $R = a C_N^2 + b C_N + c$ 

where:

a = quadratic regression factor [units  $\times$  (l/mg)<sup>2</sup>] b = linear regression factor [units  $\times$  l/mg]

c = intercept [units]

Analysed concentration (C<sub>A</sub>)  $C_A = \frac{-b + \sqrt{b^2 - 4 \, a \times (c - R)}}{2 \, a} \times \frac{d}{1000} \quad [mg/ml]$ 

where:

d = dilution factor

Accuracy  $\frac{C_A}{C_N} \times 100 \text{ [\%]}$ 

QC samples

where:

 $C_N$  = nominal concentration [mg/ml]

Accuracy  $\frac{C_A}{C_T} \times 100$  [%]

Study samples

where:

 $C_T$  = target concentration [mg/ml]

Relative difference (relative diff.)  $\frac{C_t - C_0}{C_0} \times 100 \quad [\%]$ 

where:

 $C_t$  = mean concentration of stored samples [mg/ml]  $C_0$  = mean concentration of non-stored samples [mg/ml]

#### 5.6. Specifications

Preparation of stock solution was considered acceptable if the mean accuracy was in the range 85 - 115% of the target concentration. Formulations were considered stable if the relative difference between the stored and freshly taken samples was  $\leq 10\%$ .

#### 6. RESULTS

#### 6.1. Calibration curves

A calibration curve was constructed using five concentrations. For each concentration, two responses were used. Quadratic regression analysis was performed using the least squares method with a 1/concentration<sup>2</sup> weighting factor. The coefficient of correlation (r) was > 0.99.

#### 6.2. Samples

#### 6.2.1. QC samples

The results for the QC samples are given in Table 1

The mean accuracies of the QC samples were within the criterion range of 85 - 115%. It demonstrated that the analytical method was adequate for the determination of the test item in the study samples.

# 6.2.2. Study samples

The results for the study samples are given in Table 2 and Table 3

#### Accuracy of preparation

In the vehicle, no test item was detected.

The concentrations analysed in the stock solutions were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

#### Stability

Analysis of the stock solutions after storage yielded a relative difference of  $\leq$  10%. Based on this, the stock solutions were found to be stable during storage at room temperature under normal laboratory light conditions for at least 4 hours.

#### **TABLES**

Table 1 QC samples

| Date of     | Date of     | Target        | Nominal        | Analysed      | Accuracy | Mean     |
|-------------|-------------|---------------|----------------|---------------|----------|----------|
| preparation | analysis    | concentration | concentration  | concentration |          | accuracy |
|             |             | [mg/ml]       | [mg/ml]        | [mg/ml]       | [%]      | [%]      |
| 25-Nov-2015 | 25-Nov-2015 | 16.4          | 16.4<br>16.4   | 15.7<br>15.6  | 96<br>95 | 96       |
| 25-Nov-2015 | 25-Nov-2015 | 150.1         | 150.1<br>150.1 | 143<br>144    | 95<br>96 | 96       |

Table 2 Accuracy test

| Group            | Date of analysis | Sample position | Concentration<br>[mg/ml] |              |              | uracy<br>%] |
|------------------|------------------|-----------------|--------------------------|--------------|--------------|-------------|
|                  |                  |                 | Target                   | Analysed     | Individual   | Mean        |
| Vehicle          | 25-Nov-2015      | Random          | 0<br>0                   | n.d.<br>n.d. | n.a.<br>n.a. | n.a.        |
| Low              | 25-Nov-2015      | Random          | 16.4<br>16.4             | 16.5<br>16.0 | 101<br>97    | 99          |
| Interme<br>diate | 25-Nov-2015      | Random          | 51.2<br>51.2             | 52.4<br>58.2 | 102<br>114   | 108         |
| High             | 25-Nov-2015      | Random          | 150.1<br>150.1           | 152<br>145   | 101<br>97    | 99          |

n.d. Not detected.

Table 3 Stability test

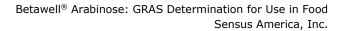
| Group | Date of analysis | Analysed concentration [mg/ml] |                   | Relative diff. |
|-------|------------------|--------------------------------|-------------------|----------------|
|       |                  | t=0 1                          | t=4 hours         | [%]            |
| Low   | 25-Nov-2015      | 16.2                           | 15.7 <sup>2</sup> | -3.1           |
| High  | 25-Nov-2015      | 149                            | 143 <sup>3</sup>  | -4.2           |

Mean of two samples at t=0.

n.a. Not applicable.

Mean of two samples at t=4 hours. Individual results were 15.7 and 15.8 mg/ml.

Mean of two samples at t=4 hours. Individual results were 140 and 145 mg/ml.





APPENDIX C4
DEVELOPMENT OF AN ANALYTICAL METHOD
FOR THE ANALYSIS OF BETAWELL
L-ARABINOSE IN DIET



# **FINAL REPORT**

#### Study Title

# DEVELOPMENT OF AN ANALYTICAL METHOD FOR THE ANALYSIS OF BETAWELL L-ARABINOSE IN DIET

**Study Director** 

J. Ciric, PhD.

**Test Facility** 

WIL Research Europe B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

Sponsor

Cosun Biobased Products B.V.
As part of Royal Cosun
Postbus 3411
4800 MG Breda
Netherlands

**Laboratory Project Identification** 

WIL Research Project 509994 Test item 206781/A

- Page 1 of 12 -

# 1. CONTENTS

| 1.   | CONTENT    | <sup>-</sup> S  | 2  |
|------|------------|---|----|
| 2.   |            | NT OF GLP COMPLIANCE  |    |
| 3.   |            | CILITY QUALITY ASSURANCE STATEMENT  |    |
| 4.   |            | ΥΥ  |    |
| 5.   | INTRODU    | CTION   | 6  |
|      |            | schedule  |    |
|      | 5.2. Purpo | se of the study   | 6  |
|      |            | tion of records and materials   |    |
|      |            | onsible personnel   |    |
| 6.   |            | _\$   |    |
|      |            | tem   |    |
|      |            |   |    |
|      |            | onic systems for data acquisition   |    |
|      |            | deviations  |    |
| 7.   | DEVELOP    | MENT OF AN ANALYTICAL METHOD  | 8  |
|      |            | line  |    |
|      |            | ents  |    |
|      |            | nary of the study   |    |
|      |            | tical method 1  |    |
|      |            | tical method 2  |    |
|      |            | usion   |    |
| FIG  | URES       |   |    |
| Figu | ure 1      | HPLC chromatograms of the 10 mg/l test substance solution [top; injection. id.1353 ] and a 5000 mg/kg QC sample [bottom; injection. id. 1371] | g  |
| Figu | ure 2      | HPLC chromatograms of the 100 mg/l test substance solution [top; injection. id.2101] and blank QC sample [bottom; injection. id. 2145].       |    |
| APF  | PENDICES   |   |    |
| App  | endix 1    | Certificate of analysis   | 11 |

# 2. STATEMENT OF GLP COMPLIANCE

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with the following GLP regulations:

- OECD Principles of Good Laboratory Practice concerning Mutual Acceptance of Data in the Assessment of Chemicals, 26 November 1997 (C(97) 186 Final);
- EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).
- The characterization of the test item supplied by the sponsor was conducted in a ISO 9001 environment.

23 February 2016

The data generated and reported are considered to be valid.

WIL Research Europe B.V.

(b) (6)

Signature

Name:

J. Ciric, PhD.

Title:

Study Director

Date:

Final report

#### 3. TEST FACILITY QUALITY ASSURANCE STATEMENT

WIL Research Europe B.V., 's-Hertogenbosch, The Netherlands

Study title: Development of an analytical method for the analysis of Betawell L-Arabinose in diet.

This report was inspected by the WIL Research Europe Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s).

The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected.

The dates of Quality Assurance inspections are given below

| Project | 509994 |
|---------|--------|
|---------|--------|

| Type of Inspections | Phase/Process  | Start<br>Inspection<br>date                              | End<br>Inspection<br>date                                | Reporting date   |
|---------------------|--|--|--|--|
| Study               | Study Plan<br>Study Plan Amendment 01<br>Study Plan Amendment 02<br>Report                                     | 10-Aug-2015<br>18-Sep-2015<br>25-Jan-2016<br>27-Jan-2016 | 10-Aug-2015<br>18-Sep-2015<br>25-Jan-2016<br>27-Jan-2016 | 10-Aug-2015<br>18-Sep-2015<br>25-Jan-2016<br>27-Jan-2016 |
| Process             | <b>Test Substance Receipt</b> Test Substance Handling  | 09-Nov-2015  | 20-Nov-2015  | 20-Nov-2015  |
|                     | Analytical and physical chemistry Test Substance Handling Exposure Observations/Measurements Specimen Handling | 30-Nov-2015  | 14-Dec-2015  | 17-Dec-2015  |

The facility inspection program is conducted in accordance with Standard Operating Procedure.

The review of the final report was completed on the date of signing this QA statement.

WIL Research Europe B.V.

|            | (b) (6)                       |                              |
|------------|-------------------------------|------------------------------|
| Signature: |                               |                              |
| Name:      | C. Mitchell E<br>Head of Qual | 3.Sc., FRQA<br>ity Assurance |
| Date:      | 22 61 2016                    |                              |

Final report

# 4. SUMMARY

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V..

- Page 5 -

#### 5. INTRODUCTION

#### 5.1. Study schedule

Experimental starting date : 12 October 2015 Experimental completion date : 04 December 2015

#### 5.2. Purpose of the study

The purpose of the study was to develop and to validate an analytical method for the quantitative analysis of Betawell L-Arabinose in diet.

#### 5.3. Retention of records and materials

Records and material pertaining to the study, which include study plan and amendments, raw data, specimens, except perishable specimens, and the final report will be retained in the archives of the test facility for a minimum of 5 years after the finalization of the report. After this period, the sponsor will be contacted to determine how the records and materials should be handled. The test facility will retain information concerning decisions made.

Perishable specimens (e.g. requiring refrigeration or freezing) will be discarded following evaluation in the study without further notice to the study sponsor.

A sample of the test item will be retained until expiry date or applicable retest date. After this period the sample(s) will be destroyed.

# 5.4. Responsible personnel

#### 5.4.1. Test facility

Study Director J. Ciric, PhD.

# 5.4.2. Sponsor Representative

Study Monitor Alex Benschop

Study Monitor Diederick Meyer

#### 6. MATERIALS

#### 6.1. Test item

#### 6.1.1. Test item information

Identification Betawell L-Arabinose

Appearance White powder

Batch C32-1

Purity/Composition See Certificate of Analysis
Test substance storage At room temperature
Stable under storage conditions until 15 May 2017 (expiry date)

The certificate of analysis is shown in Appendix 1.

# 6.1.2. Study specific test item information

Purity/composition correction factor No correction factor required

Test item handling No specific handling conditions required

Stability at higher temperatures Stable, maximum temperature: 50°C, maximum duration: 48

hours

#### 6.2. Diet

Diet Standard powder rodent diet (SM R/M-Z from SSNIFF®

Spezialdiäten GmbH, Soest, Germany).

#### 6.3. Electronic systems for data acquisition

System control, data acquisition and data processing were performed using the following program:

-Empower 3 database version 7.21 (Waters, Milford, MA, USA)

Temperature, relative humidity and/or atmospheric pressure during sample storage and/or performance of the studies was monitored continuously using the following program:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA)

#### 6.4. List of deviations

# 6.4.1. List of study plan deviations

There were no deviations from the study plan.

#### 6.4.2. List of standard operating procedures deviations

There were no deviations from standard operating procedures (SOPs).

#### 7. DEVELOPMENT OF AN ANALYTICAL METHOD

#### 7.1. Guideline

The study was based on the following guideline:

European Commission: Guidance for Generating and Reporting Methods of Analysis in Support of Pre-registration Data Requirements for Annex II (Part A, section 4) and Annex III (Part A, section 5) of Directive 91/414, SANCO/3029/99 rev. 4 (11/07/00).

#### 7.2. Reagents

Water Tap water purified by a Milli-Q water purification system

(Millipore, Bedford, MA, USA)

Acetonitrile Biosolve, Valkenswaard, The Netherlands

Dimethyl sulfoxide (DMSO) Merck Darmstadt, Germany

All reagents were of analytical grade, unless specified otherwise.

# 7.3. Summary of the study

Liquid chromatography with available detectors was not appropriate for the analysis of test item in diets, since no suitable mobile and stationary phase could be found for an appropriate separation of test item from the matrix. Different stationary phases were tested, possible various extractions, as well as different detectors such as refractive index detection or Evaporative Light Scattering Detector (ELSD). The test item could not be separated from the diet extracts using any of the conditions tested. Some of the examples are reported below. The unreported examples are filed in raw data.

A general method such as Total Organic Carbon (TOC) was considered not to be an option due to very complex matrix. Due to the properties of the test item and the complex matrix, other analytical techniques such as gas chromatography (GC) or direct UVVIS spectrophotometry are not suitable for the analysis of the test item.

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V.. The analysis of the samples was done at the Cosun Food Technology Centre (CFTC). CFTC is a sister company of Cosun Biobased Products B.V. and is specialized in sugar analysis and therefore is well-found with necessary equipment for the analysis of Betawell L-Arabinose in diet.

# 7.4. Analytical method 1

#### 7.4.1. Preparation of solutions

Stocks solutions of the test item were prepared in water at concentrations of 1000 – 2000 mg/l.

#### Calibration solutions

Five calibration solutions in the concentration range of 10 – 100 mg/l were prepared from two stock solutions. The end solution of the calibration solutions was 97/3 acetonitril/water.

#### Quality control (QC) samples

Approximately 5 g blank powder diet was spiked using pure test item at a target concentration of 5000 or 75000 mg/kg. The samples were prepared in sample containers of 150 ml. the samples were extracted at 225 rpm with 50 ml water. The shaking time was 30 minutes. The solutions were filtered through a 0.2  $\mu$ m Spartan 30/0.2 RC filter (Whatman, Dassel, Germany). The filtered phases were diluted to obtain an end solutions of 97/3 (v/v) acetonitrile/water and concentrations within the calibration range.

The blank QC sample consisting of blank medium was treated similarly to the QC samples.

#### 7.4.2. Analytical conditions and results

Instrument Acquity UPLC system (Waters, Milford, MA, USA)

Detector Acquity Refractive Index system (Waters)

Column Zic Hillic 100 mm  $\times$  2.1 mm i.d., dp =3.5  $\mu$ m (Waters)

Column temperature  $40^{\circ}\text{C} \pm 1^{\circ}\text{C}$ Injection volume  $10~\mu\text{I}$ 

Mobile phase 97/3 (v/v) acetonitrile/water

Flow 0.5 ml/min

RI detection

Sampling rate 10 points/second

Temperature 35°C
Time constant normal
Polarity positive

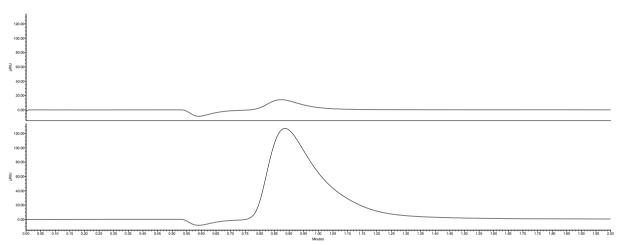


Figure 1 HPLC chromatograms of the 10 mg/l test substance solution [top; injection. id.1353 ] and a 5000 mg/kg QC sample [bottom; injection. id. 1371].

#### 7.5. Analytical method 2

#### 7.5.1. Preparation of solutions

Stocks solutions of the test item were prepared in water at concentrations of 1000 - 2000 mg/l.

#### Calibration solutions

Five calibration solutions in the concentration range of 25 – 100 mg/l were prepared from two stock solutions. The end solution of the calibration solutions was water.

#### Quality control (QC) samples

Approximately 5 g blank powder diet was spiked using pure test item at a target concentration of 5000 or 75000 mg/kg. The samples were prepared in sample containers of 150 ml. the samples were extracted at 225 rpm with 50 ml water. The shaking time was 30 minutes. The solutions were filtered through a 0.2  $\mu$ m Spartan 30/0.2 RC filter (Whatman, Dassel, Germany). The filtered phases were diluted to obtain an end solutions of water and concentrations within the calibration range.

The blank QC sample consisting of blank medium was treated similarly to the QC samples.

# 7.5.2. Analytical conditions and results

Instrument Acquity UPLC system (Waters, Milford, MA, USA)

Detector Acquity ELSD system (Waters)

Column Asahipak NH2P-50 4E, 250 mm  $\times$  4.6 mm i.d., dp = 5  $\mu$ m

(Shodex, New York, NY, USA)

Column temperature 40°C Injection volume 10 µl

Mobile phase 20/80 (v/v) acetonitrile/water

Flow 1 ml/min

**ELSD** detection

Temperature 40°C
Nebuliser gas nitrogen
Gas 25.0 psi
Nebulizer Cooling
Gain 500

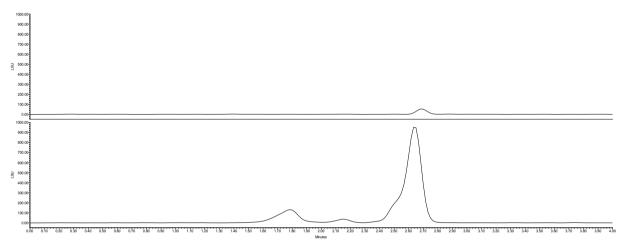


Figure 2 HPLC chromatograms of the 100 mg/l test substance solution [top; injection. id.2101] and blank QC sample [bottom; injection. id. 2145].

#### 7.6. Conclusion

It was technically not possible to develop and validate a sensitive and accurate analytical method for the analysis of Betawell L-Arabinose in diet. Therefore it was decided to determine the concentration of Betawell L-Arabinose in diet at Cosun Biobased Products B.V..

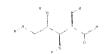
#### Appendix 1 Certificate of analysis



Certificate of analysis Specification date: 15.06.2015

# Certificate of analysis

: Betawell® Ara-P **Product name** 



| Component                            | Value           |
|--------------------------------------|-----------------|
| Arabinose                            | 99.9 wt%        |
| Glucose                              | <0.01 wt%       |
| Mannose                              | <0.01 wt%       |
| Rhamnose                             | 0.01 wt%        |
| Xylose                               | 0.03 wt%        |
| Fucose                               | <0.01 wt%       |
| Galactose                            | 0.04 wt%        |
| Galacturonic acid                    | <0.01 wt%       |
| Beet pectin derived oligosaccharides | 0.02 wt%        |
| Water content                        | 0.1 wt%         |
| Solubility ( 10% in water)           | < 20 Hazen      |
| Clarity                              | 0.85 - 0.90 FNU |

CAS-Nr.

: 5328-37-0 (for L-Arabinose) : Sugar beet

Origin Batch number

: C32-1

Batch size Product number

: total 40 kg. : 7000 ( Cosun internal number)

Appearance (color) : Whitish to white

Appearance (form)

: Powder

Smell

: Neutral

Infrared spectrum

: Conforms to structure

Minimum purity

: > 99 wt% of Dry Solids (L-arabinose, method: HPLC (C18-aq), PDA)

Functionality

: food ingredient (USA, Asia), flavor ingredient (for EU see Regulation 872/2012),

cosmetic ingredient.

Storage conditions

: Dry, keep out of sunshine.

Shelf life

: The expiry date of this product is 24 months after the production date indicated

on this certificate of analysis when properly stored and maintained.

Production date

: 15.05.2015

Betawell Ara-P, powder of arabinose page 1 of 2

COSUN
Biobased Products

Certificate of analysis Specification date: 15.06.2015

#### Additional specifications:

| Test                          | Method              | Maximum      |
|-------------------------------|---------------------|--------------|
| Total Viable Count / g (30°C) | ISO 4833:2003       | 1000 CFU / g |
| Yeasts / g                    | ISO 7954:1987       | 20 CFU / g   |
| Moulds / g                    | ISO 7954:1987       | 20 CFU/g     |
| Staph. aureus / g             | ISO 6888-3 :2003    | Absent       |
| Salmonella / 50g              | ISO 6579:2002       | Absent       |
| E. coli / g                   | ISO 16649-2:2001    | Absent       |
| Bacillus cereus / g           | ISO 7932:2004       | 100 CFU / g  |
| Coliforms / g                 | ISO 4832:2006       | Absent       |
| Enterobacteria / g            | ISO 21528-1;2004    | Absent       |
| Listeria / g                  | ISO 11290-1:1997    | Absent       |
| Clostridium perfringens/g     | ISO 7937:2004       | Absent       |
| Faecal Streps/g               | External laboratory | Absent       |
| Aflatoxins                    | External laboratory | < 0.1 μg/kg  |

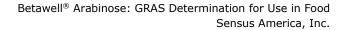
| Metals  | Value (ppm) |
|---------|-------------|
| Arsenic | <0.01       |
| Lead    | <0.01       |
| Mercury | <0.0001     |
| Cadmium | <0.005      |
| Tin     | <0.01       |
| Copper  | <0.01       |
| Silver  | <0.05       |
| Bismuth | <0.2        |

This powder is produced from sugar beet grown in the Netherlands and Germany. This material has been checked for compliance with international pesticide tolerance legislation, does not contain and/or has not been in contact with genetically modified organisms, does not contain any ingredient with an animal origin and does not contain any known allergen.

Cosun Biobased Products B.V. P.O. Box 3411, 4800 MG Breda, The Netherlands Tel +31 76 530 33 33, Fax +31 76 530 32 06

The information and recommendations in this leaflet are to the best of our knowledge, information and belief accurate at the date of publication. Nothing herein is to be construed as warranty expressed or implied. In all cases it is the responsibility of users to determine the applicability of such information or the suitability of any products for their own particular purpose.

Betawell Ara-P, powder of arabinose page 2 of 2





APPENDIX D SELECTED FOOD CODES AND CATEGORIES

| Table D-1: List of Foods and NHANES Codes Used in EDI Calculations |          |   |
|--|----------|---|
| Category   | NHANES   | Description   |
|  | Code     | <u> </u>  |
| Baked Goods  | 53201000 | COOKIE, ALMOND  |
| Baked Goods  | 53202000 | COOKIE, ADDIESALICE                                   |
| Baked Goods  | 53203000 | COOKIE, APPLESAUCE                                    |
| Baked Goods  | 53203500 | COOKIE, BISCOTTI                                      |
| Baked Goods  | 53204000 | COOKIE, BROWNIE, NS AS TO ICING                       |
| Baked Goods  | 53204010 | COOKIE, BROWNIE, W/O ICING                            |
| Baked Goods  | 53204100 | COOKIE, BROWNIE, WITH ICING OR FILLING                |
| Baked Goods  | 53204840 | COOKIE, BROWNIE, REDUCED FAT, NS AS TO ICING          |
| Baked Goods  | 53204860 | COOKIE, BROWNIE, FAT FREE, NS AS TO ICING             |
| Baked Goods  | 53205250 | COOKIE, BUTTERSCOTCH, BROWNIE                         |
| Baked Goods  | 53205260 | COOKIE, CHOCOLATE CHIR                                |
| Baked Goods  | 53206000 | COOKIE, CHOCOLATE CHIP                                |
| Baked Goods  | 53206020 | COOKIE, CHOC CHIP, HOMEMADE OR PURCHASED AT BAKERY    |
| Baked Goods  | 53206030 | COOKIE, CHOC CHIP, REDUCED FAT                        |
| Baked Goods  | 53206100 | COOKIE, CHOCOLATE MADE WITH BIGE CEREAL               |
| Baked Goods  | 53206500 | COOKIE, CHOCOLATE, MADE W/ CATMEAL & COCONUT          |
| Baked Goods  | 53206550 | COOKIE, CHOCOLATE SUDGE                               |
| Baked Goods  | 53207000 | COOKIE, CHOCOLATE OR FUNCE REPUGED FAT                |
| Baked Goods  | 53207020 | COOKIE, CHOCOLATE OR FUDGE, REDUCED FAT               |
| Baked Goods  | 53207050 | COOKIE, CHOCOLATE, W/ CHOC FILLING/COATING, FAT FREE  |
| Baked Goods  | 53208000 | COOKIE, MARSHMALLOW, CHOCOLATE-COVERED                |
| Baked Goods  | 53208200 | COOKIE, CHOCOLATE WITH ICING OR COATING               |
| Baked Goods  | 53209005 | COOKIE, CHOCOLATE, WITH ICING OR COATING              |
| Baked Goods  | 53209010 | COOKIE, SUGAR WAFER, CHOCOLATE-COVERED                |
| Baked Goods  | 53209015 | COOKIE, CHOCOLATE SANDWICH                            |
| Baked Goods  | 53209020 | COOKIE, CHOCOLATE SANDWICH, REDUCED FAT               |
| Baked Goods  | 53209100 | COOKIE, CHOCOLATE & MANUAL & CANDWICH                 |
| Baked Goods  | 53209500 | COOKIE, CHOCOLATE WASER                               |
| Baked Goods  | 53210000 | COOKIE, CHOCOLATE WAFER                               |
| Baked Goods  | 53210900 | COOKIE, GRAHAM CRACKER WITH CHOCOLATE AND MARSHMALLOW |
| Baked Goods  | 53211000 | COOKIE, BAR, W/ CHOCOLATE, NUTS, & GRAHAM CRACKERS    |
| Baked Goods  | 53215500 | COOKIE, COCONUT                                       |
| Baked Goods  | 53220000 | COOKIE, FRUIT-FILLED                                  |
| Baked Goods  | 53220010 | COOKIE, FRUIT-FILLED BAR, FAT FREE                    |
| Baked Goods  | 53220030 | COOKIE, FIG BAR                                       |
| Baked Goods  | 53220040 | COOKIE, FIG BAR, FAT FREE                             |
| Baked Goods  | 53222010 | COOKIE, FORTUNE                                       |
| Baked Goods  | 53222020 | COOKIE, CONE SHELL, ICE CREAM TYPE, WAFER / CAKE      |
| Baked Goods  | 53223000 | COOKIE, GINGERSNAPS                                   |
| Baked Goods  | 53223100 | COOKIE, GRANOLA                                       |
| Baked Goods  | 53224000 | COOKIE, LADY FINGER                                   |
| Baked Goods  | 53224250 | COOKIE, LEMON BAR                                     |
| Baked Goods  | 53225000 | COOKIE, MACAROON                                      |

| Baked Goods                | 53226000             | COOKIE, MARSHMALLOW, W/ COCONUT   |
|----------------------------|----------------------|---|
| Baked Goods                | 53226500             | COOKIE, MARSHMALLOW, W/ RICE CEREAL (NO-BAKE)   |
| Baked Goods                | 53226550             | COOKIE, MARSHMALLOW, W/ RICE CEREAL & CHOC CHIPS  |
| Baked Goods                | 53226600             | COOKIE, MARSHMALLOW, W/ RICE CEREAE & CHOC CHIPS  COOKIE, MARSHMALLOW & PEANUT BUTTER, W/ OAT CEREAL (NO- |
| Daked Goods                | 33220000             | BAKE)   |
| Baked Goods                | 53228000             | COOKIE, MERINGUE  |
| Baked Goods                | 53230000             | COOKIE, MOLASSES  |
| Baked Goods                | 53231000             | COOKIE, LEBKUCHEN   |
| Baked Goods                | 53231400             | COOKIE, MULTIGRAIN, HIGH FIBER  |
| Baked Goods                | 53233000             | COOKIE, OATMEAL   |
| Baked Goods                | 53233010             | COOKIE, OATMEAL, W/ RAISINS OR DATES  |
| Baked Goods                | 53233040             | COOKIE, OATMEAL, REDUCED FAT, NS AS TO RAISINS  |
| Baked Goods                | 53233050             | COOKIE, OATMEAL SANDWICH, W/ CREME FILLING  |
| Baked Goods                | 53233060             | COOKIE, OATMEAL, W/ CHOCOLATE CHIPS   |
| Baked Goods                | 53233080             | COOKIE, OATMEAL SANDWICH, W/ PEANUT BUTTER & JELLY FILLING  |
|                            | F2222400             | COOKE OATMEN WY CHOC & DEANIET BUTTER (NO BAYE)   |
| Baked Goods                | 53233100             | COOKIE,OATMEAL,W/ CHOC & PEANUT BUTTER (NO-BAKE)  |
| Baked Goods<br>Baked Goods | 53234000             | COOKIE, PEANUT BUTTER, WY CHOCOLATE (INCL. NACCALI)   |
|                            | 53234100             | COOKIE, PEANUT BUTTER, W/ CHOCOLATE (INCL NASSAU) COOKIE, PEANUT BUTTER W/ RICE CEREAI (NO-BAKE)          |
| Baked Goods                | 53234250             |   |
| Baked Goods<br>Baked Goods | 53235000             | COOKIE, PEANUT BUTTER SANDWICH  |
| Baked Goods                | 53235500<br>53235600 | COOKIE, W/ PEANUT BUTTER FILLING, CHOCOLATE-COATED COOKIE, PFEFFERNUSSE                                   |
| Baked Goods                | 53235000             | ·   |
| Baked Goods                | 53236100             | COOKIE, PIZZELLE (ITALIAN STYLE WAFER) COOKIE, PUMPKIN  |
| Baked Goods                | 53237000             | COOKIE, POMPKIN COOKIE, RAISIN  |
| Baked Goods                | 53237000             | COOKIE, RAISIN COOKIE, RAISIN SANDWICH, CREAM-FILLED  |
| Baked Goods                | 53237010             | COOKIE, RUM BALL (NO-BAKE)  |
| Baked Goods                | 53237300             | COOKIE, KOM BALE (NO-BAKE)  COOKIE, SANDWICH TYPE, NOT CHOCOLATE OR VANILLA                               |
| Baked Goods                | 53239000             | COOKIE, SHORTBREAD  |
| Baked Goods                | 53239010             | COOKIE, SHORTBREAD, REDUCED FAT   |
| Baked Goods                | 53239050             | COOKIE, SHORTBREAD, WITH ICING OR FILLING   |
| Baked Goods                | 53240000             | COOKIE, ANIMAL  |
| Baked Goods                | 53240010             | COOKIE, ANIMAL, WITH FROSTING OR ICING  |
| Baked Goods                | 53241500             | COOKIE, BUTTER OR SUGAR   |
| Baked Goods                | 53241600             | COOKIE, BUTTER OR SUGAR, WITH FRUIT AND/OR NUTS   |
| Baked Goods                | 53242000             | COOKIE, SUGAR WAFER   |
| Baked Goods                | 53242500             | COOKIE, TOFFEE BAR  |
| Baked Goods                | 53243000             | COOKIE, VANILLA SANDWICH  |
| Baked Goods                | 53243010             | COOKIE, VANILLA SANDWICH, EXTRA FILLING   |
| Baked Goods                | 53243050             | COOKIE, VANILLA SANDWICH, REDUCED FAT   |
| Baked Goods                | 53244010             | COOKIE, BUTTER/SUGAR, W/ CHOCOLATE ICING / FILLING  |
| Baked Goods                | 53244020             | COOKIE, BUTTER/SUGAR, W/ ICING/FILLING OTHER THAN CHOC  |
| Baked Goods                | 53246000             | COOKIE, TEA, JAPANESE   |
| Baked Goods                | 53247000             | COOKIE, VANILLA WAFER, NS AS TO TYPE  |
| Baked Goods                | 53247050             | COOKIE, VANILLA WAFER, REDUCED FAT  |
| Baked Goods                | 53247500             | COOKIE, VANILLA W/ CARAMEL, COCONUT, CHOC COATING   |
| •                          | •                    | •   |

| ı | Paked Coods | E22E1100 | COOKIE BUCELACH   |
|---|-------------|----------|---|
|   | Baked Goods | 53251100 | COOKIE, RUGELACH  |
|   | Baked Goods | 53260030 | COOKIE, CHOCOLATE CHIP, SUGAR FREE                              |
|   | Baked Goods | 53260200 | COOKIE, OATMEAL, SUGAR FREE                                     |
|   | Baked Goods | 53260300 | COOKIE, SANDWICH, SUGAR FREE                                    |
|   | Baked Goods | 53260400 | COOKIE, SUGAR OR PLAIN, SUGAR FREE                              |
|   | Baked Goods | 53260500 | COOKIE, SUGAR WAFER, SUGAR FREE                                 |
|   | Baked Goods | 53260600 | COOKIE, PEANUT BUTTER, SUGAR FREE                               |
|   | Baked Goods | 53270100 | COOKIE, P.R. (MANTECADITOS POLVORONES)                          |
|   | Baked Goods | 52101040 | CRUMPET   |
|   | Baked Goods | 52101050 | CRUMPET, TOASTED  |
|   | Baked Goods | 52101100 | BISCUIT, BAKING POWDER OR BUTTERMILK, FROM MIX                  |
|   | Baked Goods | 52101150 | BISCUIT,BAKING PWR/BUTTER MILK,REFRIG DOUGH,LOWFAT              |
|   | Baked Goods | 52102040 | BISCUIT, BAK POWDER OR BUTTERMILK, FROM REFRG DOUGH             |
|   | Baked Goods | 52103000 | BISCUIT, BAKING POWDER/BUTTERMILK TYPE, COMMERCIALLY            |
|   |             |          | BAKED   |
|   | Baked Goods | 52104010 | BISCUIT, BAKING POWDER OR BUTTERMILK, HOMEMADE                  |
|   | Baked Goods | 52104040 | BISCUIT, WHOLE WHEAT  |
|   | Baked Goods | 52104100 | BISCUIT, CHEESE   |
|   | Baked Goods | 52104200 | BISCUIT, CINNAMON-RAISIN  |
|   | Baked Goods | 52105100 | SCONES  |
|   | Baked Goods | 52105110 | SCONES, WHOLE WHEAT   |
|   | Baked Goods | 52105200 | SCONE, WITH FRUIT   |
|   | Baked Goods | 52301000 | MUFFIN, NFS   |
|   | Baked Goods | 52302010 | MUFFIN, FRUIT   |
|   | Baked Goods | 52302020 | MUFFIN, FRUIT, LOW FAT  |
|   | Baked Goods | 52302500 | MUFFIN, CHOCOLATE CHIP  |
|   | Baked Goods | 52302600 | MUFFIN, CHOCOLATE   |
|   | Baked Goods | 52303010 | MUFFIN, WHOLE WHEAT   |
|   | Baked Goods | 52303500 | MUFFIN, WHEAT   |
|   | Baked Goods | 52304000 | MUFFIN, WHOLE GRAIN   |
|   | Baked Goods | 52304010 | MUFFIN, WHEAT BRAN (INCLUDE W/ RAISINS & NUTS)                  |
|   | Baked Goods | 52304040 | MUFFIN,BRAN,W/ FRUIT, LOWFAT                                    |
|   | Baked Goods | 52304100 | MUFFIN, OATMEAL   |
|   | Baked Goods | 52304150 | MUFFIN, OAT BRAN  |
|   | Baked Goods | 52306010 | MUFFIN, PLAIN   |
|   | Baked Goods | 52306300 | MUFFIN, CHEESE  |
|   | Baked Goods | 52306500 | MUFFIN, PUMPKIN, W/ RAISINS                                     |
|   | Baked Goods | 52306550 | MUFFIN, ZUCCHINI  |
|   | Baked Goods | 52306700 | MUFFIN, CARROT (INCL W/ RAISINS/NUTS)                           |
|   | Beverages   | 92153000 | COFFEE, REGULAR, W/ CEREAL (INCLUDE W/ BARLEY)                  |
|   | Beverages   | 92153100 | COFFEE, DECAFFEINATED, W/ CEREAL (INCLUDE W/BARLEY)             |
|   | Beverages   | 92203000 | CEREAL, BEVERAGE (INCLUDE PERO, BREAK AWAY)                     |
|   | Beverages   | 92203110 | CEREAL BEVERAGE, W/BEET ROOTS, FROM POWDERED INSTANT            |
|   | Beverages   | 92205000 | RICE BEVERAGE (INCL RICE TEA)                                   |
|   | Beverages   | 92301060 | TEA, NS AS TO TYPE, PRESWEETENED W/ SUGAR                       |
|   | Beverages   | 92301080 | TEA, PRESWEETENED W/ LOW CALORIE SWEETENER                      |
|   | Beverages   | 92301100 | TEA, NS AS TO TYPE, DECAFFEINATED, UNSWEETENED                  |
|   |             | 2-301100 | 1 , 112 12 11 11 2, 113 11 2 11 11 11 11 11 11 11 11 11 11 11 1 |

| Beverages | 92301130 | TEA, NS AS TO TYPE, PRESWEETENED, NS AS TO SWEETNER   |
|-----------|----------|---|
| Beverages | 92301130 | TEA, NS AS TO TIFE, FRESWELTENED, NS AS TO SWELTNER  TEA, DECAFFEINATED, W/ SUGAR, NFS              |
| Beverages | 92301180 | TEA, DECATTEINATED, W. SOGAR, N. S. TEA, DECAFFEINATED, LOW CALORIE SWEETENER, NFS                  |
| Beverages | 92301100 | TEA, PRESWEETENED, NS SWEETENER, DECAFFEINATED  |
| Beverages | 92302200 | TEA, LEAF, PRESWEETENED W/ SUGAR  |
| Beverages | 92302300 | TEA, LEAF, PRESWEETENED W/ SOGAR  TEA, LEAF, PRESWEETENED W/ LOW CALORIE SWEETENER                  |
| Beverages | 92302300 | TEA, LEAF, PRESWEETENED, NS AS TO SWEETENER   |
| Beverages | 92302400 | TEA, LEAF, DECAFFEINATED, PRESWEETENED W/ SUGAR   |
| Beverages | 92302000 | TEA, LEAF, DECAFFEINATED, FRESWELTENED W/ SUGAR TEA, LEAF, DECAFFEINATED, LOW CALORIE SWEETENER     |
| Beverages | 92302700 | TEA, LEAF, DECAFFEINATED, PRESWEETENED, NFS   |
| Beverages | 92304000 | TEA, MADE FROM FROZEN CONCENTRATE, UNSWEETENED  |
| Beverages | 92304000 | TEA, FROM FROZ CONC, DECAF, PRESWEETND, LOW CALORIE   |
| Beverages | 92304700 | TEA, MADE FROM POWDERED INSTANT, PRESWEETENED   |
| 1         | 92305040 | TEA, MADE FROM POWDERED INSTANT, PRESWEETENED  TEA, MADE FROM POWDERED INSTANT, PRESWEETEND W/SUGAR |
| Beverages | 92303040 | TEA, MADE FROM POWDERED INSTANT, PRESWELTEND W/SOGAR  |
| Beverages | 92305050 | TEA, FROM POWDER, DECAFFEINATED, PRESWEET W/ SUGAR  |
| Beverages | 92305090 | TEA, MADE FROM POWDERED INSTANT,W/LO CAL SWEETENER  |
| Beverages | 92305110 | TEA, FROM INSTANT, DECAF, PRESWEETENED, LOW CALORIE   |
| Beverages | 92305180 | TEA ,MADE FROM POWDERED INSTANT, DECAF ,UNSWEET   |
| Beverages | 92305800 | TEA, FROM POWDER, DECAFFEINATED, PRESWEETENED   |
| Beverages | 92306000 | TEA, HERBAL (INCLUDE SASSAFRAS,LICORICE)  |
| Beverages | 92306020 | TEA, HERBAL, PRESWEETENED W/ SUGAR  |
| Beverages | 92306030 | TEA, HERBAL, PRESWEETENED W/ LOW CAL SWEETENER  |
| Beverages | 92306040 | TEA, HERBAL, PRESWEETENED, NS AS TO SWEETENER   |
| Beverages | 92306050 | TEA, MADE FROM CARAWAY SEEDS  |
| Beverages | 92306090 | TEA, HIBISCUS   |
| Beverages | 92306100 | CORN BEVERAGE(INCLUDE CORN TEA)   |
| Beverages | 92306200 | BEAN BEVERAGE (INCLUDE BEAN TEA)  |
| Beverages | 92306610 | TEA, RUSSIAN  |
| Beverages | 92306700 | TEA, CHAMOMILE  |
| Beverages | 92307000 | TEA, POWDERED INSTANT, UNSWEETENED, DRY   |
| Beverages | 92307400 | TEA, POWDERED INSTANT, SWEETENED, NS SWEETENER, DRY   |
| Beverages | 92307500 | HALF AND HALF BEVERAGE, HALF ICED TEA/HALF LEMONADE   |
| Beverages | 92307510 | HALF&HALF BEV, HALF ICED TEA/HALF LEMONADE,LOW CAL  |
| Beverages | 95101000 | BOOST, NUTRITIONAL DRINK, READY-TO-DRINK  |
| Beverages | 95101010 | BOOST PLUS, NUTRITIONAL DRINK, READY-TO-DRINK   |
| Beverages | 95102000 | CARNATION INSTANT BREAKFAST, NUTRITIONAL DRINK, REGULAR, RTD  |
| Beverages | 95102010 | CARNATION INSTANT BREAKFAST, NUTRITIONAL DRINK, SUGAR FREE,   |
| Beverages | 95103000 | ENSURE, NUTRITIONAL SHAKE, READY-TO-DRINK   |
| Beverages | 95103010 | ENSURE PLUS, NUTRITIONAL SHAKE, READY-TO-DRINK  |
| Beverages | 95104000 | GLUCERNA, NUTRITIONAL SHAKE, READY-TO-DRINK   |
| Beverages | 95105000 | KELLOGG'S SPECIAL K PROTEIN SHAKE   |
| Beverages | 95106000 | MUSCLE MILK, READY-TO-DRINK   |
| Beverages | 95106010 | MUSCLE MILK, LIGHT, READY-TO-DRINK  |
| Beverages | 95110000 | SLIM FAST SHAKE, MEAL REPLACEMENT, REGULAR, READY-TO-   |
|           |          | DRINK   |

| Beverages<br>Beverages | 95110010<br>95110020 | SLIM FAST SHAKE, MEAL REPLACEMENT, SUGAR FREE, RTD<br>SLIM FAST SHAKE, MEAL REPLACEMENT, HIGH PROTEIN, RTD |
|------------------------|----------------------|--|
| Beverages              | 95120000             | NUTRITIONAL DRINK OR MEAL REPLACEMENT, READY-TO-DRINK, NFS   |
| Beverages              | 95120010             | NUTRITIONAL DRINK OR MEAL REPLACEMENT, HIGH PROTEIN, RTD   |
| Beverages              | 95120020             | NUTRITIONAL DRINK OR MEAL REPLACEMENT, HI PROT, LIGHT, RTD   |
| Beverages              | 95120050             | NUTRITIONAL DRINK OR MEAL REPLACEMENT, LIQUID, SOY-BASED   |
| Beverages              | 95201000             | CARNATION INSTANT BREAKFAST, NUTRITIONAL DRINK MIX, REG,PDR  |
| Beverages              | 95201010             | CARNATION INSTANT BREAKFAST, NUTR DRINK MIX, SUGAR FREE,PDR  |
| Beverages              | 95201200             | EAS WHEY PROTEIN POWDER  |
| Beverages              | 95201300             | EAS SOY PROTEIN POWDER   |
| Beverages              | 95201500             | HERBALIFE, NUTRITIONAL SHAKE MIX, HIGH PROTEIN, POWDER   |
| Beverages              | 95201600             | ISOPURE PROTEIN POWDER   |
| Beverages              | 95201700             | KELLOGG'S SPECIAL K20 PROTEIN WATER MIX  |
| Beverages              | 95202000             | MUSCLE MILK, REGULAR, POWDER   |
| Beverages              | 95202010             | MUSCLE MILK, LIGHT, POWDER   |
| Beverages              | 95210000             | SLIM FAST SHAKE MIX, POWDER  |
| Beverages              | 95210010             | SLIM FAST SHAKE MIX, SUGAR FREE, POWDER  |
| Beverages              | 95210020             | SLIM FAST SHAKE MIX, HIGH PROTEIN, POWDER  |
| Beverages              | 95220000             | NUTRITIONAL DRINK MIX OR MEAL REPLACEMENT, POWDER, NFS   |
| Beverages              | 95220010             | NUTRITIONAL DRINK MIX OR MEAL REPLACEMENT, HIGH PRO, PDR,NFS   |
| Beverages              | 95230000             | PROTEIN POWDER, WHEY BASED, NFS  |
| Beverages              | 95230010             | PROTEIN POWDER, SOY BASED, NFS   |
| Beverages              | 95230020             | PROTEIN POWDER, LIGHT, NFS   |
| Beverages              | 95230030             | PROTEIN POWDER, NFS  |
| Beverages              | 95310200             | FULL THROTTLE ENERGY DRINK   |
| Beverages              | 95310400             | MONSTER ENERGY DRINK   |
| Beverages              | 95310500             | MOUNTAIN DEW AMP ENERGY DRINK  |
| Beverages              | 95310550             | NO FEAR ENERGY DRINK   |
| Beverages              | 95310555             | NO FEAR MOTHERLOAD ENERGY DRINK  |
| Beverages              | 95310560             | NOS ENERGY DRINK   |
| Beverages              | 95310600             | RED BULL ENERGY DRINK  |
| Beverages              | 95310700             | ROCKSTAR ENERGY DRINK  |
| Beverages              | 95310750             | SOBE ENERGIZE ENERGY JUICE DRINK   |
| Beverages              | 95310800             | VAULT ENERGY DRINK   |
| Beverages              | 95311000             | ENERGY DRINK   |
| Beverages              | 95312400             | MONSTER ENERGY DRINK, LO CARB  |
| Beverages              | 95312500             | MOUNTAIN DEW AMP ENERGY DRINK, SUGAR-FREE  |
| Beverages              | 95312550             | NO FEAR ENERGY DRINK, SUGAR-FREE   |
| Beverages              | 95312555             | NOS ENERGY DRINK, SUGAR-FREE   |
| Beverages              | 95312560             | CRANBERRY JUICE ENERGY DRINK, HI VIT C & B, W/LOW CAL SWTNR  |
|                        |                      |  |

| Beverages | 95312600 | RED BULL ENERGY DRINK, SUGAR-FREE                               |
|-----------|----------|---|
| Beverages | 95312000 | ROCKSTAR ENERGY DRINK, SUGAR-FREE                               |
| Beverages | 95312700 | VAULT ZERO ENERGY DRINK   |
| _         |          | XS ENERGY DRINK   |
| Beverages | 95312900 |   |
| Beverages | 95312905 | XS GOLD PLUS ENERGY DRINK                                       |
| Beverages | 95320200 | GATORADE THIRST QUENCHER SPORTS DRINK                           |
| Beverages | 95320500 | POWERADE SPORTS DRINK   |
| Beverages | 95321000 | FRUIT-FLAVORED THIRST QUENCHER BEVERAGE                         |
| Beverages | 95322200 | GATORADE G2 THIRST QUENCHER SPORTS DRINK, LOW CALORIE           |
| Beverages | 95322500 | POWERADE ZERO SPORTS DRINK, LOW CALORIE                         |
| Beverages | 95323000 | FRUIT-FLAV SPORTS DRINK OR THIRST QUENCHER BEVERAGE, LOW        |
|           |          | CAL   |
| Beverages | 95330100 | FLUID REPLACEMENT, ELECTROLYTE SOLUTION                         |
| Beverages | 95330500 | FLUID REPLACEMENT, 5% GLUCOSE IN WATER                          |
| Beverages | 95341000 | FUZE SLENDERIZE FORTIFIED LOW CALORIE FRUIT JUICE BEVERAGE      |
| Beverages | 95342000 | MONAVIE ACAI BLEND BEVERAGE                                     |
| Cereal    | 57104000 | APPLE JACKS CEREAL  |
| Cereal    | 57107000 | BOOBERRY CEREAL   |
| Cereal    | 57117000 | CAP'N CRUNCH CEREAL   |
| Cereal    | 57117500 | CAP'N CRUNCH'S CHRISTMAS CRUNCH CEREAL                          |
| Cereal    | 57119000 | CAP'N CRUNCH'S CRUNCH BERRIES CEREAL                            |
| Cereal    | 57120000 | CAP'N CRUNCH'S PEANUT BUTTER CRUNCH CEREAL                      |
| Cereal    | 57124200 | CHOCOLATE FLAVORED FROSTED PUFFED CORN CEREAL                   |
| Cereal    | 57125000 | CINNAMON TOAST CRUNCH CEREAL                                    |
| Cereal    | 57125900 | HONEY NUT CLUSTERS CEREAL                                       |
| Cereal    | 57126000 | COCOA KRISPIES CEREAL   |
| Cereal    | 57127000 | COCOA PEBBLES CEREAL  |
| Cereal    | 57128000 | COCOA PUFFS CEREAL  |
| Cereal    | 57130000 | COOKIE-CRISP CEREAL (INCLUDE ALL FLAVORS)                       |
| Cereal    | 57139000 | COUNT CHOCULA CEREAL  |
| Cereal    | 57201900 | DORA THE EXPLORER CEREAL  |
| Cereal    | 57211000 | FRANKENBERRY CEREAL   |
| Cereal    | 57213000 | FROOT LOOPS CEREAL  |
| Cereal    | 57213850 | FROSTED CHEERIOS CEREAL   |
| Cereal    | 57214000 |   |
| Cereal    | 57214000 | FROSTED MINI-WHEATS CEREAL (INCL ALL FLAVORS) FROSTY O'S CEREAL |
|           |          |   |
| Cereal    | 57216000 | FROSTED RICE CEREAL, NFS  |
| Cereal    | 57223000 | FRUITY PEBBLES CEREAL   |
| Cereal    | 57305100 | LUCKY CHARMS CEREAL W/ MARSHMALLOWS                             |
| Cereal    | 57305150 | FROSTED OAT CEREAL W/ MARSHMALLOWS                              |
| Cereal    | 57305160 | MALT-O-MEAL BLUEBERRY MUFFIN TOPS                               |
| Cereal    | 57305165 | MALT-O-MEAL CINNAMON TOASTERS                                   |
| Cereal    | 57305170 | MALT-O-MEAL COCO-ROOS CEREAL                                    |
| Cereal    | 57305174 | MALT-O-MEAL COLOSSAL CRUNCH                                     |
| Cereal    | 57305175 | MALT-O-MEAL COCOA DYNO-BITES                                    |

| Cereal | 57305180 | MALT-O-MEAL CORN BURSTS CEREAL                             |
|--------|----------|--|
| Cereal | 57305200 | MALT-O-MEAL CRISPY RICE CEREAL                             |
| Cereal | 57305210 | MALT-O-MEAL FROSTED FLAKES                                 |
| Cereal | 57305215 | MALT-O-MEAL FROSTED MINI SPOONERS                          |
| Cereal | 57305300 | MALT-O-MEAL FRUITY DYNO-BITES                              |
| Cereal | 57305400 | MALT-O-MEAL HONEY GRAHAM SQUARES                           |
| Cereal | 57305600 | MALT-O-MEAL MARSHMALLOW MATEYS CEREAL                      |
| Cereal | 57306800 | MALT-O-MEAL TOOTIE FRUITIES (RTE CEREAL)                   |
| Cereal | 57307600 | MINI-SWIRLZ CINNAMON BUN CEREAL, KELLOGG'S                 |
| Cereal | 57335550 | REESE'S PEANUT BUTTER PUFFS CEREAL                         |
| Cereal | 57339500 | RICE KRISPIES TREATS CEREAL, KELLOGG'S                     |
| Cereal | 57407100 | TRIX CEREAL  |
| Cereal | 53710400 | FIBER ONE CHEWY BAR  |
| Cereal | 53710500 | KELLOGG'S NUTRI-GRAIN CEREAL BAR                           |
| Cereal | 53710502 | KELLOGG'S NUTRI-GRAIN YOGURT BAR                           |
| Cereal | 53710504 | KELLOGG'S NUTRI-GRAIN FRUIT AND NUT BAR                    |
| Cereal | 53710600 | MILK 'N CEREAL BAR   |
| Cereal | 53710700 | KELLOGG'S SPECIAL K BAR                                    |
| Cereal | 53710800 | KASHI GOLEAN CHEWY BARS                                    |
| Cereal | 53710802 | KASHI TLC CHEWY GRANOLA BAR                                |
| Cereal | 53710804 | KASHI GOLEAN CRUNCHY BARS                                  |
| Cereal | 53710806 | KASHI TLC CRUNCHY GRANOLA BAR                              |
| Cereal | 53710900 | NATURE VALLEY CHEWY TRAIL MIX GRANOLA BAR                  |
| Cereal | 53710902 | NATURE VALLEY CHEWY GRANOLA BAR WITH YOGURT COATING        |
| Cereal | 53710904 | NATURE VALLEY SWEET AND SALTY GRANOLA BAR                  |
| Cereal | 53710906 | NATURE VALLEY CRUNCHY GRANOLA BAR                          |
| Cereal | 53711000 | QUAKER CHEWY GRANOLA BAR                                   |
| Cereal | 53711002 | QUAKER CHEWY 90 CALORIE GRANOLA BAR                        |
| Cereal | 53711004 | QUAKER CHEWY 25% LESS SUGAR GRANOLA BAR                    |
| Cereal | 53711006 | QUAKER CHEWY DIPPS GRANOLA BAR                             |
| Cereal | 53712000 | SNACK BAR, OATMEAL   |
| Cereal | 53712100 | GRANOLA BAR, NFS   |
| Cereal | 53712200 | GRANOLA BAR, LOWFAT, NFS                                   |
| Cereal | 53712210 | GRANOLA BAR, NONFAT  |
| Cereal | 53713000 | GRANOLA BAR, REDUCED SUGAR, NFS                            |
| Cereal | 53713100 | GRANOLA BAR, PEANUTS , OATS, SUGAR, WHEAT GERM             |
| Cereal | 53714200 | GRANOLA BAR, CHOCOLATE-COATED, NFS                         |
| Cereal | 53714210 | GRANOLA BAR, WITH COCONUT, CHOCOLATE-COATED                |
| Cereal | 53714220 | GRANOLA BAR WITH NUTS, CHOCOLATE-COATED                    |
| Cereal | 53714230 | GRANOLA BAR, OATS, NUTS, COATED WITH NON-CHOCOLATE COATING |
| Cereal | 53714250 | GRANOLA BAR, COATED WITH NON-CHOCOLATE COATING             |
| Cereal | 53714300 | GRANOLA BAR, HIGH FIBER, COATED W/ NON-CHOC YOGURT COATING |
| Cereal | 53714400 | GRANOLA BAR, WITH RICE CEREAL                              |
| Cereal | 53714500 | BREAKFAST BAR, NFS   |
| Cereal | 53714510 | BREAKFAST BAR, DATE, WITH YOGURT COATING                   |

| Cereal   | 53714520    | BREAKFAST BAR, CEREAL CRUST WITH FRUIT FILLING, LOWFAT |
|----------|-------------|--|
| Cereal   | 53720100    | BALANCE ORIGINAL BAR                                   |
| Cereal   | 53720200    | CLIF BAR   |
| Cereal   | 53720300    | POWERBAR   |
| Cereal   | 53720400    | SLIM FAST ORIGINAL MEAL BAR                            |
| Cereal   | 53720500    | SNICKERS MARATHON PROTEIN BAR                          |
| Cereal   | 53720500    | SNICKERS MARATHON FROTEIN BAR                          |
| Cereal   | 53720600    | SOUTH BEACH LIVING MEAL BAR                            |
| Cereal   | 53720610    | SOUTH BEACH LIVING HIGH PROTEIN BAR                    |
| Cereal   | 53720010    | TIGER'S MILK BAR                                       |
| Cereal   | 53720700    | ZONE PERFECT CLASSIC CRUNCH NUTRITION BAR              |
| Cereal   | 53720800    | NUTRITION BAR OR MEAL REPLACEMENT BAR, NFS             |
|          |             | ·  |
| Cereal   | 54420010    | MULTIGRAIN MIXTURE, PRETZELS, CEREAL &/ CRACKERS, NUTS |
| Cereal   | 56200300    | CEREAL, COOKED, INSTANT, NG AG TO CRAIN                |
| Cereal   | 56200350    | CEREAL, COOKED, INSTANT, NS AS TO GRAIN                |
| Cereal   | 56201700    | CORNSTARCH W/ MILK, EATEN AS CEREAL                    |
| Cereal   | 56205200    | RICE, FRZ DES,NONDAIRY,NOT CHOC (INCL RICE DREAM)      |
| Cereal   | 56205230    | RICE DESSERT BAR,FRZ,NOT CHOC,NONDAIRY,CAROB,COVER     |
| Cereal   | 56205240    | RICE DESSERT BAR,FRZ,CHOC,NONDAIRY,CHOC COVERED        |
| Cereal   | 56207190    | WHOLE WHEAT CEREAL, COOKED, NS AS TO ADDED FAT         |
| Cereal   | 56207200    | WHOLE WHEAT CEREAL, COOKED, NO FAT ADDED               |
| Cereal   | 56207210    | WHOLE WHEAT CEREAL, COOKED, FAT ADDED                  |
| Cereal   | 56207300    | WHOLE WHEAT CEREAL, W/ BARLEY, COOKED, NO FAT ADDED    |
| Cereal   | 56207330    | WHOLE WHEAT CEREAL, WHEAT & BARLEY, FAT ADDED          |
| Cereal   | 56207340    | WHOLE WHEAT CEREAL, WHEAT & BARLEY, ADDED FAT NS       |
| Cereal   | 56207350    | WHEAT CEREAL, CHOC FLAVORED, COOKED W/ MILK            |
| Cereal   | 56207360    | WHEAT CEREAL, CHOC FLAVORED, COOKED, NO FAT ADDED      |
| Cereal   | 56207370    | WHEAT CEREAL, CHOC FLAV,COOKED,NS AS TO ADDED FAT      |
| Cereal   | 56208500    | OAT BRAN CEREAL, COOKED, NO FAT ADDED                  |
| Cereal   | 56208510    | OAT BRAN CEREAL, COOKED, FAT ADDED                     |
| Cereal   | 56208520    | OAT BRAN CEREAL, COOKED, NS AS TO ADDED FAT            |
| Cereal   | 56208530    | OAT BRAN CEREAL, MADE W/ MILK, NO FAT ADDED            |
| Cereal   | 56208540    | OAT BRAN CEREAL, MADE W/ MILK, FAT ADDED               |
| Cereal   | 56208550    | OAT BRAN CEREAL, MADE W/ MILK, NS AS TO ADDED FAT      |
| Cereal   | 56210000    | NESTUM, CEREAL   |
| Cereal   | 57000000    | CEREAL, NFS  |
| Cereal   | 57000050    | KASHI CEREAL, NS AS TO READY-TO-EAT OR COOKED          |
| Cereal   | 57000100    | OAT CEREAL, NFS  |
| Cereal   | 57100100    | CEREAL, READY-TO-EAT, NFS                              |
| Cereal   | 57101000    | ALL-BRAN CEREAL  |
| Cereal   | 57102000    | ALPEN CEREAL   |
| Cereal   | 57103000    | ALPHA-BITS CEREAL                                      |
| Cereal   | 57103020    | ALPHA-BITS W/ MARSHMALLOWS CEREAL                      |
| Cereal   | 57103050    | AMARANTH FLAKES CEREAL                                 |
| Cereal   | 57106050    | BANANA NUT CRUNCH CEREAL (POST)                        |
| Cereal   | 57106100    | BASIC 4 (RTE CEREAL)                                   |
| 1 25.55. | 1 5. 230200 |  |

| Cereal | 57110000 | ALL-BRAN BRAN BUDS CEREAL, KELLOGG'S (FORMERLY BRAN BUDS)     |
|--------|----------|---|
| Cereal | 57111000 | BRAN CHEX CEREAL  |
| Cereal | 57124000 | CHEX CEREAL, NFS  |
| Cereal | 57131000 | CRUNCHY CORN BRAN CEREAL, QUAKER                              |
| Cereal | 57132000 | CORN CHEX CEREAL  |
| Cereal | 57137000 | CORN PUFFS CEREAL   |
| Cereal | 57143000 | CRACKLIN' OAT BRAN CEREAL                                     |
| Cereal | 57144000 | CRISP CRUNCH CEREAL   |
| Cereal | 57148000 | CRISPIX CEREAL  |
| Cereal | 57148500 | CRISPY BROWN RICE CEREAL                                      |
| Cereal | 57151000 | CRISPY RICE CEREAL  |
| Cereal | 57206000 | FAMILIA CEREAL  |
| Cereal | 57206700 | FIBER ONE CEREAL  |
| Cereal | 57206800 | FIBER 7 FLAKES CEREAL, HEALTH VALLEY                          |
| Cereal | 57207000 | BRAN FLAKES CEREAL, NFS (FORMERLY 40% BRAN FLAKES, NFS)       |
| Cereal | 57209000 | NATURAL BRAN FLAKES CEREAL, POST                              |
| Cereal | 57219000 | FRUIT & FIBRE CEREAL, NFS                                     |
| Cereal | 57221000 | FRUIT & FIBRE CEREAL, W/ DATES, RAISINS, & WALNUTS            |
| Cereal | 57221650 | FRUIT HARVEST CEREAL, KELLOGG'S                               |
| Cereal | 57221800 | FRUIT WHIRLS CEREAL   |
| Cereal | 57224000 | GOLDEN GRAHAMS CEREAL   |
| Cereal | 57230000 | GRAPE-NUTS CEREAL   |
| Cereal | 57231200 | GREAT GRAINS, RAISIN, DATE, & PECAN, WHOLE GRAIN CEREAL, POST |
| Cereal | 57231250 | GREAT GRAINS DOUBLE PECAN WHOLE GRAIN CEREAL, POST            |
| Cereal | 57237100 | HONEY BUNCHES OF OATS HONEY ROASTED CEREAL                    |
| Cereal | 57238000 | HONEYCOMB CEREAL, PLAIN                                       |
| Cereal | 57239000 | HONEYCOMB CEREAL, STRAWBERRY                                  |
| Cereal | 57239100 | HONEY CRUNCH CORN FLAKES CEREAL, KELLOGG'S                    |
| Cereal | 57240100 | HONEY NUT CHEX CEREAL   |
| Cereal | 57241200 | HONEY NUT SHREDDED WHEAT CEREAL, POST                         |
| Cereal | 57302100 | KING VITAMAN CEREAL   |
| Cereal | 57303100 | KIX CEREAL  |
| Cereal | 57304100 | LIFE CEREAL (PLAIN & CINNAMON)                                |
| Cereal | 57305500 | MALT-O-MEAL HONEY & NUT TOASTY O'S CEREAL                     |
| Cereal | 57306100 | MALT-O-MEAL PUFFED RICE CEREAL                                |
| Cereal | 57306120 | MALTO-O-MEAL PUFFED WHEAT CEREAL                              |
| Cereal | 57306130 | MALT-O-MEAL RAISIN BRAN                                       |
| Cereal | 57306500 | MALT-O-MEAL GOLDEN PUFFS CEREAL (FORMERLY SUGAR PUFFS)        |
| Cereal | 57306700 | MALT-O-MEAL TOASTED OAT CEREAL                                |
| Cereal | 57307010 | MAPLE PECAN CRUNCH CEREAL, POST                               |
| Cereal | 57307500 | MILLET, PUFFED (CEREAL)                                       |
| Cereal | 57308150 | MUESLIX CEREAL, NFS   |
| Cereal | 57316450 | OATMEAL CRISP W/ ALMONDS CEREAL                               |
| Cereal | 57316500 | OATMEAL CRISP, RAISIN   |

| Cereal      | 57316710 | OH'S, HONEY GRAHAM CEREAL                               |
|-------------|----------|---|
| Cereal      | 57319000 | 100% NATURAL CEREAL, PLAIN, QUAKER                      |
| Cereal      | 57320500 | 100 % NATURAL CEREAL, W/ OATS, HONEY & RAISINS, QUAKER  |
| Cereal      | 57321500 | 100% NATURAL WHOLEGRAIN CEREAL W/ RAISINS, LOWFAT,      |
|             |          | QUAKER  |
| Cereal      | 57323000 | SWEET CRUNCH CEREAL, QUAKER (FORMERLY POPEYE)           |
| Cereal      | 57325000 | PRODUCT 19 CEREAL                                       |
| Cereal      | 57326000 | PUFFINS CEREAL  |
| Cereal      | 57327450 | QUAKER OAT BRAN CEREAL                                  |
| Cereal      | 57327500 | QUAKER OATMEAL SQUARES CEREAL (FORMERLY QUAKER OAT      |
| Compal      | E7220000 | SQUARES)  |
| Cereal      | 57328000 | QUISP CEREAL NEC  |
| Cereal      | 57329000 | RAISIN BRAN CEREAL, NFS                                 |
| Cereal      | 57331000 | RAISIN BRAN CEREAL, POST                                |
| Cereal      | 57332100 | RAISIN NUT BRAN CEREAL                                  |
| Cereal      | 57336000 | RICE CHEX CEREAL  |
| Cereal      | 57340000 | PUFFED RICE CEREAL                                      |
| Cereal      | 57341000 | SHREDDED WHEAT 'N BRAN CEREAL                           |
| Cereal      | 57341200 | SMART START STRONG HEART ANTIOXIDANTS CEREAL, KELLOGG'S |
| Cereal      | 57344000 | SPECIAL K CEREAL  |
| Cereal      | 57346500 | OATMEAL HONEY NUT HEAVEN, QUAKER                        |
| Cereal      | 57347000 | CORN POPS CEREAL  |
| Cereal      | 57349020 | REDUCED SUGAR FROSTED FLAKES CEREAL, KELLOGG'S          |
| Cereal      | 57355000 | GOLDEN CRISP CEREAL                                     |
| Cereal      | 57401100 | TOASTED OAT CEREAL                                      |
| Cereal      | 57406100 | TOTAL CEREAL  |
| Cereal      | 57408100 | UNCLE SAM CEREAL  |
| Cereal      | 57409100 | WAFFLE CRISP CEREAL, POST                               |
| Cereal      | 57410000 | WEETABIX WHOLE WHEAT CEREAL                             |
| Cereal      | 57411000 | WHEAT CHEX CEREAL                                       |
| Cereal      | 57412000 | WHEAT GERM CEREAL, PLAIN                                |
| Cereal      | 57413000 | WHEAT GERM CEREAL, W/ SUGAR & HONEY                     |
| Cereal      | 57416000 | PUFFED WHEAT CEREAL, PLAIN                              |
| Cereal      | 57418000 | WHEATIES CEREAL   |
| Cereal      | 57603200 | RICE BRAN CEREAL, UNCOOKED                              |
| Cereal      | 59003000 | MEAT SUBSTITUTE, CEREAL- & VEGETABLE PROTEIN-BASED      |
| Chewing Gum | 91800100 | CHEWING GUM, NFS  |
| Chewing Gum | 91801000 | CHEWING GUM, SUGARED                                    |
| Chewing Gum | 91802000 | CHEWING GUM, SUGARLESS                                  |
| Condiments  | 27150370 | SARDINES W/ MUSTARD SAUCE (MIXTURE)                     |
| Condiments  | 27130370 | CHEESEBURGER, W/ MAYO & TOMATO/CATSUP, ON BUN           |
| Condiments  | 27510230 | CHEESEBURGER W/ TOMATO & TOMATO/CATSUP, ON BUN          |
| Condiments  | 27510310 | CHEESEBURGER, 1/4 LB MEAT, W/ TOMATO/CATSUP, BUN        |
| Condiments  | 27510320 | DOUBLE CHEESEBURGER W/TOMATO & OR CATSUP, ON BUN        |
| Condiments  | 27510330 | DOUBLE CHEESEBURGER, W/ MAYO & TOMATO, ON BUN           |
| Condiments  | 27510340 | CHEESEBURGER, 1/4 LB MEAT, W/ MAYO & TOMATO, ON BON     |
| Condinients | 2/310330 | BUN   |

| _             | _        |   |
|---------------|----------|---|
| Condiments    | 27510355 | CHEESEBURGER, 1/3 LB MEAT, W/MAYO, TOMATO, ON BUN               |
| Condiments    | 27510360 | BACON CHEESEBURGER, W/MAYO/SALAD DRSG,                          |
|               |          | TOMATO/CATSUP,ON BUN  |
| Condiments    | 27510375 | DOUBLE CHEESEBURGER(2 PATTIES,1/4 LB EA)                        |
| Condiments    | 27510380 | W/TOMATO/CATSUP/BUN TRIPLE CHEESEBURGER W/ MAYO, TOMATO, ON BUN |
| Condiments    | 27510380 | DOUBLE BACON CHEESEBURGER (2 PATTIES), W/ TOMATO/CATSUP         |
| Condinients   | 2/310363 | DOUBLE BACON CHEESEBURGER (2 PATTIES), W/ TOMATO/CATSUP         |
| Condiments    | 27510400 | BACON CHEESEBURGER, 1/4 LB MEAT, W/ TOMATO, ON BUN              |
| Condiments    | 27510430 | DOUBLE BACON CHEESEBURGER,                                      |
|               |          | W/MAYO/DRSG,TOMATO/CATSUP,ON BUN                                |
| Condiments    | 27510440 | BACON CHEESEBURGER, 1/4 LB,                                     |
| Condiments    | 27510445 | W/MAYO/DRSG,TOMATO/CATSUP,ON BUN                                |
| Condiments    | 27510445 | BACON CHEESEBURGER, 1/3 LB MEAT, W/TOMATO +/OR CATSUP,          |
| Condiments    | 27510510 | HAMBURGER, W/ TOMATO & OR CATSUP, ON BUN                        |
| Condiments    | 27510520 | HAMBURGER, W/ MAYO & TOMATO/CATSUP, ON BUN                      |
| Condiments    | 27510540 | DOUBLE HAMBURGER W/TOMATO & OR CATSUP, ON BUN                   |
| Condiments    | 27510560 | HAMBURGER, 1/4 LB MEAT W/ MAYO & TOMATO/CATSUP, ON BUN          |
|               |          |   |
| Condiments    | 27510610 | HAMBURGER, 1 OZ MEAT, TOMATO, ON MINIATURE BUN                  |
| Condiments    | 27510620 | HAMBURGER, 1/4 LB MEAT, W/ TOMATO & OR CATSUP, BUN              |
| Condiments    | 27510680 | DOUBLE HAMBURGER (1/2 LB MEAT), W/ TOM/CATSUP, BUN              |
| Condiments    | 27510690 | DOUBLE HAMBURGER,1/2 LB MEAT,W/MAYO&TOM/CATSUP,BUN              |
| Condiments    | 27517010 | WRAP SANDWICH FILLED WITH BEEF PATTY, CHEESE, TOMATO,           |
|               | 27540000 | SPREAD  |
| Condiments    | 27518000 | WRAP SAND W/BEEF PATTY,BAC, CHS, TOM,SPREAD                     |
| Condiments    | 74401010 | TOMATO CATSUP   |
| Condiments    | 74401110 | TOMATO CATSUP, REDUCED SODIUM                                   |
| Condiments    | 74402010 | TOMATO CHILI SAUCE (CATSUP TYPE)                                |
| Condiments    | 75411010 | CORN, SCALLOPED OR PUDDING (INCLUDE CORN SOUFFLE)               |
| Condiments    | 75503100 | MUSTARD PICKLES (INCL CHOW-CHOW, HOT DOG RELISH)                |
| Condiments    | 75506010 | MUSTARD (INCL HORSERADISH MUSTARD, CHINESE MUSTARD)             |
| Condiments    | 75506100 | MUSTARD SAUCE   |
| Condiments    | 83105500 | HONEY MUSTARD DRESSING  |
| Condiments    | 83204500 | HONEY MUSTARD DRESSING, LIGHT                                   |
| Condiments    | 83300500 | HONEY MUSTARD DRESSING, FAT FREE                                |
| Confectionary | 91520100 | YOOKAN, JAPANESE DESSERT MADE W/ BEAN PASTE & SUGAR             |
| Confectionary | 91560100 | HAUPIA (COCONUT PUDDING)  |
| Confectionary | 91580000 | GELATIN, FROZ, WHIPPED, ON STICK (INCL JELLO GLTN POPS)         |
| Confectionary | 91611050 | ICE POP FILLED W/ ICE CREAM, ALL FLAVOR VARIETIES               |
| Confectionary | 91611100 | ICE POP, SWEETENED W/ LOW CALORIE SWEETENER                     |
| Confectionary | 91700010 | CANDY, NFS  |
| Confectionary | 91700500 | M&M'S ALMOND CHOCOLATE CANDIES                                  |
| Confectionary | 91701010 | ALMONDS, CHOCOLATE-COVERED                                      |
| Confectionary | 91701020 | ALMONDS, SUGAR-COATED (INCL JORDAN ALMONDS)                     |
| Confectionary | 91701030 | ALMONDS, YOGURT-COVERED   |
| Confectionary | 91702010 | BUTTERSCOTCH MORSELS  |
| Confectionary | 91703010 | CARAMEL CANDY, CHOC-FLAVOR ROLL (INCL TOOTSIE ROLL)             |

| Confectionary | 91703020 | CARAMEL CANDY, NOT CHOCOLATE                             |
|---------------|----------|--|
| Confectionary | 91703020 | CARAMEL CANDY, W/ NUTS                                   |
| Confectionary | 91703030 | CARAMEL CANDY, WY NOTS  CARAMEL CANDY, CHOCOLATE COVERED |
| Confectionary | 91703050 | CARAMEL CANDY, W/ NUTS & CEREAL, CHOCOLATE-COVERED       |
| Confectionary | 91703060 | CARAMEL CANDY, W/ NUTS, CHOCOLATE-COVERED                |
| Confectionary | 91703000 | ROLOS CANDY  |
| Confectionary | 91703070 | CARAMEL, ALL FLAVORS, SUGAR FREE                         |
| Confectionary | 91703000 | TOBLERONE, MILK CHOCOLATE W/ HONEY & ALMOND NOUGAT       |
| Confectionary | 91703130 | TWIX CARAMEL COOKIE BARS                                 |
| Confectionary | 91703250 | TWIX CHOCOLATE FUDGE COOKIE BARS                         |
| Confectionary | 91703230 | TWIX CHOCOLATE FOOGE COOKIE BARS                         |
| Confectionary | 91703300 | WHATCHAMACALLIT CANDY                                    |
| Confectionary | 91703400 | NUTS, CAROB-COATED                                       |
| Confectionary | 91703600 | ESPRESSO COFFEE BEANS, CHOCOLATE-COVERED                 |
| Confectionary | 91705000 | MILK CHOCOLATE CANDY, PLAIN                              |
| Confectionary | 91705010 | MILK CHOCOLATE CANDY, WITH CEREAL                        |
| Confectionary | 91705020 | KIT KAT CANDY BAR  |
| Confectionary | 91705040 | CHOCOLATE, MILK, W/ NUTS, NOT ALMONDS OR PEANUTS         |
| Confectionary | 91705050 | MILK CHOCOLATE CANDY, WITH FRUIT AND NUTS                |
| Confectionary | 91705060 | MILK CHOCOLATE CANDY, WITH ALMONDS                       |
| Confectionary | 91705070 | CHOCOLATE, MILK, W/ PEANUTS (INCLUDE MR GOODBAR)         |
| Confectionary | 91705070 | CHOCOLATE CANDY WITH FONDANT AND CARAMEL                 |
| Confectionary | 91705200 | CHOCOLATE, SEMI-SWEET                                    |
| Confectionary | 91705300 | CHOCOLATE CANDY, SWEET OR DARK                           |
| Confectionary | 91705300 | CHOCOLATE, SWEET OR DARK, WITH ALMONDS                   |
| Confectionary | 91705310 | CHOCOLATE CANDY, WHITE                                   |
| Confectionary | 91705410 | CHOCOLATE CANDY, WHITE, W/ ALMONDS                       |
| Confectionary | 91705420 | CHOCOLATE, WHITE, W/ CEREAL, CANDY                       |
| Confectionary | 91705430 | KIT KAT WHITE  |
| Confectionary | 91705500 | MEXICAN CHOCOLATE (TABLET)                               |
| Confectionary | 91706000 | COCONUT CANDY, CHOCOLATE-COVERED                         |
| Confectionary | 91706100 | COCONUT CANDY, NO CHOCOLATE COVERING                     |
| Confectionary | 91706400 | COCONUT CANDY, P.R. STYLE                                |
| Confectionary | 91707000 | FONDANT CANDY  |
| Confectionary | 91707010 | FONDANT CANDY, CHOCOLATE COVERED                         |
| Confectionary | 91708000 | FRUIT PEEL, CANDIED                                      |
| Confectionary | 91708010 | FRUIT CANDY BAR  |
| Confectionary | 91708020 | SOFT FRUIT CONFECTION                                    |
| Confectionary | 91708030 | FRUIT LEATHER / FRUIT SNACKS CANDY                       |
| Confectionary | 91708040 | FUN FRUITS CREME SUPREMES CANDY                          |
| Confectionary | 91708070 | TAMARIND CANDY   |
| Confectionary | 91708100 | FRUIT SNACKS CANDY W/ HI VIT C                           |
| Confectionary | 91708150 | YOGURT COVERED FRUIT SNACKS CANDY, W/ ADDED VITAMIN C    |
| Confectionary | 91708160 | YOGURT COVERED FRUIT SNACKS CANDY ROLLS, W/ HIGH VITAMIN |
| Confectionary | 91709000 | C<br>GUMDROPS, CHOCOLATE-COVERED                         |

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| Confectionary | 91713010 | FUDGE, CHOCOLATE, CHOCOLATE-COATED                   |
| Confectionary | 91713020 | FUDGE, CHOCOLATE, CHOCOLATE-COATED, W/ NUTS          |
| Confectionary | 91713030 | FUDGE, CHOCOLATE                                     |
| Confectionary | 91713040 | FUDGE, CHOCOLATE, W/ NUTS                            |
| Confectionary | 91713050 | FUDGE, PEANUT BUTTER                                 |
| Confectionary | 91713060 | FUDGE, PEANUT BUTTER, W/ NUTS                        |
| Confectionary | 91713070 | FUDGE, VANILLA                                       |
| Confectionary | 91713080 | FUDGE, VANILLA, W/ NUTS                              |
| Confectionary | 91713090 | FUDGE, DIVINITY                                      |
| Confectionary | 91713100 | FUDGE, BROWN SUGAR (PANUCHI)                         |
| Confectionary | 91715000 | FUDGE, CARAMEL AND NUT, CHOCOLATE-COATED CANDY       |
| Confectionary | 91715100 | SNICKERS CANDY BAR                                   |
| Confectionary | 91715200 | BABY RUTH CANDY BAR                                  |
| Confectionary | 91715300 | 100 GRAND BAR (INCL \$100,000 BAR)                   |
| Confectionary | 91716010 | HALVAH, PLAIN  |
| Confectionary | 91716110 | HALVAH, CHOCOLATE-COVERED                            |
| Confectionary | 91718000 | HONEY-COMBED HARD CANDY, PEANUT BUTTER               |
| Confectionary | 91718050 | HONEY-COMBED CANDY, PEANUT BUTTER, CHOC-COVERED      |
| Confectionary | 91718100 | BUTTERFINGER CANDY BAR                               |
| Confectionary | 91718110 | BUTTERFINGER CRISP                                   |
| Confectionary | 91718110 | JIMMIES (INCLUDE CHOCOLATE-FLAVORED SPRINKLES)       |
| Confectionary | 91718200 | LADOO, ROUND BALL, ASIAN-INDIAN DESSERT              |
| -             |          | LICORICE CANDY                                       |
| Confectionary | 91721000 |  |
| Confectionary | 91723000 | MARSHMALLOW CHOCOLATE COVERED                        |
| Confectionary | 91723010 | MARSHMALLOW, CHOCOLATE-COVERED                       |
| Confectionary | 91723020 | MARSHMALLOW, CANDY-COATED                            |
| Confectionary | 91723050 | MARSHMALLOW, COCONUT-COATED                          |
| Confectionary | 91726000 | NOUGAT CANDY, W. CARAMEL CHOCOLATE COVERED           |
| Confectionary | 91726110 | NOUGAT CANDY, W/ CARAMEL, CHOCOLATE-COVERED          |
| Confectionary | 91726130 | MILKY WAY BAR  |
| Confectionary | 91726140 | MILKY WAY MIDNIGHT BAR (FORMERLY MILKY WAY DARK BAR) |
| Confectionary | 91726150 | MARS ALMOND BAR (FORMERLY MARS BAR)                  |
| Confectionary | 91726410 | NOUGAT CANDY, CHOCOLATE-COVERED                      |
| Confectionary | 91726420 | 3 MUSKETEERS BAR                                     |
| Confectionary | 91726425 | 3 MUSKETEERS TRUFFLE CRISP BAR                       |
| Confectionary | 91727010 | NUTS, CHOCOLATE-COVERED, NOT ALMONDS OR PEANUTS      |
| Confectionary | 91728000 | NUT ROLL, FUDGE OR NOUGAT, CARAMEL & NUTS            |
| Confectionary | 91728500 | SUGARED PECANS (SUGAR & EGG WHITE COATING)           |
| Confectionary | 91731000 | PEANUTS, CHOCOLATE-COVERED                           |
| Confectionary | 91731010 | M&M'S PEANUT CANDIES                                 |
| Confectionary | 91731060 | M&M'S PEANUT BUTTER CHOCOLATE CANDIES                |
| Confectionary | 91731100 | PEANUTS, SUGAR-COATED                                |
| Confectionary | 91731150 | PEANUTS, YOGURT-COVERED                              |
| Confectionary | 91732000 | PEANUT CANDY BAR                                     |
| Confectionary | 91732100 | PLANTERS PEANUT CANDY BAR                            |
| Confectionary | 91733000 | PEANUT BRITTLE                                       |
| Confectionary | 91733200 | PEANUT BAR, CHOCOLATE COVERED CANDY                  |
|               |          |  |

| Confectionary | 91734000  | PEANUT BUTTER CANDY, CHOCOLATE-COVERED                     |
|---------------|-----------|--|
| Confectionary | 91734100  | REESE'S PEANUT BUTTER CUPS                                 |
| Confectionary | 91734200  | REESE'S PIECES CANDY                                       |
| Confectionary | 91734300  | REESE'S STICKS   |
| Confectionary | 91734400  | REESE'S FAST BREAK   |
| Confectionary | 91734450  | REESE'S CRISPY CRUNCHY BAR                                 |
| Confectionary | 917344500 | PEANUT BUTTER MORSELS CANDY                                |
| Confectionary | 91735000  | PRALINES   |
| Confectionary | 91736000  | PINEAPPLE CANDY, P.R. STYLE                                |
| Confectionary | 91730000  | RAISINS, CHOCOLATE-COVERED                                 |
| Confectionary | 91739600  | RAISINS, YOGURT-COVERED                                    |
| Confectionary | 91742010  | SESAME CRUNCH CANDY (SAHADI)                               |
| Confectionary | 91742010  | GUMDROPS   |
| Confectionary | 91745010  | HARD CANDY   |
| Confectionary | 91745040  | BUTTERSCOTCH HARD CANDY                                    |
| Confectionary | 91745100  | SKITTLES CANDY   |
| Confectionary | 91745100  | SUGAR-COATED CHOCOLATE DISCS CANDY                         |
| Confectionary | 91746100  | M&M'S MILK CHOCOLATE CANDIES                               |
| Confectionary | 91746120  | SIXLETS CANDY  |
| Confectionary | 91746150  | EASTER EGG, CANDY-COATED CHOCOLATE                         |
| Confectionary | 91746200  | M&M'S PRETZEL CHOCOLATE CANDIES                            |
| Confectionary | 91750000  | TAFFY  |
| Confectionary | 91760000  | TOFFEE, PLAIN  |
| Confectionary | 91760100  | TOFFEE, CHOCOLATE COVERED (INCL HEATH BAR, SKOR)           |
| Confectionary | 91760200  | TOFFEE, CHOCOLATE-COATED, W/ NUTS                          |
| Confectionary | 91760500  | TRUFFLES   |
| Confectionary | 91760700  | WAX CANDY, LIQUID FILLED                                   |
| Confectionary | 91770000  | DIETETIC OR LOW CALORIE CANDY, NFS                         |
| Confectionary | 91770010  | DIETETIC OR LOW CALORIE GUMDROPS                           |
| Confectionary | 91770010  | DIETETIC OR LOW CALORIE HARD CANDY                         |
| Confectionary | 91770020  | DIETETIC OR LOW CALORIE CANDY, CHOCOLATE-COVERED           |
| Confectionary | 91770050  | MINTS, DIETETIC OR LOW CALORIE                             |
| Dessert       | 13200110  | PUDDING, NFS   |
| Dessert       | 13210110  | PUDDING, BREAD (INCLUDE W/ RAISINS)                        |
| Dessert       | 13210110  | PUERTO RICAN BREAD PUDDING MADE W/ EVAP MILK & RUM         |
| Dessert       | 13210160  | DIPLOMAT PUDDING, P.R. (BUDIN DIPLOMATICO)                 |
| Dessert       | 13210180  | PUDDING, MEXICAN BREAD (CAPIROTADA)                        |
| Dessert       | 13210190  | PUDDING, MEXICAN BREAD (CAPIROTADA), LOWER FAT             |
| Dessert       | 13210220  | PUDDING, CHOCOLATE, NS AS TO FROM DRY MIX/RTE              |
| Dessert       | 13210250  | PUDDING, CHOC, LO CAL, W/ART SWTNER, NS DRY/RTE            |
| Dessert       | 13210280  | PUDDING, NOT CHOC, NS FROM DRY OR RTE                      |
| Dessert       | 13210290  | PUDDING, NOT CHOC, LO CAL, W/ART SWTNER, NS DRY MIX OR RTE |
|               |           |  |
| Dessert       | 13210410  | PUDDING, RICE  |
| Dessert       | 13210450  | PUDDING, RICE FLOUR, W/ NUTS (INDIAN DESSERT)              |
| Dessert       | 13210500  | PUDDING, TAPIOCA, MADE FROM HOME RECIPE, MADE W/ MILK      |
| Dessert       | 13210520  | PUDDING, TAPIOCA, MADE FROM DRY MIX, MADE W/ MILK          |

| Dessert | 13210530 | PUDDING, TAPIOCA, CHOCOLATE, MADE W/ MILK                        |  |
|---------|----------|--|--|
| Dessert | 13210530 | PUDDING, COCONUT   |  |
| Dessert | 13210710 | PUDDING, INDIAN (MILK, MOLASSES, CORNMEAL-BASED)                 |  |
| Dessert | 13210750 | PUDDING, PUMPKIN   |  |
| Dessert | 13210810 | P.R. PUMPKIN PUDDING (FLAN DE CALABAZA)                          |  |
| Dessert | 13220110 | PUDDING, NOT CHOCOLATE, PREPARED FROM DRY MIX, MILK ADDED        |  |
| 2633616 | 13220110 | TODDING/NOT GROCOL (TEXTILED THOSE DICTION) IZER (NDDED          |  |
| Dessert | 13220120 | PUDDING,CHOCOLATE,PREPARED FROM DRY MIX,MILK ADDED               |  |
| Dessert | 13220210 | PUDDING,NOT CHOC,FROM DRY,LOW CAL,ARTIFICIAL                     |  |
| Dessert | 13220220 | SWEET,W/MILK PUDDING,CHOC,FROM DRY,LOW CAL,ARTIFICIAL SWEET,MILK |  |
|         |          | ADDED  |  |
| Dessert | 13220230 | PUDDING, RTE, CHOCOLATE, RED FAT                                 |  |
| Dessert | 13220235 | PUDDING, RTE, CHOCOLATE, FAT FREE                                |  |
| Dessert | 13220240 | PUDDING, RTE, FLAVORS OTHER THAN CHOCOLATE, RED FAT              |  |
| Dessert | 13220245 | PUDDING, RTE, FLAVORS OTHER THAN CHOCOLATE, FAT FREE             |  |
| Dessert | 13230110 | PUDDING, RTE, FLAVORS OTHER THAN CHOCOLATE                       |  |
| Dessert | 13230120 | PUDDING, RTE, LOW CAL, W/ARTIFICIAL SWTNR, NOT CHOC              |  |
| Dessert | 13230130 | PUDDING, RTE, CHOCOLATE  |  |
| Dessert | 13230140 | PUDDING,RTE, LO CAL/ W ART SWTNER, CHOC                          |  |
| Dessert | 13230200 | PUDDING, RTE, CHOC & NON-CHOC FLAVORS COMBINED                   |  |
| Dessert | 13230500 | PUDDING, READY-TO-EAT, TAPIOCA                                   |  |
| Dessert | 13230510 | PUDDING, READY-TO-EAT, TAPIOCA, FAT FREE                         |  |
| Dessert | 13241000 | PUDDING, W/ FRUIT & VANILLA WAFERS                               |  |
| Dessert | 13252200 | MILK DESSERT OR MILK CANDY, P.R. (DULCE DE LECHE)                |  |
| Dessert | 13252500 | BARFI/BURFI,INDIAN DESSERT,FROM MILK/CREAM/RICOTTA               |  |
| Dessert | 14610200 | COTTAGE CHEESE, W/ GELATIN DESSERT                               |  |
| Dessert | 14610210 | COTTAGE CHEESE, W/ GELATIN DESSERT & FRUIT                       |  |
| Dessert | 14610250 | COTTAGE CHEESE W/ GELATIN DESSERT & VEGETABLES                   |  |
| Dessert | 53344300 | DESSERT PIZZA  |  |
| Dessert | 53386000 | PIE, PUDDING, NOT CHOCOLATE                                      |  |
| Dessert | 53386050 | PIE, PUDDING, NOT CHOC, INDIVIDUAL SIZE                          |  |
| Dessert | 53386250 | PIE, PUDDING, CHOC, W/ CHOC COATING, INDIVID SIZE                |  |
| Dessert | 53386500 | PIE, PUDDING, NOT CHOC, CHOC-COATED, INDIVID SIZE                |  |
| Dessert | 53391200 | VANILLA WAFER DESSERT BASE                                       |  |
| Dessert | 53415100 | CRISP, APPLE, APPLE DESSERT                                      |  |
| Dessert | 53420000 | CREAM PUFF/ECLAIR, CUSTARD/CREAM-FILLED, NS ICING                |  |
| Dessert | 53420250 | CREAM PUFFS, NO FILLING OR ICING                                 |  |
| Dessert | 53430000 | CREPE, DESSERT TYPE, NS AS TO FILLING                            |  |
| Dessert | 53430100 | CREPE, DESSERT TYPE, CHOCOLATE-FILLED                            |  |
| Dessert | 53430200 | CREPE, DESSERT TYPE, FRUIT-FILLED                                |  |
| Dessert | 53430300 | CREPE, DESSERT TYPE, ICE CREAM-FILLED                            |  |
| Dessert | 53441210 | BASBOUSA (SEMOLINA DESSERT DISH)                                 |  |
| Dessert | 53452100 | PASTRY, FRUIT-FILLED   |  |
| Dessert | 53452120 | PASTRY, ASIAN, MADE WITH BEAN OR LOTUS SEED PASTE FILLING        |  |
| Dessert | 53452130 | PASTRY, ASIAN, MADE WITH BEAN PASTE AND SALTED EGG YOLK FILL     |  |

| Dessert | 53452150 | PASTRY, CHINESE (INCLUDE 9-LAYER PUDDING)   |
|---------|----------|---|
| Dessert | 53452170 | PASTRY, COOKIE TYPE, FRIED(INCL POLISH PACZKI)  |
| Dessert | 53452200 | PASTRY, ITALIAN, W/ CHEESE (INCLUDE CANNOLI)  |
| Dessert | 53452400 | PASTRY, PUFF  |
| Dessert | 53452420 | PASTRY, PUFF, CUSTARD/CREAM FILLED, ICED/NOT ICED   |
| Dessert | 53452450 | CHEESE PASTRY PUFF  |
| Dessert | 53452500 | PASTRY, MAINLY FLOUR & WATER, FRIED   |
| Dessert | 53500100 | BREAKFAST PASTRY, NFS   |
| Dessert | 53510000 | DANISH PASTRY, PLAIN/SPICE (INCL W/ ICING)  |
| Dessert | 53510000 | DANISH PASTRY, W/ FRUIT   |
| Dessert | 53510100 | DANISH PASTRY, W/ CHEESE  |
| Dessert | 53520000 | DOUGHNUT, NS AS TO CAKE OR YEAST  |
| Dessert | 53520000 | DOUGHNUT, NS AS TO CARE OR TEAST  DOUGHNUT, CAKE TYPE   |
| Dessert | 53520110 | DOUGHNUT, CARE TIPE DOUGHNUT, CHOCOLATE, CAKE TYPE  |
| Dessert | 53520120 | DOUGHNUT, CAKE TYPE, CHOCOLATE COVERED  |
| Dessert | 53520140 | DOUGHNUT, CAKE TYPE, CHOCOLATE COVERED, W/ PEANUTS  |
| Dessert | 53520130 | DOUGHNUT, CARE TYPE, CHOCOLATE COVERED, W/ PLANOTS  DOUGHNUT, CHOCOLATE, CAKE TYPE, WITH CHOCOLATE ICING  |
| Dessert | 53520100 | DOUGHNUT, CHOCOLATE, CARE TYPE, WITH CHOCOLATE ICING DOUGHNUT, CHOCOLATE, RAISED OR YEAST, WITH CHOCOLATE |
| Dessert | 33321100 | ICING   |
| Dessert | 53521230 | DOUGHNUT, CUSTARD-FILLED, WITH ICING  |
| Dessert | 53610100 | COFFEE CAKE, CRUMB OR QUICK-BREAD TYPE  |
| Dessert | 53610170 | COFFEE CAKE, CRUMB OR QUICK-BREAD TYPE, W/ FRUIT  |
| Dessert | 53610200 | COFFEECAKE, CRUMB OR QUICK-BREAD TYPE, CHEESE FILLD   |
| Dessert | 58118110 | CORNSTARCH COCONUT DESSERT, P.R. (TEMBLEQUE)  |
| Dessert | 58118210 | CORNMEAL COCONUT DESSERT, P.R.  |
| Dessert | 58149110 | NOODLE PUDDING (INCLUDE KUGEL)  |
| Dessert | 58149160 | NOODLE PUDDING,W/ MILK  |
| Dessert | 58157110 | SPICEY RICE PUDDING, P.R.   |
| Dessert | 58157210 | RICE PUDDING MADE W/ COCONUT MILK, P.R.   |
| Dessert | 58164210 | RICE DESSERT/SALAD W/ FRUIT   |
| Dessert | 63402990 | FRUIT SALAD (W/ CITRUS) W/ PUDDING  |
| Dessert | 63403000 | FRUIT SALAD (NO CITRUS FRUITS) W/ PUDDING   |
| Dessert | 63403100 | FRUIT DESSERT W/ CREAM & OR PUDDING & NUTS  |
| Dessert | 71702000 | POTATO PUDDING  |
| Dessert | 91304010 | TOPPING, BUTTERSCOTCH OR CARAMEL  |
| Dessert | 91304020 | TOPPING, CHOCOLATE, THICK, FUDGE TYPE   |
| Dessert | 91304030 | TOPPING, FRUIT  |
| Dessert | 91304040 | TOPPING, MARSHMALLOW  |
| Dessert | 91304060 | TOPPING, NUT (WET)  |
| Dessert | 91304070 | TOPPING, PEANUT BUTTER, THICK FUDGE TYPE  |
| Dessert | 91304080 | TOPPING, FRUIT, UNSWEETENED   |
| Dessert | 91304090 | TOPPING, CHOC FLAVOR HAZELNUT SPREAD (INCL NUTELLA)   |
| Dessert | 91304250 | TOPPING, MILK CHOCOLATE W/ CEREAL   |
| Dessert | 91304300 | TOPPING, CHOCOLATE, HARD COATING  |
| Dessert | 91305010 | ICING, CHOCOLATE  |
| Dessert | 91305020 | ICING, WHITE  |
| Dessert | 91351020 | TOPPING, DIETETIC   |

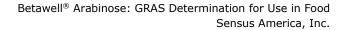
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|----------------|----------|--|
| Dessert        | 91361040 | DESSERT SAUCE  |
| Dessert        | 91500200 | GELATIN POWDER, SWEETENED, DRY                         |
| Dessert        | 91501010 | GELATIN DESSERT  |
| Dessert        | 91501015 | GELATIN SNACKS   |
| Dessert        | 91501020 | GELATIN DESSERT W/ FRUIT                               |
| Dessert        | 91501030 | GELATIN DESSERT W/ WHIPPED CREAM                       |
| Dessert        | 91501040 | GELATIN DESSERT W/ FRUIT & WHIPPED CREAM               |
| Dessert        | 91501050 | GELATIN DESSERT W/ CREAM CHEESE                        |
| Dessert        | 91501060 | GELATIN DESSERT W/ SOUR CREAM                          |
| Dessert        | 91501070 | GELATIN DESSERT W/ FRUIT & SOUR CREAM                  |
| Dessert        | 91501080 | GELATIN DESSERT W/ FRUIT & CREAM CHEESE                |
| Dessert        | 91501090 | GELATIN DESSERT W/ FRUIT, VEGETABLES, & NUTS           |
| Dessert        | 91501100 | GELATIN SALAD W/ VEGETABLES                            |
| Dessert        | 91501110 | GELATIN DESSERT W/ FRUIT & WHIPPED TOPPING             |
| Dessert        | 91501120 | GELATIN DESSERT W/ FRUIT & VEGETABLES                  |
| Dessert        | 91510100 | GELATIN POWDER, DIETETIC, DRY                          |
| Dessert        | 91511010 | GELATIN DESSERT, DIETETIC, W/ LO CAL SWEETENER         |
| Dessert        | 91511020 | GELATIN DESSERT, DIET, W/ FRUIT, LO CAL SWEETNER       |
| Dessert        | 91511030 | GELATIN DESSERT, DIETETIC, W/ WHIPPED TOPPING          |
| Dessert        | 91511050 | GELATIN DESSERT, DIETETIC, W/ CREAM CHEESE             |
| Dessert        | 91511060 | GELATIN DESSERT, DIETETIC, W/ SOUR CREAM               |
| Dessert        | 91511070 | GELATIN DESSERT, DIETETIC, W/ FRUIT & SOUR CREAM       |
| Dessert        | 91511080 | GELATIN DESSERT, DIETETIC, W/ FRUIT & CREAM CHEESE     |
| Dessert        | 91511090 | GELATIN DESSERT, DIETETIC, W/ FRUIT & VEGETABLES       |
| Dessert        | 91511100 | GELATIN DESSERT, DIETETIC, W/ VEGETABLES               |
| Dessert        | 91511110 | GELATIN DESSERT, DIETETIC, W/ FRUIT & WHIP TOPPING     |
| Dessert        | 91512010 | DANISH DESSERT PUDDING                                 |
| Frozen Dessert |          | YOGURT, FROZEN, NS AS TO FLAVOR, NS TO TYPE OF MILK    |
| Frozen Dessert |          | YOGURT, FROZEN, NOT CHOCOLATE, TYPE OF MILK NS         |
| Frozen Dessert |          | YOGURT, FROZEN, CHOCOLATE, TYPE OF MILK NS             |
| Frozen Dessert | 11460150 | YOGURT, FROZEN, NS AS TO FLAVOR, LOWFAT MILK           |
| Frozen Dessert | 11460160 | YOGURT, FROZEN, CHOCOLATE, LOWFAT MILK                 |
| Frozen Dessert | 11460170 | YOGURT, FROZEN, NOT CHOCOLATE, LOWFAT MILK             |
| Frozen Dessert | 11460190 | YOGURT, FROZEN, NS AS TO FLAVOR, NONFAT MILK           |
| Frozen Dessert | 11460200 | YOGURT, FROZEN, CHOCOLATE, NONFAT MILK                 |
| Frozen Dessert | 11460250 | YOGURT,FROZEN,NOT CHOCOLATE,W/ SORBET/SORBET-COATED    |
| F D            | 11460200 | VOCUPT FROZEN, NOT CHOCOLATE NONEAT MILIC              |
| Frozen Dessert |          | YOGURT, FROZEN, NOT CHOCOLATE, NONFAT MILK             |
| Frozen Dessert |          | YOGURT, FROZEN, CHOCOLATE, WHOLE MILK                  |
| Frozen Dessert |          | YOGURT, FROZEN, NOT CHOCOLATE, WHOLE MILK              |
| Frozen Dessert |          | YOGURT, FROZEN, CHOCOLATE, CHATER                      |
| Frozen Dessert |          | YOGURT, FROZEN, CANDWIGH                               |
| Frozen Dessert |          | YOGURT, FROZEN, CONE, CHOCOLATE                        |
| Frozen Dessert |          | YOGURT, FROZEN, CONE, NOT CHOCOLATE                    |
| Frozen Dessert |          | YOGURT, FROZEN, CONE, NOT CHOCOLATE                    |
| Frozen Dessert |          | YOGURT, FROZEN, CONE, NOT CHOCOLATE, LOWFAT MILK       |
| Frozen Dessert | 11480020 | YOGURT, WHOLE MILK, BF, W/FRUIT& MULTIGRAIN CEREAL,NFS |

| Frozen Dessert                   | 11480030             | YOGURT, WHOLE MILK, BF, W/FRUIT&MULTIGRAIN CEREAL + IRON                               |  |
|----------------------------------|----------------------|--|--|
| Frozen Dessert                   | 11480040             | YOGURT, WHOLE MILK, BF, W/FRUIT&MULTIGRAIN CEREAL + DHA                                |  |
| Frozen Dessert                   | 11541400             | MILK SHAKE WITH MALT (INCL MALTED MILK W/ICE CREAM)                                    |  |
| Frozen Dessert                   | 12140110             | WHIPPED TOPPING, DAIRY BASED, FAT FREE, PRESSURIZED                                    |  |
|                                  |                      | CONTAINR   |  |
| Frozen Dessert                   | 12220000             | WHIPPED TOPPING, NONDAIRY, NS AS TO CND/FRZ/POWDER                                     |  |
| Frozen Dessert                   | 12220100             | WHIPPED TOPPING, NONDAIRY, PRESSURIZED CAN   |  |
| Frozen Dessert                   | 12220200             | WHIPPED TOPPING, NONDAIRY, FROZEN (INCL COOL WHIP)                                     |  |
| Frozen Dessert                   | 12220250             | WHIPPED TOPPING, NONDAIRY, FZN, LOWFAT (INCL COOL)                                     |  |
| Frozen Dessert<br>Frozen Dessert | 12220270<br>12220280 | WHIPPED TOPPING, NONDAIRY, FROZEN, FAT FREE  |  |
| Frozen Dessert                   | 13110000             | WHIPPED TOPPING, NONDAIRY, FROZEN, SUGAR FREE ICE CREAM, NFS                           |  |
| Frozen Dessert                   | 13110000             | ICE CREAM, REGULAR, NOT CHOCOLATE  |  |
| Frozen Dessert                   | 13110100             | ICE CREAM, REGULAR, CHOCOLATE  |  |
| Frozen Dessert                   | 13110110             | ICE CREAM, RICH, FLAVORS OTHER THAN CHOCOLATE  |  |
| Frozen Dessert                   | 13110120             | ICE CREAM, RICH, CHOCOLATE   |  |
| Frozen Dessert                   | 13110130             | ICE CREAM, RICH, NS AS TO FLAVOR   |  |
| Frozen Dessert                   | 13110200             | ICE CREAM, SOFT SERVE, NOT CHOCOLATE   |  |
| Frozen Dessert                   | 13110210             | ICE CREAM, SOFT SERVE, CHOCOLATE   |  |
| Frozen Dessert                   | 13110220             | ICE CREAM, SOFT SERVE, NS AS TO FLAVOR   |  |
| Frozen Dessert                   | 13110310             | ICE CREAM, NO SUGAR ADDED, NS AS TO FLAVOR   |  |
| Frozen Dessert                   | 13110320             | ICE CREAM, NO SUGAR ADDED, FLAVORS OTHER THAN CHOCOLATE                                |  |
| Francis Daggart                  | 13110330             | TOT ODEAM, NO CUCAD ADDED, CHOCOLATE   |  |
| Frozen Dessert<br>Frozen Dessert | 13110330             | ICE CREAM, NO SUGAR ADDED, CHOCOLATE ICE CREAM BAR OR STICK, NOT CHOC- OR CAKE-COVERED |  |
| Frozen Dessert                   | 13120030             | ICE CREAM BAR/STICK, CHOCOLATE COVERED   |  |
| Frozen Dessert                   | 13120100             | ICE CREAM BAR, CHOCOLATE/CARAMEL COVERED, W/ NUTS                                      |  |
| Frozen Dessert                   | 13120110             | ICE CREAM BAR,RICH CHOC ICE CREAM,THICK CHOC COVER                                     |  |
| Frozen Dessert                   | 13120121             | ICE CREAM BAR,RICH ICE CREAM,THICK CHOC COVER  |  |
| Frozen Dessert                   | 13120130             | ICE CREAM BAR/STICK,RICH ICE CREAM,CHOC COVER,W/NUT                                    |  |
| Frozen Dessert                   | 13120140             | ICE CREAM BAR/STICK, CHOC ICE CREAM, CHOC COVER  |  |
| Frozen Dessert                   | 13120300             | ICE CREAM BAR, CAKE-COVERED  |  |
| Frozen Dessert                   | 13120310             | ICE CREAM BAR, STICK OR NUGGET, WITH CRUNCH COATING                                    |  |
| Frozen Dessert                   | 13120400             | ICE CREAM BAR/STICK W/ FRUIT   |  |
| Frozen Dessert                   | 13120500             | ICE CREAM SANDWICH   |  |
| Frozen Dessert                   | 13120550             | ICE CREAM COOKIE SANDWICH (INCLUDE CHIPWICH)   |  |
| Frozen Dessert                   | 13120700             | ICE CREAM CONE, W/ NUTS, NOT CHOCOLATE   |  |
| Frozen Dessert                   | 13120710             | ICE CREAM CONE, CHOC-COVERED, W/ NUTS, NOT CHOC  |  |
| Frozen Dessert                   | 13120720             | ICE CREAM CONE, CHOC-COVERED OR DIPPED, NOT CHOC                                       |  |
| Frozen Dessert                   | 13120730             | ICE CREAM CONE, NO TOPPING, NOT CHOCOLATE  |  |
| Frozen Dessert                   | 13120740             | ICE CREAM CONE, NO TOPPING, NS AS TO FLAVOR  |  |
| Frozen Dessert                   | 13120750             | ICE CREAM CONE, W/NUTS, CHOCOLATE ICE CREAM  |  |
| Frozen Dessert                   | 13120760             | ICE CREAM CONE, CHOC-COVERED, CHOC ICE CREAM   |  |
| Frozen Dessert                   | 13120770             | ICE CREAM CONE, NO TOPPING, CHOCOLATE ICE CREAM  |  |
| Frozen Dessert                   | 13120780             | ICE CREAM CONE, CHOC-COVERED, W/NUT, CHOC ICE CREAM                                    |  |
| Frozen Dessert                   | 13120790             | ICE CREAM SUNDAE CONE (INCL DRUMSTICK, ALL FLAVORS)                                    |  |

| Frozen Dessert | 13120800 | ICE CREAM SODA, NOT CHOCOLATE                                |  |
|----------------|----------|--|--|
| Frozen Dessert |          | ICE CREAM SODA, CHOCOLATE                                    |  |
| Frozen Dessert | 13121000 | ICE CREAM SUNDAE, TOPPING NS, W/ WHIPPED CREAM               |  |
| Frozen Dessert |          | ICE CREAM SUNDAE, FRUIT TOPPING, W/ WHIPPED CREAM            |  |
| Frozen Dessert | 13121200 | ICE CREAM SUNDAE, PREPACKAGED, NOT CHOCOLATE                 |  |
| Frozen Dessert | 13121300 | ICE CREAM SUNDAE, CHOCOLATE TOPPING, W/ WHIPPED CREAM        |  |
| Frozen Dessert | 13121400 | ICE CREAM SUNDAE, NOT FRUIT/ CHOC TOP,W/ WHIP CREAM          |  |
| Frozen Dessert | 13121500 | CE CREAM SUNDAE, FUDGE TOPPING, W/ CAKE                      |  |
| Frozen Dessert | 13122100 | ICE CREAM PIE, NO CRUST                                      |  |
| Frozen Dessert | 13122500 | ICE CREAM PIE, COOKIE CRUST, FUDGE TOPPING, WHIP CREAM       |  |
| Frozen Dessert | 13126000 | ICE CREAM, FRIED   |  |
| Frozen Dessert | 13127000 | DIPPIN' DOTS, ICE CREAM, FLAVORS OTHER THAN CHOCOLATE        |  |
| Frozen Dessert | 13127010 | DIPPIN' DOTS, ICE CREAM, CHOCOLATE                           |  |
| Frozen Dessert |          | LT ICE CREAM, NS FLAV ( ICE MILK)                            |  |
| Frozen Dessert | 13130300 | LIGHT ICE CREAM, NOT CHOCOLATE (FORMERLY ICE MILK)           |  |
| Frozen Dessert | 13130310 | LIGHT ICE CREAM, CHOCOLATE (FORMERLY ICE MILK)               |  |
| Frozen Dessert | 13130320 | LIGHT ICE CREAM, NO SUGAR ADDED, NS AS TO FLAVOR             |  |
| Frozen Dessert | 13130330 | LIGHT ICE CREAM, NO SUGAR ADDED, NOT CHOCOLATE               |  |
| Frozen Dessert | 13130340 | LIGHT ICE CREAM, NO SUGAR ADDED, CHOCOLATE                   |  |
| Frozen Dessert | 13130590 | LIGHT ICE CREAM, SOFT SERVE, NS FLAVOR (FORMERLY ICE MILK)   |  |
|                | 12122600 | LIGHT TOT OPEN COST OFFICE MOT CHOO (FORMERLY TOT MILL)      |  |
| Frozen Dessert | 13130600 | LIGHT ICE CREAM, SOFT SERVE, NOT CHOC (FORMERLY ICE MILK)    |  |
| Frozen Dessert | 13130610 | LIGHT ICE CREAM, SOFT SERVE CHOC (TASTEE FRZ, DAIRY QUEEN)   |  |
| Frozen Dessert | 13130620 | LIGHT ICE CREAM, SOFT SERVE CONE, NOT CHOC (DAIRY QUEEN)     |  |
| Frozen Dessert | 13130630 | LIGHT ICE CREAM, SOFT SERVE CONE, CHOC (FORMERLY ICE MILK)   |  |
| Frozen Dessert | 13130640 | LIGHT ICE CREAM, SOFT SERVE CONE, NS FLAV(FORMERLY ICE MILK) |  |
| Frozen Dessert | 13130700 | LIGHT ICE CREAM, SOFT SERVE, BLENDED W/ CANDY OR COOKIES     |  |
| Frozen Dessert | 13135000 | ICE CREAM SANDWICH, MADE W/ LIGHT ICE CREAM, NOT CHOCOLATE   |  |
| Frozen Dessert | 13135010 | ICE CREAM SANDWICH, MADE W/ LIGHT CHOCOLATE ICE CREAM        |  |
| Frozen Dessert | 13136000 | ICE CREAM SANDWICH, MADE W/ LIGHT, NO SUGAR ADDED ICE CREAM  |  |
| Frozen Dessert | 13140100 | LIGHT ICE CREAM,BAR/STICK, CHOC-COATED (FORMERLY ICE MILK)   |  |
| Frozen Dessert | 13140110 | LIGHT ICE CREAM,BAR, CHOC COVERED,W/NUTS (FORMERLY ICE MILK) |  |
| Frozen Dessert | 13140450 | LIGHT ICE CREAM,CONE, NFS (FORMERLY ICE MILK)                |  |
| Frozen Dessert | 13140500 | LIGHT ICE CREAM,CONE, NOT CHOCOLATE (FORMERLY ICE MILK)      |  |
| _              |          | ,  |  |
| Frozen Dessert |          | LIGHT ICE CREAM,CONE, CHOCOLATE (FORMERLY ICE MILK)          |  |
| Frozen Dessert | 13140570 | LIGHT ICE CREAM, NO SUGAR ADDED, CONE, NS AS TO FLAVOR       |  |
| Frozen Dessert | 13140575 | LIGHT ICE CREAM, NO SUGAR ADDED, CONE, NOT CHOC              |  |
| Frozen Dessert | 13140580 | LIGHT ICE CREAM, NO SUGAR ADDED, CONE, CHOCOLATE             |  |

| Frozen Dessert | 13140600 | LIGHT ICE CREAM, SUNDAE, SOFT SERVE, CHOC/FUDGE TOP (ICE MILK) |  |
|----------------|----------|--|--|
| Frozen Dessert | 13140630 | LIGHT ICE CREAM, SUNDAE, SOFT SERVE, FRUIT TOPPING (ICE MILK)  |  |
| Frozen Dessert | 13140650 | LIGHT ICE CREAM, SUNDAE, SOFT SERVE, NOT FRUIT/CHOC TOPPING    |  |
| Frozen Dessert | 13140660 | LIGHT ICE CREAM, SUNDAE, CHOC / FUDGE TOP (W/O WHIP CREAM)     |  |
| Frozen Dessert | 13140670 | LIGHT ICE CREAM, SUNDAE, FRUIT TOP (W/O WHIP CREAM) (ICE MILK) |  |
| Frozen Dessert | 13140680 | LIGHT ICE CREAM, SUNDAE, NO FRUIT/CHOC TOP (W/O WHIP CREAM)    |  |
| Frozen Dessert | 13140700 | LIGHT ICE CREAM,CREAMSICLE OR DREAMSICLE (FORMERLY ICE MILK)   |  |
| Frozen Dessert | 13140710 | LIGHT ICE CREAM, CREAMSICLE OR DREAMSICLE, NO SUGAR ADDED      |  |
| Frozen Dessert | 13140900 | LIGHT ICE CREAM, FUDGESICLE (FORMERLY ICE MILK)                |  |
| Frozen Dessert | 13142000 | MILK DESSERT BAR/STICK, FROZEN, W/ COCONUT                     |  |
| Frozen Dessert | 13160150 | FAT FREE ICE CREAM, NO SUGAR ADD, CHOC                         |  |
| Frozen Dessert | 13160160 | FAT FREE ICE CREAM, NO SUGAR ADD, FLAVORS OTHER THAN CHOO      |  |
| Frozen Dessert | 13160400 | FAT FREE ICE CREAM, FLAVORS OTHER THAN CHOC                    |  |
| Frozen Dessert | 13160410 | FAT FREE ICE CREAM, CHOC                                       |  |
| Frozen Dessert | 13160420 | FAT FREE ICE CREAM, NS AS TO FLAVOR                            |  |
| Frozen Dessert | 13161000 | MILK DESSERT BAR, FROZEN, MADE FROM LOWFAT MILK                |  |
| Frozen Dessert | 13161500 | MILK DESSERT SANDWICH BAR, FROZEN, DIETARY                     |  |
| Frozen Dessert | 13161520 | MILK DESSERT SANDWICH BAR,FRZ,W/LOW-CAL SWEET,LOFAT            |  |
| Frozen Dessert | 13161600 | MILK DES BAR, FROZEN, LOFAT MILK&LO CAL SWEETENER              |  |
| Frozen Dessert | 13161630 | LIGHT ICE CREAM,BAR/STICK, W/ LOW-CAL SWEETENER, CHOC          |  |
| Frozen Dessert | 32120100 | EGG DESSERT, CUSTARD-LIKE, W/ WATER & SUGAR, P.R.              |  |
| Frozen Dessert | 41480000 | TOFU FROZEN DESSERT, NOT CHOCOLATE (INCL TOFUTTI)              |  |
| Frozen Dessert | 41480010 | TOFU FROZEN DESSERT, CHOCOLATE (INCLUDE TOFUTTI)               |  |

| Table D-2:     | Table D-2: Special Food Considerations for EDI Calculations    |   |  |  |  |
|----------------|--|---|--|--|--|
| NHANES<br>Code | Description  | Assumed<br>Condiment<br>Weight<br>Percent |  |  |  |
| 27150370       | SARDINES W/ MUSTARD SAUCE (MIXTURE)                            | 0.05                                      |  |  |  |
| 27510310       | CHEESEBURGER W/ TOMATO & OR CATSUP, ON BUN                     | 0.05                                      |  |  |  |
| 27510320       | CHEESEBURGER, 1/4 LB MEAT,W/ TOMATO/CATSUP, BUN                | 0.05                                      |  |  |  |
| 27510330       | DOUBLE CHEESEBURGER W/TOMATO & OR CATSUP, ON BUN               | 0.05                                      |  |  |  |
| 27510350       | CHEESEBURGER, 1/4 LB MEAT, W/ MAYO & TOMATO/CATSUP, ON BUN     | 0.05                                      |  |  |  |
| 27510360       | BACON CHEESEBURGER, W/MAYO/SALAD DRSG, TOMATO/CATSUP,ON<br>BUN | 0.05                                      |  |  |  |
| 27510400       | BACON CHEESEBURGER, 1/4 LB MEAT, W/ TOMATO, ON BUN             | 0.05                                      |  |  |  |
| 27510510       | HAMBURGER, W/ TOMATO & OR CATSUP, ON BUN                       | 0.05                                      |  |  |  |
| 27510560       | HAMBURGER, 1/4 LB MEAT W/ MAYO & TOMATO/CATSUP, ON BUN         | 0.05                                      |  |  |  |
| 27510620       | HAMBURGER, 1/4 LB MEAT, W/ TOMATO & OR CATSUP, BUN             | 0.05                                      |  |  |  |
| 27510690       | DOUBLE HAMBURGER,1/2 LB MEAT,W/MAYO&TOM/CATSUP,BUN             | 0.05                                      |  |  |  |





APPENDIX F GRAS EXPERT PANEL REPORT



# expert Panel Consensus Report on the Generally Recognized as Safe Status of the Proposed Uses of Betawell® Arabinose, a Sugar Extracted from Beets

Ramboll Environ US Corporation (Ramboll Environ), on behalf of Cosun Biobased Products B.V. (Cosun), convened a panel of experts (Expert Panel), qualified by their scientific training and experience to evaluate the safety of food ingredients, to determine the safety, suitability and the Generally Recognized As Safe (GRAS) status of the proposed uses of Cosun's L-arabinose derived from sugar beet pulp, referred to by Cosun as Betawell® Arabinose (also herein "the Ingredient"). The Expert Panel Members were Joseph F. Borzelleca, Ph.D. (Professor Emeritus, Virginia Commonwealth University School of Medicine); Judith K. Jones, M.D., Ph.D. (President and CEO, The Degge Group, Ltd. and President, Pharmaceutical Education & Research Institute), and John A. Thomas, Ph.D., ATS (Adjunct Professor, Department of Pharmacology & Toxicology, Indiana University School of Medicine).

The Expert Panel, independently and collectively, critically evaluated the available information presented in documents prepared by Ramboll Environ (the GRAS dossier). This information consisted of the description of the substance (including the identity and physical and chemical properties), analyses demonstrating and confirming the purity and manufacturing consistency of the product, the chemical identity of Betawell® Arabinose, and product specifications. A critical overview of the history of use (consumer exposure), intended conditions of use, levels of use and estimated daily intakes (EDIs) from the intended conditions of use, its regulatory status, product stability and safety assessment of the Cosun Betawell® Arabinose ingredient was provided by Ramboll Environ to the Expert Panel. The Expert Panel reviewed and evaluated this information and also evaluated other materials deemed appropriate and necessary for this review.

As part of its independent and collective critical evaluation, the Expert Panel convened by teleconference on 30 March 2017 with representatives of Ramboll Environ. At the conclusion of its deliberations, the Expert Panel unanimously agreed to the conclusions described herein. A summary of the basis for these conclusions follows.

# Description of Betawell® Arabinose, the Manufacturing Process, and Product Specifications

The subject of this GRAS determination is L-arabinose, a pentose (five carbon or C5) sugar commonly found in the pectin and hemicellulose of plants and fruits. The Chemical Abstracts Service Registry Number (CASRN) for arabinose is 5328-37-0. The empirical formula for Betawell® Arabinose is  $C_5H_{10}O_5$  and the structure of Betawell® Arabinose is

Figure 1. Structural Formula of Betawell® Arabinose



Betawell® Arabinose is extracted from sugar beets grown in the Netherlands and Germany. Cosun sources the sugar beet as pulp directly from nearby sugar mills. The sugar beet pulp undergoes hydrolysis with enzymes (the enzymatic process; food use approved enzymes) or sodium hydroxide (the alkaline process). The remaining solid material is removed by a decanter centrifuge resulting in a hydrolysate. The hydrolysate is filtered with a nanofiltration membrane to separate the arabinose-containing oligosaccharides from the other carbohydrates. The oligosaccharide stream is collected and further hydrolyzed by the addition of nitric acid. The product is a diluted syrup with a high relative L-arabinose content (approximately 40% by weight). The syrup is further purified by removing organic acids and salts by two ion exchange columns, and the remaining oligosaccharides by an ultrafiltration membrane.

The purified syrup contains a mixture of C5 and C6 sugars. The C6 sugars are removed by a digestion step using baker's yeast (Saccharomyces cerevisiae). The yeast is removed by a microfiltration step. The syrup is then heated to evaporate the liquid and subsequently cooled to form the L-arabinose crystals. This step can be repeated two or three times to optimize the production of L-arabinose. The L-arabinose crystals are centrifuged and dried. After a grinding step to remove solid particles and lumps, the L-arabinose is packaged in food approved bags and/or bag in boxes.

Cosun has established specifications for their Betawell® Arabinose ingredient to ensure that a consistent food-grade ingredient is produced. The chemical, physical and microbiological specifications of Betawell® Arabinose are presented in Table 1. Cosun analyzed three typical batches to ensure a consistent product compliant with their specifications is generated. These tested batches met the established specifications demonstrating that the Betawell® Arabinose ingredient complies with appropriate specifications for the food-grade ingredient and that a consistent product can be and is produced. This compliance and consistency in specifications is confirmed in the certificates of analysis of the ingredient.

Stability tests confirmed that Betawell® Arabinose has a shelf life of 24 months when stored in dry conditions out of sunlight.

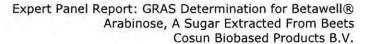
# History of Exposure and Use

Arabinose is a ubiquitous sugar that occurs in common foods both as a monosaccharide and as a component of polysaccharides. Arabinose is a major component of dietary fibers such as sugar beet fiber and gum arabic, both GRAS food ingredients. Arabinose is also chemically very similar to existing non-nutritive sweeteners such as psicose, ribose and tagatose which are GRAS. Arabinose is a recognized food ingredient in Japan where it may be added to foods used to maintain blood sugar levels. The U.S. general population is currently exposed to naturally occurring arabinose and to chemically similar monosaccharides at high levels. The estimated background consumption of L-arabinose is up to 5.8 g/day including arabinose in naturally occurring polysaccharides if the adequate intake of fiber (up to 38 g/day) is consumed.

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|                                  |               | Alkaline Process |        |        | Enzymatic Process |        |             | Analytical |                  |
|----------------------------------|---------------|------------------|--------|--------|-------------------|--------|-------------|------------|------------------|
| Parameter                        | Specification | Units            | C61-1  | C62-1  | C65-1             | C7-1   | C12-1       | C15-1      | Method           |
| Arabinose                        | ≥99.0         | wt%              | >99.5  | >99.9  | >99.9             | 99.8   | 99.5        | >99.0      | Dionex-PAD       |
| Fucose                           |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.01        | < 0.01     | Dionex-PAD       |
| Rhamnose                         |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.12        | 0.07       | Dionex-PAD       |
| Galactose                        |               | wt%              | 0.13   | < 0.01 | 0.03              | < 0.1  | 0.03        | 0.01       | Dionex-PAD       |
| Glucose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Mannose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Xylose                           | 18            | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | 0.06        | 0.03       | Dionex-PAD       |
| Fructose                         |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Sucrose                          |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Other saccharides, total         | ≤1.0          | wt%              | < 1.0  | < 1.0  | < 1.0             | 0.1    | 0.22        | 0.11       | Dionex-PAD       |
| Galacturonic acid                |               | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Glucuronic acid                  | 4.4           | wt%              | < 0.01 | < 0.01 | < 0.01            | < 0.1  | < 0.01      | < 0.01     | Dionex-PAD       |
| Dry matter                       | ≥99.0         | wt%              | 99.9   | 99.95  | 99.98             |        |             | 99.8       | 3 hours 105 °C   |
| APHA color                       | 4.0           | hazen            | 0      | <1     | 0                 | 9      | <del></del> |            | 10% Solution     |
| Moisture                         | 0.3           | wt%              |        |        |                   | 0.1    | 0.22        | 0.11       |                  |
| Turbidity                        |               | FNU              | 2.7    | 1.50   | 1.2               |        |             |            | 10% Solution     |
| Microbiological <sup>1</sup>     |               |                  |        |        |                   |        |             |            |                  |
| Aerobic plate count 30 °C        | ≤1000         | cfu/g            | 32     | 7      | 6                 | 0      | 25          | 2.5        | ISO 4833:2003    |
| Molds                            | ≤20           | cfu/g            | 0      | 0      | 0                 | 0      | 2.5         | 0          | ISO 7954:1987    |
| Yeasts                           | ≤20           | cfu/g            | 0      | 0      | 0                 | 0      | 0           | 0          | ISO 7954:1987    |
| Clostridium perfringens / 10 g   | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 7937:2004    |
| Listeria / 10 g                  | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 11290-1:1997 |
| Bacillus cereus                  | ≤100          | cfu/g            | 0      | 0      | 0                 | 0      | 0           | 0          | ISO 7932:2004    |
| Staph. aureus / g                | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 6888-3:2003  |
| Enterobacteriaceae (kwal) / 10 g | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 21528-1:2004 |
| Salmonella / 10 g                | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 6579:2002    |
| E. coli / 10 g                   | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 16649-2:2001 |
| Coliforms / 10 g                 | Absent        |                  | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 4832:2006    |
| Fecal Streptococci               | <10 / Absent  | cfu/g            | <10    | <10    | <10               | Absent | Absent      | Absent     | KF Agar Method   |
| Cronobacter sakazakii / 10 g     | Absent        | U.U/ 9           | Absent | Absent | Absent            | Absent | Absent      | Absent     | ISO 22964:2006   |





|                             |               | Alkaline Process |         |         | Enzymatic Process |         |         | Analytical |                 |
|-----------------------------|---------------|------------------|---------|---------|-------------------|---------|---------|------------|-----------------|
| Parameter                   | Specification | Units            | C61-1   | C62-1   | C65-1             | C7-1    | C12-1   | C15-1      | Method          |
| Metals                      |               |                  |         |         |                   |         |         |            |                 |
| Antimony                    |               | mg/kg            | < 0.005 | < 0.005 | < 0.005           | < 0.005 | < 0.005 | < 0.005    | ICP-MS          |
| Arsenic                     |               | mg/kg            | < 0.01  | < 0.01  | <0.01             | < 0.01  | < 0.01  | < 0.01     | ICP-MS          |
| Cadmium                     |               | mg/kg            | < 0.005 | < 0.005 | <0.005            | < 0.005 | < 0.005 | < 0.005    | ICP-MS          |
| Copper                      |               | mg/kg            | 0.066   | 0.02    | 0.027             | 0.011   | 0.11    | 0.03       | ICP-MS          |
| Lead                        |               | mg/kg            | < 0.01  | < 0.01  | < 0.01            | < 0.01  | < 0.01  | < 0.01     | ICP-MS          |
| Mercury                     |               | µg/kg            | < 0.5   | < 0.5   | <0.5              | < 0.5   | < 0.5   | < 0.5      | ICP-MS          |
| Molybdenum                  |               | µg/kg            | < 0.01  | < 0.01  | 0.03              | 0.01    | < 0.01  | 0.03       | ICP-MS          |
| Tin                         |               | mg/kg            | < 0.01  | < 0.01  | < 0.01            | < 0.01  | < 0.01  | < 0.01     | ICP-MS          |
| Bismuth                     |               | mg/kg            | < 0.2   | <0.2    | <0.2              | < 0.2   | < 0.2   | < 0.2      | Analog §64 LFGI |
| Silver                      |               | mg/kg            | < 0.05  | < 0.05  | < 0.05            | < 0.05  | < 0.05  | < 0.05     | Analog §64 LFG  |
| Total metals                | < 0.3         | mg/kg            | < 0.3   | < 0.3   | < 0.3             | 0.21    | 0.11    | 0.06       | NA              |
| Toxins                      |               |                  |         |         |                   |         |         |            |                 |
| Aflatoxin B1                | < 0.05        | μg/kg            | < 0.05  | < 0.05  | < 0.05            | < 0.05  | < 0.05  | < 0.05     | IM W8333        |
| Aflatoxin B2                | < 0.02        | μg/kg            | < 0.02  | < 0.02  | < 0.02            | < 0.02  | < 0.02  | < 0.02     | IM W8333        |
| Aflatoxin G1                | < 0.05        | μg/kg            | < 0.05  | < 0.05  | < 0.05            | < 0.05  | < 0.05  | < 0.05     | IM W8333        |
| Aflatoxin G2                | < 0.03        | µg/kg            | < 0.03  | < 0.03  | < 0.03            | < 0.03  | < 0.03  | < 0.03     | IM W8333        |
| Aflatoxins Total            | < 0.15        | μg/kg            | < 0.15  | < 0.15  | < 0.15            | < 0.15  | < 0.15  | < 0.15     | IM W8333        |
| Pesticides (see Appendix D) | Various       | Various          | Meets   | Meets   | Meets             | Meets   | Meets   | Meets      | Various         |

Notes and Abbreviations:

<sup>--</sup> = not reported; cfu/g = colony forming units per gram; mg or  $\mu$ g/kg = milligrams or micrograms per kilogram; NA = Not Applicable; IM = Internal Method  $^{1}$ The method specifies the sample size, plates, and colony counts.



# **Proposed Uses and Estimated Daily Intakes**

The proposed use of Betawell® Arabinose is as an ingredient in foods and beverages as a carbohydrate source, a partial replacement of sucrose by 2 to 30%, or as a complete replacement of other sweetening systems as an arabinose/sucrose mixture with an arabinose composition of 2-30%. Betawell® Arabinose is proposed for use in the general population in the foods and use levels shown in Table 2.

Estimates of potential intakes of the ingredient resulting from these intended uses (Table 2) were calculated using food consumption data reported in the 2009-2010 and 2011-2012 NHANES and can be found in Table 3. The estimated daily intakes (EDI) of Cosun Betawell® Arabinose at the 90<sup>th</sup> percentile range from 4.1 to 22 g/p/d. This is consistent with the EDIs of similar GRAS non-nutritive sugar substitutes (up to 30 g/d tagatose or psicose). When the EDIs are calculated by replacement of sucrose, they range from 202 – 684 mg Betawell® Arabinose/kg-bw/day at the 90<sup>th</sup> percentile across all populations evaluated and again assuming the maximum sucrose replacement level of 30%.

Betawell® Arabinose is not intended for infant foods and these intakes are largely the result of the beverages category; Betawell® Arabinose is intended for adults limiting their sucrose intake by the use of "low sugar," "energy," and "sports nutrition" foods and beverages. Notably, the EDIs can be skewed high when applying the use level by weight to the beverages category (Table 2). To address this, the NHANES data were evaluated based on the sucrose content of the foods and assumed the maximum use level of 30% replacement of sucrose by Betawell® Arabinose (Table 3). This approach addresses the beverages category more accurately while remaining relatively consistent with the use level by weight approach used with the other food categories.

The estimates of intake presented in Table 3 are likely large overestimates of actual intake of L-arabinose resulting from the proposed uses in food. In the calculations of estimated intakes, any reported intake of a food corresponding to one of the proposed use categories (Table 2) was assumed to contain maximum use levels of Betawell® Arabinose across all food categories and all users were assumed to be consuming these foods in all categories. It is likely that consumers may consume only a subset of these foods containing added Betawell® Arabinose, and not all products may contain the maximum proposed use levels; therefore, these estimated intakes are likely overestimates of typical intakes.

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| Food Category                | Example foods   | Proposed<br>Use Level<br>(weight %) |
|------------------------------|---|-------------------------------------|
| Baked goods, baking mixes    | Cakes, brownies, pastries, cookies  | 0.1-10                              |
| Beverages                    | Soft drinks, energy drinks, sports and isotonic drinks, instant drink preparations and meal replacers, teas                             | 0.1-10                              |
| Cereal-based products        | Breakfast cereals, cereal bars  | 0.1-10                              |
| Bars                         | Breakfast bars, granola bars, energy bars, diet/meal replacement bars   | 0.1-10                              |
| Chewing gum                  |   | 0.1-10                              |
| Condiments                   | Ketchup   | 0.1-10                              |
| Confectionary and frostings  | Hard candies, soft candies, cough drops, toffees, chocolates, compressed goods, fondants, frostings, fillings, crèmes, toppings, nougat | 0.1-15                              |
| Dairy products               | Yogurt  | 0.1-10                              |
| Frozen dairy desserts        | Ice cream and other frozen dairy dessert mixes  | 0.1-15                              |
| Fruit and water ices         |   | 0.1-15                              |
| Gelatins, puddings, desserts |   | 0.1-10                              |
| Snack foods                  |   | 0.1-15                              |
| Spreads                      | Jams, jellies, nut and peanuts spreads  | 0.1-10                              |
| Toppings                     | Sweet sauces, syrups  | 0.1-10                              |
| Others                       | Sports nutrition, energy-reduced foods, meal replacement/slimming foods   | 0.1-10                              |

| Table 3. Betawell® Arabinose Estimated Daily I | Intakes Comparison (90th percentile)1 |
|--|---------------------------------------|
|--|---------------------------------------|

| Age Group         | n    | 30% Sugar<br>Replacement<br>(mg/kg-bw/d) | Body<br>weight²<br>(kg) | EDI<br>(g/p/d) |
|-------------------|------|--|-------------------------|----------------|
| Infants, < 12 mo  | 104  | 543                                      | 7.5                     | 4.1            |
| Infants, 12-23 mo | 368  | 684                                      | 11                      | 7.8            |
| Toddlers, 2-5 y   | 1524 | 616                                      | 16                      | 10             |
| 6-11 y            | 1092 | 546                                      | 32                      | 17             |
| 12-18 y           | 977  | 341                                      | 64                      | 22             |
| 19-49 y           | 2290 | 244                                      | 80                      | 19             |
| 50+ y             | 2070 | 202                                      | 80                      | 16             |

Notes and Abbreviations:

bw = body weight; d = day; EDI = estimated daily intake; g = gram(s); kg = kilogram(s); mg = milligram(s); mo = month(s); p = person; y = year(s).

 $^{1}$ Data from NHANES 2009-2012, two day averages where both days were recorded, and one day value where only one day was recorded.

<sup>2</sup>U.S. Environmental Protection Agency. Exposure Factors Handbook: 2011 Edition. National Center for Environmental Assessment, Washington, DC; EPA/600/R-09/052F; where age ranges span multiple weights the weights were averaged.



#### **Intended Effect**

The intended technical effects of the Betawell® Arabinose are as a nonnutritive sweetening substance having less than two percent of the caloric value of sucrose per equivalent unit of sweetening capacity (21 CFR 170.3(o)(19)) and/or as a synergist used to act or react with another food ingredient to produce a total effect different or greater than the sum of the effects produced by the individual ingredients (21 CFR 170.3(o)(31)). That is, the arabinose would act with the sucrase/sucrose complex to produce the effect of reduced or delayed sucrose uptake.

# Safety Assessment

There are several substances closely related to arabinose for which GRNs have been submitted. These include D-ribose, a C5 sugar very similar to arabinose, D-tagatose, an epimer of D-fructose isomerized at C-4, and D-psicose, an epimer of D-fructose isomerized at C-3. D-Ribose is the subject of GRN 243, D-tagatose is the subject of GRNs 78 and 352 and D-psicose is the subject of GRNs 400 and 498. The EDIs for these substances range from approximately 4.5 to 30 grams per person per day (g/p/d). These substances are very similar to L-arabinose in both structure and proposed uses and are generally recognized as safe food ingredients.

Numerous studies in humans and a variety of animal species and *in vitro* studies evaluating L-arabinose have reported that L-arabinose prevents, delays, or limits the uptake of glucose and fructose derived from the splitting of sucrose by the enzyme sucrase. L-arabinose appears to bind to the sucrase or sucrase-sucrose complex and prevent enzymatic activity for a short duration (two plus hours). The L-arabinose ultimately separates from the sucrase and normal enzymatic activity is restored.

Adverse effects identified from clinical studies included "mild" diarrhea at the highest study concentrations (up to 45 g/p/d) which for some was a transient effect that resolved after several days of continued consumption. For the others, the duration was not reported or the subjects dropped out of the study.

# Biodisposition: Absorption, Distribution, Metabolism, Kinetics and Excretion

L-Arabinose ingested by humans is readily catabolized and exhaled, excreted in urine, or used as a carbon substrate by the microbiome. A single case report suggests that there may be people with errors in metabolism that cannot metabolize arabinose; however, no adverse effect was reported and the arabinose was excreted in the urine.

Most studies evaluating aspects of arabinose biodisposition in humans focus on the effect arabinose has on sucrase activity in the small intestine. The studies did not evaluate absorption of L-arabinose from the stomach. In the small intestine, arabinose at sufficient levels (> 1% of the sucrose present) can inhibit the sucrase enzyme which hydrolyzes sucrose, resulting in lowered absorption of glucose and fructose into the blood stream. The exact metabolic pathway of L-arabinose has not been investigated, though the literature suggest that L-arabitol dehydrogenase plays a significant role in the catabolism of L-arabinose. After intravenous injection, the disappearance of L-arabinose from the blood follows first-order kinetics with a rate of approximately 0.77% per minute (comparable to other pentoses) with greater than 85% of the injected L-arabinose excreted in urine within 24 hours and only 0.8% expired via respiration within six hours. In the colon, L-arabinose may also be fermented by gut bacteria based on an *in vitro* model of gut microbes. Thus, L-arabinose may be absorbed into the blood stream from the small intestine and excreted in urine or catabolized by L-arabitol dehydrogenase, or fermented by microbes in the colon.



# Toxicological Studies

Toxicological studies with Betawell® Arabinose support the safety of L-arabinose generally but also demonstrate the safety of Betawell® Arabinose. The 90-day dietary toxicity study conducted in accordance with OECD test guideline 408 with Betawell® Arabinose reported NOAELs of 2218 mg Betawell® Arabinose/kg-bw/day in male Wistar rats and 2614 mg Betawell® Arabinose/kg-bw/day in female Wistar rats, the highest concentration tested (30,000 ppm). Betawell® Arabinose is neither mutagenic nor genotoxic under the test conditions.

Studies regarding the acute toxicity of arabinose were not identified, however, arabinose is expected to have an acute toxicity comparable to similar GRAS saccharides such as psicose, ribose, and tagatose.

A critical evaluation of the available evidence indicates that Betawell® Arabinose in the specific foods fortified at the proposed use levels are safe and suitable for the general population.

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# Conclusions

We, the members of the Expert Panel, have independently and collectively, critically evaluated the available information on Betawell® Arabinose, a sugar extracted from beets, manufactured by Cosun Biobased Products B.V., presented in the dossier prepared by Ramboll Environ and summarized herein, and other information deemed appropriate. We unanimously conclude that the proposed uses of Betawell® Arabinose, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting the food grade specifications presented in the dossier, as a food ingredient in baked goods and baking mixes, beverages and bars (energy, snack, and sports nutrition), cereal-based products, confectionary and frostings, chewing gum, condiments, dairy products (frozen desserts, ice creams and yogurts), desserts (gelatins, puddings, etc.), fruit and water ices, spreads, snack foods, and sweet sauces and syrups, are safe and suitable.

We further unanimously conclude that the proposed uses of Betawell® Arabinose, manufactured consistent with cGMP and meeting the food grade specifications presented in the dossier, as a food ingredient in baked goods and baking mixes, beverages and bars (energy, snack, and sports nutrition), cereal-based products, confectionary and frostings, chewing gum, condiments, dairy products (frozen desserts, ice creams and yogurts), desserts (gelatins, puddings, etc.), fruit and water ices, spreads, snack foods, and sweet sauces and syrups, are Generally Recognized As Safe (GRAS) based on scientific procedures.

It is our opinion that other experts, qualified by scientific training and experience, and evaluating the same data and information, would concur with these conclusions.

|  | (b) (b)           |   |
|--|-------------------|---|
| Joseph F. Borzelleca, Ph.D.<br>Chair of the Expert Panel<br>Professor Emeritus | Signature         |   |
| Department of Pharmacology & Toxicology  | Date: 13 May 2017 |   |
| School of Medicine,  | Date.             |   |
| Virginia Commonwealth University   | V                 |   |
| Richmond, Virginia   |                   |   |
| Judith K. Jones, M.D., Ph.D.   | Signature:        | _ |
| President and CEO  |                   |   |
| The Degge Group, Ltd   |                   |   |
| President  | Date:             |   |
| Pharmaceutical Education & Research Institu<br>Arlington, VA                   | ute               |   |
| John A. Thomas, Ph.D., A.T.S. Adjunct Professor                                | Signature:        | _ |
| Department of Pharmacology & Toxicology  |                   |   |
| Indiana University School of Medicine Indianapolis, Indiana                    | Date:             | - |



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| Chair of the Expert Panel  | Signature:   |              |
|--|--------------|--------------|
| Professor Emeritus Department of Pharmacology & Toxicology School of Medicine, Virginia Commonwealth University Richmond, Virginia | Date:        | (b) (6)      |
| Judith K. Jones, M.D., Ph.D. President and CEO   | Signature:   |              |
| The Degge Group, Ltd<br>President<br>Pharmaceutical Education & Research Institu<br>Arlington, VA                                  | Date:<br>ute | May 15, 5017 |
| John A. Thomas, Ph.D., A.T.S. Adjunct Professor  | Signature:   |              |
| Department of Pharmacology & Toxicology<br>Indiana University School of Medicine<br>Indianapolis, Indiana                          | Date:        | -            |



# Conclusions

We, the members of the Expert Panel, have independently and collectively, critically evaluated the available information on Betawell® Arabinose, a sugar extracted from beets, manufactured by Cosun Biobased Products B.V., presented in the dossier prepared by Ramboll Environ and summarized herein, and other information deemed appropriate. We unanimously conclude that the proposed uses of Betawell® Arabinose, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting the food grade specifications presented in the dossier, as a food ingredient in baked goods and baking mixes, beverages and bars (energy, snack, and sports nutrition), cereal-based products, confectionary and frostings, chewing gum, condiments, dairy products (frozen desserts, ice creams and yogurts), desserts (gelatins, puddings, etc.), fruit and water ices, spreads, snack foods, and sweet sauces and syrups, are safe and suitable.

We further unanimously conclude that the proposed uses of Betawell® Arabinose, manufactured consistent with cGMP and meeting the food grade specifications presented in the dossier, as a food ingredient in baked goods and baking mixes, beverages and bars (energy, snack, and sports nutrition), cereal-based products, confectionary and frostings, chewing gum, condiments, dairy products (frozen desserts, ice creams and yogurts), desserts (gelatins, puddings, etc.), fruit and water ices, spreads, snack foods, and sweet sauces and syrups, are Generally Recognized As Safe (GRAS) based on scientific procedures.

It is our opinion that other experts, qualified by scientific training and experience, and evaluating the same data and information, would concur with these conclusions.

| Joseph F. Borzelleca, Ph.D. Chair of the Expert Panel Professor Emeritus   | Signature: |             |
|--|------------|-------------|
| Department of Pharmacology & Toxicology<br>School of Medicine,<br>Virginia Commonwealth University<br>Richmond, Virginia | Date:      |             |
| Judith K. Jones, M.D., Ph.D. President and CEO   | Signature: |             |
| The Degge Group, Ltd   |            |             |
| President  | Date:      |             |
| Pharmaceutical Education & Research Institu<br>Arlington, VA   | ite        |             |
|  |            | (b) (6)     |
| John A. Thomas, Ph.D., A.T.S.<br>Adjunct Professor   | Signature: | -           |
| Department of Pharmacology & Toxicology Indiana University School of Medicine Indianapolis Indiana                       | Date:      | 15 May 2017 |

584 pages have been removed in accordance with copyright laws. The removed reference citations are found at Section 7 List of Supporting Data and Information (in accordance with 21 CFR §170.255)

From: Gavin P Thompson

To: West-Barnette, Shayla; Bewry, Nadine; Carlson, Susan

Cc: "Benschop, Alex"; "Volz, Carl"; Meera Cush

Subject: RE: Regarding GRN 782

**Date:** Wednesday, August 08, 2018 2:20:05 PM

Attachments: <u>image001.png</u>

GRN 782 Request - Sensus signature.pdf

Importance: High

Drs. Carlson, Bewry, and West-Barnette,

Please find attached the signed letter from Sensus, the Notifier for GRN 782, requesting withdrawal of GRN 782.

As discussed in this letter, this action is being taken as a result of consultation with FDA GRN review staff. The Notifier intends to address FDA's comments and requests, consult further with FDA, and make a subsequent notification submission.

A signed paper original ("wet signature") of the letter also has been mailed to your attention.

Regards, Gavin

#### Gavin P Thompson, PhD

Principal Consultant

D +1 (602) 734 7704 M +1 (703) 589 8023

gthompson@ramboll.com

http://www.ramboll.com/contact/environ/gthompson

From: Gavin P Thompson

**Sent:** Tuesday, August 07, 2018 4:28 PM

To: West-Barnette, Shayla <Shayla.WestBarnette@fda.hhs.gov>

Cc: Bewry, Nadine < Nadine. Bewry@fda.hhs.gov>

Subject: RE: Regarding Yesterday's Discussion About Our Evaluation of GRN 782

**Importance:** High

Drs. Bewry and West-Barnette,

Please be advised that the Notifier (Sensus America Inc.) intends to submit a request for withdrawal. I have a call scheduled to review the letter tomorrow morning (August 8, 2018) and will be sending the signed letter shortly thereafter.

Regards, Gavin

#### Gavin P Thompson, PhD

Principal Consultant

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gthompson@ramboll.com

http://www.ramboll.com/contact/environ/gthompson

From: West-Barnette, Shayla [mailto:Shayla.WestBarnette@fda.hhs.gov]

# inspired by inulin

Via Express Courier and Electronic Mail

Nadine Bewry, PhD, MPH
Consumer Safety Officer | Toxicology Reviewer

Shayla West-Barnette, PhD Supervisory Consumer Safety Officer

GRAS Notification Program
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

August 2, 2018

GRN No. 782: L-Arabinose Request for Withdrawal

Dear Drs. Bewry and West-Barnette:

In accordance with the Final Rule for Substances Generally Recognized as Safe (GRAS) (Fed. Reg. 81(159):54960-55055, August 17, 2016), Sensus America, Inc. (Sensus) submitted a Notification to the Food and Drug Administration (FDA) of our GRAS Determination for the ingredient, L-arabinose derived from sugar beet pulp for use in foods for the general population. FDA assigned this notice GRN No. 782.

In response to our consultations with you, we hereby request withdrawal of GRN 782. We request that this action be taken by FDA without prejudice to a re-submission of a new GRAS Notice after we undertake the following:

- Address the scientific and technical issues outlined and discussed by the FDA review team in the teleconference with you (July 24, 2018); and
- Participate in a pre-submission meeting (pre-notification consultation) with you to discuss our revised GRAS
  conclusion and allow you to provide any remaining input before we resubmit a revised GRAS notice.

Yours sincerely,
(b) (6)

Carl Volz
General Manager
Sensus America, Inc.

CC: Alex Benschop, Sensus B.V. Gavin P. Thompson, PhD, Ramboll US Corp.

