

GR



ORIGINAL SUBMISSION

000255

**SELF GRAS NOTIFICATION FOR  
HYDROGENATED STARCH HYDROLYSATE**

2000 OCT -4 P 1: 21

000256

**NOTIFICATION OF  
SELF GRAS DETERMINATION**

**Name of Notifiers :** Grain Processing Corporation  
1600 Oregon Street  
Muscatine, IA 52761

and

SPI Polyols Inc.  
321 Cherry lane  
New Castle, DE 19720

**Address :** All communications on this matter are to be sent to :  
Ms. Rani Thomas  
Director of Quality and Regulatory Affairs  
Grain Processing Corporation  
1600 Oregon Street  
Muscatine, IA 52761

**Name of Generally  
Recognized as safe  
Substance(GRAS)** Hydrogenated starch hydrolysate

**Dated :** September 11, 2000

000257



**TABLE OF CONTENTS**

**TABLE OF CONTENTS**

**Page No.**

Letter for Self GRAS determination..... 1

**Attachments**

i. Description of Substance..... 5

ii. Use of Hydrogenated Starch Hydrolysate..... 9

iii. Information to Establish General Recognition of HSH in Food..... 11  
Safety..... 12

Carcinogenicity and mutagenicity ..... 13

Functionality..... 15

iv. Comparison of Roquette, Lonza and GPC/SPI processes..... 16

v. Review of properties of Hydrogenated Starch Hydrolysate  
prepared by GPC/SPI, Roquette Freres(Lycasin®) and Lonza  
(Hystar®) by Dr. Linhardt ..... 19

vi. Statement of data information and availability..... 26

**Appendix A**

**Part 1 – Specifications** ..... 27

**Part 2– Details of Manufacturing Process**..... 29

**Appendix B**

Typical formulas using Hydrogenated Starch Hydrolysate..... 34

**Appendix C**

Potential per capita consumption of HSH..... 40

**Appendix D**

Carcinogenicity publications used as references..... 42

**Appendix E**

**Safety Studies**

Exhibit S1.0 Hystar® 6075 acute oral LD50.....50

Exhibit S1.2 GPC/SPI HSH acute oral LD50.....59

Exhibit S2.0 Roquette Freres Toxicity information..... .67





## GRAIN PROCESSING CORPORATION

1600 Oregon St., Muscatine, Iowa 52761-1494 USA ■ Phone 319-264-4265 ■ FAX 319-264-4289

September 18, 2000

Office of Premarket Approval (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C St. S.W,  
Washington, DC 20204

Re: Notice for Self- GRAS determination of hydrogenated malto-oligosaccharide (Hydrogenated Starch Hydrolysate)

Dear Sir or Madam:

In accordance with the notification procedure (proposed regulation 170.36), Grain Processing Corporation (GPC) at 1600 Oregon Street, Muscatine, Iowa 52761, and SPI Polyols (SPI), 321 Cherry Lane in New Castle, Delaware 19720, submit this notification for Self-GRAS determination of hydrogenated malto-oligosaccharides which fits within the definition of hydrogenated starch hydrolysate(HSH). GPC/SPI view that the use of hydrogenated malto-oligosaccharides is exempt from premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because GPC/SPI have determined that the use of hydrogenated malto-oligosaccharides is GRAS. This Self- GRAS determination is based on scientific procedures.

As in the proposed regulation by FDA, GPC/SPI are submitting the following information to establish the use of this substance is GRAS.

**Hydrogenated Starch Hydrolysate**

- a) HSH is a concentrated, aqueous solution of sorbitol ( $C_6 H_{14} O_6$ ), maltitol ( $C_{12} H_{24} O_{11}$ ), maltitriol ( $C_{18} H_{34} O_{16}$ ) and hydrogenated polysaccharides. It is produced by the transition metal catalytic hydrogenation of glucose syrup or polymers of glucose.
- b) The GPC/SPI ingredients meet the following specifications:  
total solids not less than 50% for the liquid product and not less than 90% for the dry product; sorbitol not more than 10%, maltitol not more than 10%, hydrogenated tri to hexasaccharides between 5 and 35 %, hydrogenated saccharides higher than hexa greater than 50%; arsenic (As) not more than 10 parts per million; chloride not more than 50 parts per million; heavy metals (such as lead) not

000262

more than 10 parts per million; reducing sugars not more than 1.0%, residue on ignition; not more than 0.1%; sulfate not more than 100 parts per million; total sugars (after hydrolysis) not more than 97% on the dry basis.

- c) The ingredient is used as a flavoring agent and adjuvant as defined in CFR 170.3 (o) of this chapter; formulation aid as defined in CFR 170.3 (o)(14) of this chapter; humectant as defined in CFR 170.3 (o)(21) of this chapter, processing aid as defined in CFR 170.3 (o)(24) of this chapter, stabilizer and thickener as defined in CFR 170.3 (o)(28) of this chapter; surface-finishing agent as defined in CFR 170.3 (o) (30) of this chapter; and texturizer as defined in CFR 170.3 (o) (32) of this chapter.
- d) The ingredient is used in food at levels not to exceed good manufacturing practices. Current practices in the use of HSH result in maximum levels of:

Food Use:	Liquid HSH	Dry HSH
Hard Candy	99%	60%
Soft Candy	90%	50%
Chewing Gum	25%	45%
Bakery	35%	25%
Ice cream	20%	15%

Grain Processing Corporation and SPI Polyols will market HSH under several trade names. Grain Processing Corporation is headquartered and has manufacturing facilities in Muscatine, Iowa and Washington, Indiana. SPI Polyols, Inc. is headquartered and has manufacturing facilities in New Castle, Delaware and Mapleton, Illinois.

Detailed information on the chemistry, composition and manufacture of this hydrogenated starch hydrolysate (HSH) is presented in the text. This hydrogenated starch hydrolysate is a mixture of polysaccharides of varying chain length where 0 - 10% is sorbitol, 0 - 10% is maltitol, and greater than 30% is hydrogenated saccharides with 8 or more units.

The GRAS determination is based on scientific procedures. This substance has been used in foods for long periods of time. It has been marketed extensively by Roquette and Lonza for years. We have reviewed the scientific data submitted by Roquette Freres in their petition for hydrogenated glucose syrup. Our process is essentially equivalent to the process of Lonza and Roquette Freres. The HSH products produced by Roquette Freres and Lonza have been used in food for more than ten years. In support of the GRAS filing of this new hydrogenated starch hydrolysate, Grain Processing Corporation and SPI Polyols will site data submitted by Roquette in its Lycasin® 80/55 petition (84G-003) regarding numerous studies relating to the safety of the ingredient, including reports on

- Digestion, absorption, distribution and excretion
- Subchronic toxicity
- Genetic toxicity
- Reproduction
- Biological tolerance
- Human exposure
- Acute oral LD<sub>50</sub>
- Laxation effect

An acute oral LD<sub>50</sub> study of this new HSH is included in Appendix E.

It is our belief that the definition of an HSH fits the description of our product, hydrogenated malto-oligosaccharides as GPC/SPI products are derived from cornstarch, and are hydrolyzed to a starch hydrolysate and hydrogenated using the same technology and methods used to produce other HSH products. GPC/SPI products have less DP1,2, and 3 in comparison to other available HSH products in that they are less hydrolysed than existing Hydrogenated Starch Hydrolysates. See attached report comparing the Roquette, Lonza and GPC processes (Attachment iv on page 16).

Citing data contained in the Lycasin® and Hystar® petitions and chemistry data supplied in this petition, it can be predicted that the new HSH products produced by GPC/SPI will be digested similarly and broken down in the digestive tract into its two GRAS congeners glucose and sorbitol. The GPC/SPI product should have a reduced laxative effect due to the lesser amount of sorbitol present in the HSH product. Since the GPC/SPI HSH products differ from existing HSH products only in the carbohydrate profile, it is our technical opinion that the GPC/SPI products do not pose any toxicological and health concerns.

Dr. Robert Linhardt, Professor, Departments of Chemistry, Pharmacy and Chemical Engineering of the University of Iowa has reviewed the GRAS information submitted by Lonza, Roquette and the GRAS information put together by Grain Processing Corporation and SPI Polyols. According to Dr. Linhardt, the GPC/SPI product(s) is sufficiently similar in chemical composition to the Lonza product to make it behave identically with respect to the biological evaluation required for GRAS approval. On the basis of the data provided this appears to be the case. In particular the GPC product is clearly very similar to the Lonza product except for its somewhat higher theoretical molecular weight, permitting the conclusion that these products are biologically equivalent. A report from Dr. Linhardt is attached to this document (Attachment v on page 19).

Please call if you have any questions. All communications on this matter are to be sent to:

Ms. Rani Thomas  
Director of Quality and Regulatory Affairs

Grain Processing Corporation  
1600 Oregon Street  
Muscatine, IA 52761

Thanking you,  
Yours sincerely

Grain Processing Corporation  
and SPI Polyols

Dr. David Abbott  
Senior Vice President of Research and Development  
Grain Processing Corporation, 1600 Muscatine, IA 52761

Ms. Janice Binger  
Vice President Sales and Marketing  
SPI Polyols Inc, 321 Cherry Lane, DE 19720

000266

**i. Description of the substance**

i. Description of the GPC/SPI Substance(a) Common or Usual Name

The principle common name of the product is hydrogenated starch hydrolysate (HSH). Other names that have also been used include hydrogenated glucose syrup, hydrogenated glucose solids, reduced malto-oligosaccharide, stabilised carbohydrate polymer and polyalditol.

(b) Chemical Name

A mixture of sorbitol (1,2,3,4,5,6-hexol hexane), maltitol (4-O- $\alpha$ -D-glucopyranosyl-D-glucitol), and hydrogenated polysaccharides containing greater than 3 D-glucopyranosyl units joined by  $\alpha$ -1-4 linkages and terminated with a D-glucityl unit.

(c) Chemical Abstracts Service (CAS) Registry Number

The CAS number of hydrogenated starch hydrolysate is 68425-17-2.

(d) Empirical Formulae

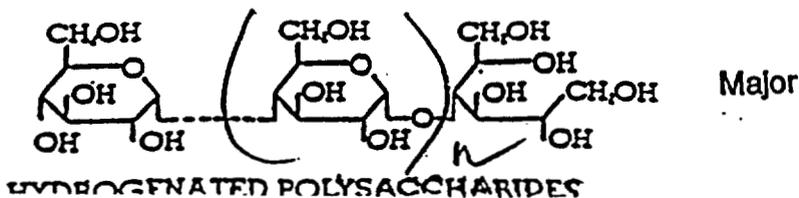
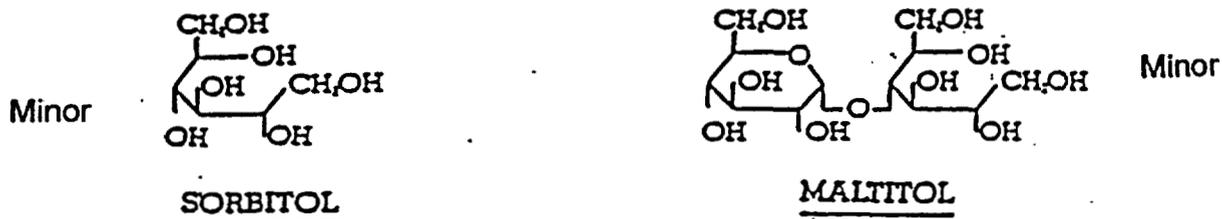
The empirical formulae of the components of hydrogenated starch hydrolysate are:

Sorbitol:	$C_6H_{14}O_6$
Maltitol:	$C_{12}H_{24}O_{11}$
Hydrogenated Polysaccharides:	$C_{12}H_{24}O_{11}$ plus $C_6H_{10}O_5$ For each additional glucose moiety in the chain.

The theoretical molecular weight of the hydrogenated starch hydrolysates ranges from approximately 1000-3600.

(e) Structural Formulae

The structural formulae of the components are:



000268

(f) Specifications for Food-Grade Material

The specifications for food-grade hydrogenated starch hydrolysate are as follows:

Total Solids	Not less than 90% for dry product Not less than 50% for liquid product
Sorbitol	Not more than 10% (dry product basis)
Maltitol	<10%
Hydrogenated Tri- to hexasaccharides	Between 5 and 35% (dry product basis)
Hydrogenated saccharides higher than hexa	greater than 50% (dry product basis)
Arsenic (as As)	Not more than 10 ppm
Chloride	Not more than 50 ppm
Heavy metals (as Pb)	Not more than 10 ppm
Reducing sugars	Not more than 1%
Residue on ignition	Not more than 0.1%
Sulfate	Not more than 100 ppm
Total sugars (after Hydrolysis)	Not more than 97% (dry product basis)

We have made 2 lots representing 6 reaction batches of the material and the material meets the specifications listed above.

The qualitative analysis of Hydrogenated Starch Hydrolysate in the foods to which it has been added may be accomplished by extraction of the sorbitol and maltitol moieties with appropriate solvents, followed by gas chromatography of the extracts. Similarly, the quantity of hydrogenated starch hydrolysate occurring in food may be estimated by determining the amount of maltitol recovered and applying an appropriate factor. Information on the sensitivity and reproducibility of the method has also been developed.

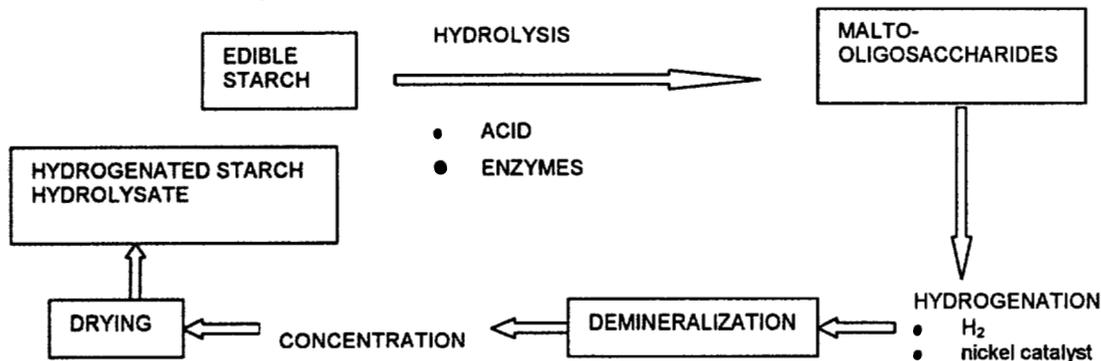
(g) Quantitative Composition

Hydrogenated starch hydrolysate consists of approximately 5% water and approximately 95% total solids for dry product, of which not more than

10% is sorbitol, not more than 10% is maltitol, and the remainder is hydrogenated polysaccharides. For liquid product the solids is >50%.

(h) Manufacturing Process

The manufacturing process used to produce hydrogenated starch hydrolysates are the same as that used to produce sorbitol, as shown below and as presented in greater detail in Appendix A (Part 2). No new or novel procedures are used in this process.



More specifically, food grade edible starch is enzymatically hydrolyzed by using alpha-amylase and acid to reach 4-35 dextrose equivalent liquid malto-oligosaccharides.

The liquid malto-oligosaccharides are hydrogenated by using nickel catalyst. After hydrogenation, the liquid hydrogenated starch hydrolysate is filtered, demineralized on ion-exchange resins. The material can be concentrated to 50 percent or greater dry substance syrup or dried to a powder of approximately 5% moisture.

The products produced by this method consist of hydrogenated starch hydrolysates corresponding to the range of saccharides identified in the original liquid malto-oligosaccharides, since the conversion of the sugars by hydrogenation of their end reducing units is virtually complete. During the hydrogenation process only the dextrose and reducing end units in the oligo- and higher saccharides are converted into sorbitol units and glucityl units as shown diagrammatically in Appendix A (Part 2).

In addition to the materials and chemicals mentioned above, lime, sodium hydroxide, sulfuric acid, active carbon, soda ash and filtration earth are also used in the manufacturing process, all of which are commonly used in glucose-dextrose and sorbitol manufacture.

The product obtained by the process described above is a colorless, odorless, bland tasting liquid or powder.



ii. Use of Hydrogenated Starch Hydrolysate

ii. Use of Hydrogenated Starch Hydrolysate

(a) Date when Use Began

Information available to us indicates that Roquette began marketing Lycasin® 80/55 in the United States in 1977, since which time it has been used in hard candies on the basis of self-determination of its GRAS status by candy manufacturers. In a similar manner, Lonza submitted petition in 1985 for their HSH products. GPC and SPI began laboratory testing Hydrogenated Starch Hydrolysate in the United States in 1997. The major components of Hydrogenated Starch Hydrolysate, i.e., maltitol and hydrogenated polysaccharides, however occur at relatively low levels in the GRAS substance sorbitol, which was first used in food in the United States more than 50 years ago.

(b) Information on Past Uses in Food

Roquette's petition indicates that Roquette's Lycasin® products have been approved for use in food in Europe since 1963, as indicated below.

Country	Year of Approval
Sweden	1963 (reaffirmed in 1975)
Switzerland	1968
Norway	1975
Finland	1975 (reaffirmed in 1980)
Denmark	1976

(c) Foods in Which Used, Levels of Use, and For What Purpose

Current practices in the use of HSH result in maximum levels of:

Food Use:	Liquid HSH	Dry HSH
Hard Candy	99%	60%
Soft Candy	90%	50%
Chewing Gum	25%	45%
Bakery	35%	25%
Ice cream	20%	15%

Hydrogenated Starch Hydrolysate has a unique combination of desirable properties, including high viscosity, hydroscopicity, binding capacity, anticrystallizing capacity, low reactivity and is stable under all normal-manufacturing conditions.

iii. Information of Established  
General Recognition of  
HSH in food

000274

iii. INFORMATION TO ESTABLISH GENERAL RECOGNITION OF HSH IN  
FOOD

## SAFETY

The following is in regard to the Safety of Grain Processing Corporation and SPI Polyols hydrogenated starch hydrolysates (HSH) also commonly referred to as hydrogenated glucose syrups, hydrogenated dextrans, reduced dextrans, reduced malto-oligosaccharides, stabilised carbohydrate and polyalditol. Per capita consumption of HSH is referenced in Appendix C.

HSH produced by Grain Processing Corporation and SPI Polyols as described in Section I - Description of the substance, intended as direct food additives, are produced by hydrogenation of GRAS malto-oligosaccharides. The resultant HSH products are completely non-toxic. The acute oral toxicity is reported at >10g/kg. See Appendix E, Exhibits S1.2 for reports of the acute oral toxicity for SPI/GPC hydrogenated starch hydrolysate.

In order to further substantiate the safe use of Hydrogenated starch hydrolysate, reference is made to Lonza Corporation GRAS affirmation Petition Submission (1985); and reference is made to Roquette Corporation GRAS affirmation Petition Submission #84G-0003. See Appendix E, Exhibit S1.0 and Exhibit S2.

SPI Polyols and Grain Processing Corporation believe that these data can be used for the safety assessment of the new hydrogenated starch hydrolysate, since the composition of GPC/SPI HSH product is significantly similar to Lonza's Hystar® and Roquette Corporation's Lycasin® products. The chronic toxicity and metabolic pathways of the new hydrogenated starch hydrolysate will be the same as those elucidated in the Lonza and Roquette petitions, thus leading to the metabolites sorbitol and glucose for which safety has been established.

Further, the new HSH contain Sorbitol, the DP – 1 hydrogenate in varying degrees but less than the Hystar® and Lycasin® products. See Table on Page 18 on carbohydrate profiles.

### Laxative Potential

Lonza in their GRAS Petition reported laxation effects of a variety of Hystar® products. The Hystar® composition with the highest amount of DP – 1 hydrogenate (sorbitol) produced the most pronounced laxative response. Conversely, those Hystars® with larger amounts of DP – 4+ showed significantly reduced degrees of laxation. Based on these results an acceptable range of consumption of approximately 50g per day for Hystar® 7000 to 100g per day for Hystar® 6075 was established.

Based upon comparisons of carbohydrate profiles as shown on page 18, it is our position that the acceptable range of consumption will be at least 100g/day as established by Hystar® 6075, the product with the most similar carbohydrate profile.

### Carcinogenicity and mutagenicity

A review of the current available literature concerning the Carcinogenicity and Mutagenicity of polyols, in general and mannitol in particular furnishes no indication of carcinogenic potential. The references used and a publication of the key reference is included in Appendix D.

The World Health Organization Technical Report, Series 868 (1997) entitled "Evaluation of Certain Food Additives and Contaminants" reports that long-term feeding studies in mice and dogs showed no adverse effects. A body of literature relating to rat feeding studies does implicate polyols in chromaffin cell proliferation and adrenal medullary hyperplasia. However, the mechanism and the direct role of polyols is still the subject of debate. After considering and evaluating the various issues relevant to the rat feeding studies the WHO report concluded that "the occurrence of proliferative lesions of the adrenal medulla in rats fed polyols and lactose is a species-specific phenomena and is not relevant to the toxicological evaluation of these substances in humans." Regarding studies in humans the WHO study findings concluded that "consumption of these polyols by human volunteers in controlled studies and by the public at large has not been associated with any significant effects." Several citations have also written that polyols are not mutagenic in the Ames test and other test methodologies.

In summary, that body of literature that directly addresses the issue of carcinogenic potential of polyols concludes that these materials are not mutagenic.

HYDROGENATED STARCH HYDROLYSATE  
USE IN FOOD AND  
APPLICATION FORMULAS

## HYDROGENATED STARCH HYDROLYSATE USE IN FOODS

This section describes the function of the new GPC/SPI HSH products as they are used in foods.

### Functionality / Applications

The new HSH products from GPC/SPI are unique from other HSH products currently in the market in the amount of the longer polysaccharide chains contained in the product. This characteristic will provide increased thickening and ease of drying over other HSH products. This functionality can expand the use of HSH for texture modification, crystallization inhibition and building solids to aid in drying. In addition, the lower amounts of the smaller molecular weight sugar alcohols in the GPC/SPI product contributes to a lower sweetness profile that is more compatible with savory flavor systems.

Similar to other HSH products currently in the market, the GPC/SPI HSH products are more stable to chemical and thermal reactions than many sugars, maltodextrin, or other carbohydrate products, due to the hydrogenation of the reducing end of the polysaccharide chains. Without the reducing group, the polysaccharide chains do not participate in Maillard Browning, nor do they caramelize until heated sufficiently to break the chains and expose reducing end groups. HSH is also generally less fermentable by microorganisms making them particularly useful in chewing gums and candies.

Applications where the GPC/SPI HSH products appear particularly useful include:

#### Food Uses

Hard Candy

Soft Candy

Chewing Gum

Chocolate Compound Coatings

Bakery Products

Fillings and Icings

Syrups

Sauces

Ice Cream

Beverage Mixes

The sample formulas listed in Appendix B are examples of food applications for the GPC/SPI HSH. These applications utilize the HSH for thickening and crystal modification.

IV. Comparison of Roquette,  
Lonza and GPC/SPI  
Processes

000280

**iv. Comparison of Roquette, Lonza and GPC/SPI processes**

To: R. Antrim, R. Thomas

Project: 4125

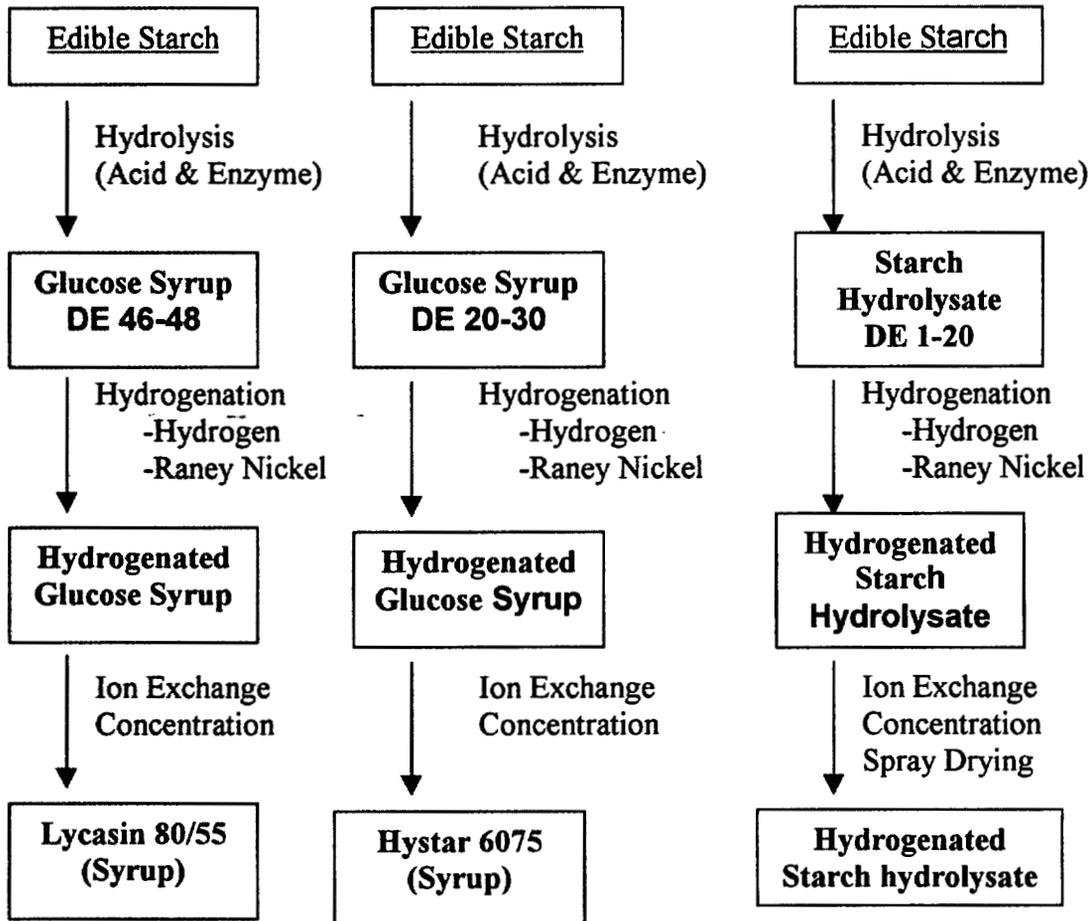
From: Frank Barresi

Jan. 27, 2000

Subject: Roquette ,Lonza, GPC/SPI Hydrogenated Starch Hydrolysates:

The following is a general description of the three processes used to produce hydrogenated starch hydrolysates. The Roquette process is obtained from the GRAS petition for "Hydrogenated Glucose Syrup" (Lycasin 80/55). The Lonza process is obtained from the GRAS petition for "Hydrogenated Starch Hydrolysate" (Hystar 6075). The GPC/SPI process is described in the patent application "Reduced Malto-Oligosaccharides" and has been outlined below for direct comparison to the Roquette and Lonza processes.

Roquette – Lycasin 80/55	Lonza – Hystar 6075	GPC/SPI – Hydrogenated Malto oligosaccharides
--------------------------	---------------------	---



As can be seen from the flow diagrams, the three processes follow identical pathways and are different only in the degree of starch hydrolysis. This is further outlined in the following carbohydrate profiles:

Degree of Polymerization	Roquette – Lycasin 80/55*	Lonza – Hystar 6075**	GPC/SPI Hydrogenated Starch Hydrolysate HSH A***
DP 1	8%	12-15%	0.3-3.3
DP 2	50-55	6-9	4.2-8.2
DP 3	---	8-11	6.3-10.3
DP 4	---	---	4.4-8.4
DP > 4	---	69 max.	---
DP 5	---	---	3.9-7.9
DP 6	---	---	9.4-13.4
DP 3-6	20-25	---	--
DP > 6	15-20	---	--
DP 7	---	---	7.5-11.5
DP 8	---	---	1.9-5.9
DP > 8	---	---	42.6-50.6

\* p. 10 of the Roquette GRAS petition

\*\* p. 000020 of the Lonza GRAS petition

\*\*\* p. 9 of the GPC PCT WO 99/36442– “Reduced Malto-Oligosaccharides”

cc. Project 4125 file.

000284

v. Review of properties of HSH by Dr. Linhardt, Professor of the University  
of Iowa

FINAL REPORT

**Review of Properties of Hydrogenated Starch Hydrolyzate (HSH) prepared by GPC,  
Roquette Freres (Lycasin) and Lonza (Hystar)**

Prepared for  
Grain Processing Corporation (GPC)  
Prepared by  
Dr. Robert J. Linhardt  
Professor, Departments of Chemistry,  
Pharmacy and Chemical Engineering

Date Submitted

February 8, 2000

## Background

Dr. Linhardt was approached by GPC Inc. of Muscatine, Iowa to act as a consultant in the evaluation of their HSH product for its equivalency to the HSH products of Roquette Freres and Lonza. The purpose of this independent evaluation was to support a GRAS affirmation petition to the Food and Drug Administration (FDA). GPC gave oral presentations of the process used for the production of their HSH product and provided the following written documentation.

1. PCT/US99/01098 Titled: "Reduced Malto-Oigosacchaarides", published July 22, 1999 (WO99/36442), issued to GPC.
2. US Patent No. 5,493,014, February 20, 1996, Titled: "Hypocariogenic hydrogenated starch hydrolysate process for preparing it and the application of this hydrolysate issued to Roquette Freres.
3. A 1994 publication on HSH by the Caloric Control Council.
4. A letter dated April 5, 1995 from Dr. Saltsman of the FDA confirming the energy value of HSH.
5. An internal GPC document describing their HSH product, its specifications, manufacturing process, the methods used in its analysis and potential application.
6. A brochure produced by GPC describing their Maltrin product line of maltodextrins and corn syrup solids for pharmaceuticals. These maltodextrins are GRAS and represent the immediate precursor of the GPC HSH product. BPC Analytical method for determination of DP.
7. ~~Towards a Rational Design of Commercial Maltodextrins: A Mechanistic Approach~~ by Leon M. Marchal, 1999.
8. Viscosity data on M180 and Reduced Maltodextrins Solutions from GPC Comparison of Roquette/Lonza/GPC Processes prepared by F. Barresi of GPC 1/27/2000.
9. The GRAS Petition 5 GO304 filed by Lonza Inc. for their HSH product Hystar 6075 provided by the FDA through the Freedom of Information Act.
10. The GRAS Petition filed by Roquette Corporation for their HSH product Lycas in 80/55 provided by SPI Polyols.

## Outline of Evaluation Process

After having read all of the material provided, three issues will be addressed: 1. Are the starting materials used in the Roquette Freres, Lonza and GPC processes the same?; 2. Will the

processes used in the preparation of these three products lead to a chemically equivalent HSH?; and 3. Are these HSH products chemically equivalent and would the chemical equivalence of these three HSH products, as demonstrated by the analytical methods applied, lead to bioequivalent products?

### 1. Equivalence of starting materials and immediate precursors of hydrogenation

All three products are derived from edible starch which is hydrolyzed with acid and enzymes to obtain precursor for hydrogenation.

Lycasin, the Roquette Freres product, is prepared from the hydrogenation of glucose syrup. The Roquette GRAS petition shows a DE of 46-48 for the glucose syrup starting material.

Hystar 6075, the Lonza product, is prepared from the hydrogenation of glucose syrup with a dextrose equivalent (DE) 26 (DE 20-30), a viscosity of 200 P (66% solids) at 100°F (38°C) containing 5% degree of polymerization (DP)1, 14% DP2, 14% DP3 and 67% > DP4. This material corresponds to commercial glucose corn syrup prepared by acid and enzymatic hydrolysis of starch.

GPC product is prepared from the hydrogenation of starch hydrolysate. GPC starch hydrolysates have average DE values ranging from 4-7 to 16.5-19.5 (M040 to M180). The distribution of components range from 0.3% to 1.6% DP1, 0.9%-5.8% DP2, 1.4%-7.8% DP3 and 96%-80% > DP4 (M040 to M180) theoretical number average molecular weight of 3600-1000 is given for M040 and M180, respectively A DP average for these products range from 22.1 (M040) to 6.2 (M180). The viscosity M180 (70% solids) is 80-90 P at 35°C.

Comparison of the properties of all three hydrogenation precursors clearly demonstrate that while none are chemically identical, the GPC hydrogenation precursor is most similar to the Lonza hydrogenation precursor based on DP distributions. Moreover, the Lonza hydrogenation precursor is very dissimilar to the Roquette hydrogenation precursor based on this same parameter. The differences among the three precursors is primarily associated with differences in average molecular weight suggested by the different DE values reported.

In summary, there is little (if any) difference in the structure of the components present in each of the three hydrogenation precursors. There are differences in the distribution of components, particularly between the Roquette and the Lonza hydrogenation precursors.

### 2. Equivalence of Reduction Process

The Roquette Freres process utilizes catalytic (Raney Nickel) hydrogenation at 130°C and 725 psi followed by filtration to remove catalyst and decolorization with activated carbon, demineralization by cationic and anionic exchange and concentration to 70-85%. No information is provided on the reaction pH and reaction time.

The Lonza process utilizes catalytic (Raney nickel) hydrogenation. No information on reaction temperature, pressure, pH or time are provided. This reaction is followed by filtration, anionic, cationic exchange and mixed bed ion exchanges, concentration, safety filtration and filling.

The GPC process utilizes catalytic (Raney nickel GD 3110) hydrogenation. The reaction product is filtered to remove catalyst, demineralized using strong cation ( $H^+$ ) and weak anion (OH) exchange resins and following an optional activated carbon decolorization step the product is concentrated for filling.

The specific details of the GPC process are available from the documentation provided while the two other commercial processes are described in much more general terms. The GPC process is close to (or within the specifications of) the other processes suggesting an equivalency of all three processes. The advantages listed in the GPC process suggest it may represent somewhat milder hydrogenation conditions accounting for the claimed improvements of the final GPC HSH product.

### 3. Equivalence of the HSH Products

The GPC HSH product is compared to the Lonza and the Roquette Freres HSH products in Table 1. The data presented is less complete for the Lonza and Roquette Freres products than for the GPC product. The DE of the GPC product, 0.3-0.98 is slightly higher than those for the other two products < 0.2. The DP1 component for the Roquette and Lonza products are comparable while the GPC product has a slightly lower content of DP1 component. The DP2 component of the GPC product is comparable to the Lonza product but both are much lower than the DP2 component of the Roquette Freres product. The DP3 and DP>4 components for the Lonza and GPC products are comparable. The DP3-6 components of the Roquette and GPC products are similar but these products differ greatly in the DP>6 components.

In summary the GPC product most closely resembles the Lonza product, having a DP distribution that is nearly identical to this product within the accuracy of the methods used. While the GPC and Lonza products are similar to each other, they are both dissimilar in DP distribution to the Roquette Freres product. The theoretical molecular weight of the GPC product is considerably higher than that presented for either the Lonza and Roquette products

All three HSH products differ in the distribution of the components present. The structures of the identified components, however, are the same. The hydrogenation conditions used by GPC appear to be milder (The precise hydrogenation conditions for the Lonza and Roquette products are not defined in their GRAS petitions.) resulting in less breakdown of the hydrogenation precursor leading to a higher theoretical molecular weight for the GPC product. The milder hydrogenation conditions used in the GPC process would undoubtedly result in less side-products, affording a more pure GPC product.

Roquette and Lonza present considerable biological data on their HSH products aimed at establishing safety and functionality. These data include: 1) acute oral toxicity LD<sub>50</sub> data in rats; 2) laxative activity; digestion, absorption and excretion; 4) subchronic, 90 day, toxicity in dogs; 5) genetic toxicity/carcinogenicity, both *in vitro* and *in vivo*; 6) reproduction toxicity in rats over 3 generations; 7) digestive and biological tolerance in man; and 8) estimated potential human exposure based on predicted consumption.

At issue is whether or not the GPC product(s) is sufficiently similar in chemical composition to the Lonza product to make it behave identically with respect to the biological evaluation required for GRAS approval. On the basis of the data provided this appears to be the case. In particular, the GPC product is clearly very similar to the Lonza product except for its somewhat higher theoretical molecular, permitting the conclusion that these products are biologically equivalent.

Despite the similarity between the GPC and Lonza product, it is still difficult to envision GRAS approval in the absence of any biological studies on the GPC product. In this reviewer's opinion, an acute oral toxicity (LD<sub>50</sub> in rats) should be included with the GRAS petition being prepared by GPC. Additional studies such as *in vitro* evaluation of cariogenicity (a beneficial activity) and laxative activity in dogs (a possible adverse activity) might be useful in helping to market the GPC product.

Table 1 Properties of HSH Products

Degree of Polymerization	Roquette-Lycasin 80/55*	Lonza-Hystar 6075**	GPC Hydrogenated M180***
DP1	8%	12-15%	0.3-3.3
DP2	50-55	6-9	4.2-8.2
DP3	---	8-11	6.3-10.3
DP4	---	---	4.4-8.4
DP>4	---	69 max.	69-85
DP5	---	---	3.9-7.9
DP6	---	---	9.4-13.4
DP3-6	20-25	---	24-40
DP>6	15-20	---	52-68
DP7	---	---	7.5-11.5
DP8	---	---	1.9-5.9
DP>8	---	---	42.6-50.6
DE	<0.2	<0.2	0.3-0.98
Theor MW	630	600-750	1000

\* Roquette GRAS petition

\*\* Lonza GRAS petition

\*\*\* GPC PCT WO 99/36442- "Reduced Malto-Oligosaccharides"



**vi. Statement of data information and availability**

The information supporting the GRAS determination is available for FDA review and copying or would be sent to FDA on request.

000292.001

Appendix A

000293

**Appendix A**  
**Part I**  
**Specifications**

000294



Specifications

Parameters	Specification	
Dextrose equivalent	<1.0	
%Moisture	10.0% max	
%Solids(liquid product)	50% min	
Ash	0.1%	
pH	4-7	
Heavy metals	<10ppm	
Chlorides	50ppm max	
Sulfates	100 ppm max	
Arsenic	<2.5ppm	

000294.001



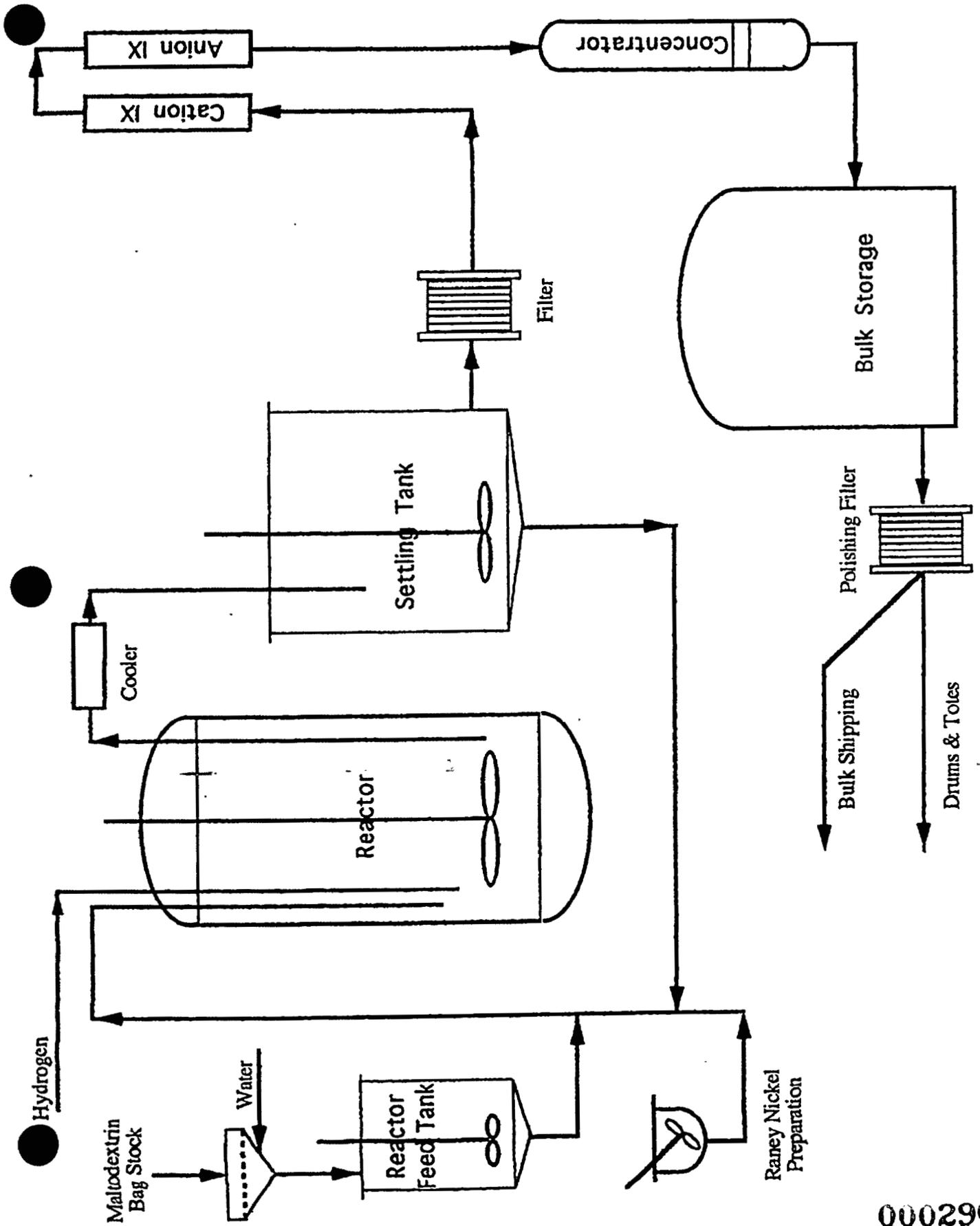
**Appendix A**

**Part 2**

**Details of manufacturing process**

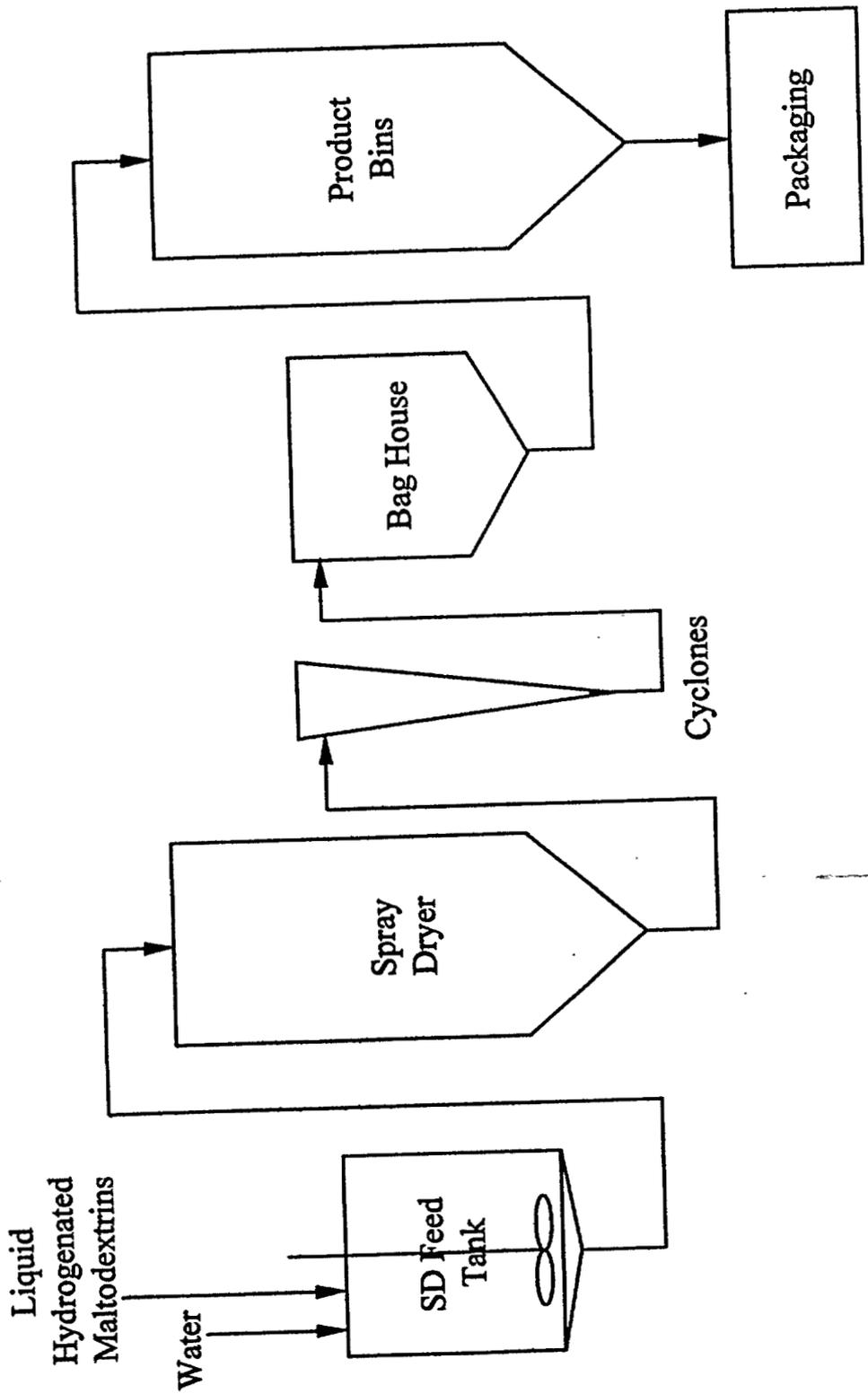
-----

SK-CEL-02  
KL 2/21/00



Hydrogenation of Maltodextrins - SPI Polyols, Inc.

000296

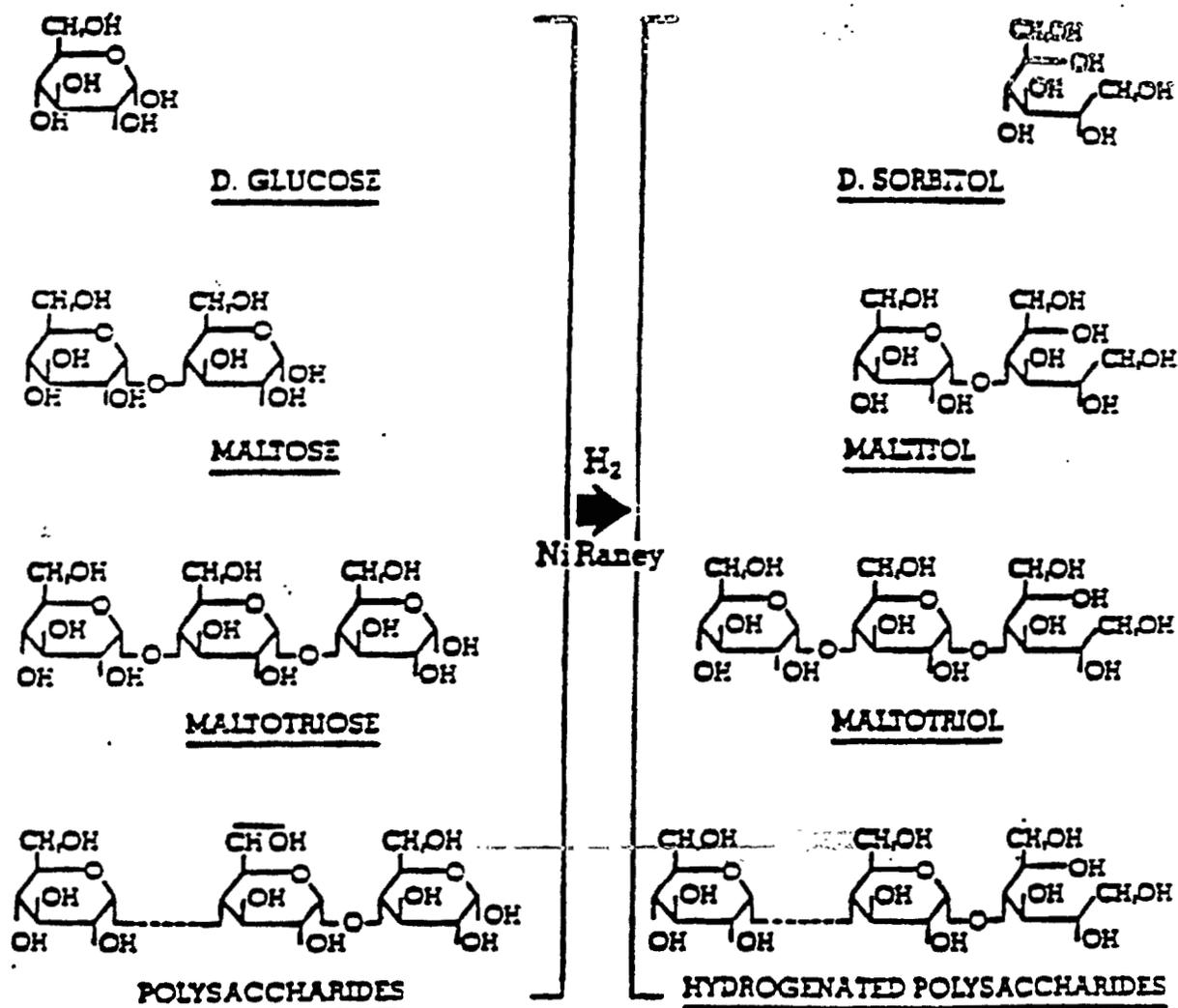


Drying of Hydrogenated Maltodextrins -  
Grain Processing Corporation

MU 3/3/00

# HYDROGENATION

## HYDROGENATED STARCH HYDROLYSATE



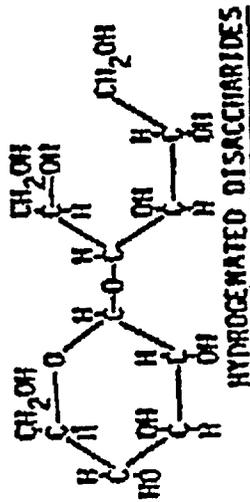
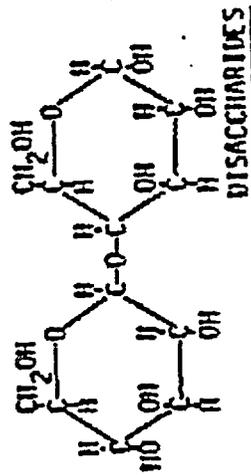
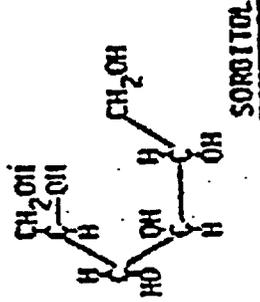
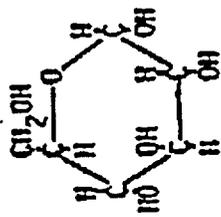
SCHEMATIC PRODUCTION PROCESS

FOR HYSTARS

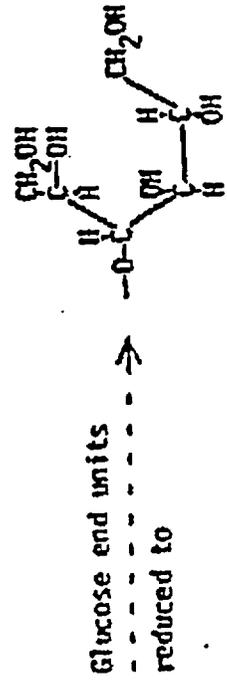
HYDROLYSED STARCH  
DE: 4-20

Raney Ni hydrogenation  
(H<sub>2</sub> + Ni Catalyst)

HYDROGENATED STARCH  
HYDROLYSATE



+  
OLIGOSACCHARIDES  
+  
POLYSACCHARIDES



----->  
Glucose end units  
reduced to

Appendix B

APPENDIX B

**Appendix B**

**Typical formulas using Hydrogenated Starch Hydrolysate**

The following are typical formulations using HSH for the preparation of the above mentioned food uses. It should be noted that in many cases HSH is used with sugar in the final product, therefore the purpose of this notification is to recommend HSH not as a substitute for sugar but as an adjunct, which improves flavor, increases solids and extends shelf life. With this information, the following recipes offer typical formulas using HSH.

## NO SUCROSE ADDED YELLOW CAKE

<u>Ingredients</u>	<u>Percent by weight</u>
(A) Hydrogenated Starch Hydrolysate (HSH)	26.80
Cake Flour	25.40
Water	14.85
Creamtex (Durkee)	12.00
Whole Milk Powder	0.65
Salt	0.60
(B) Water	4.70
(C) Water	10.00
Whole Egg Powder (Henningsen)	3.50
Baking Powder	1.20
Vanilla Extract (2X)	0.30

Procedure

1. Withhold water and blend dry ingredients in part (A).
2. Slowly add water from part (A) to dry ingredients and mix for 5 to 6 minutes at speed #2 in Hobart mixer. Scrape bowl.
3. Add part (B) and mix for an additional 3 minutes.
4. Add part (C) and mix for 4 minutes. Scrape bowl.
5. Bake 450 grams in an 8 x 8 inch pan at 350°F for 30 minutes.

## NO SUCROSE ADDED PANCAKE SYRUP

<u>Ingredients</u>	<u>Percent by weight</u>
Water	50.277
Hydrogenated Starch Hydrolysate (HSH)	48.720
CMC 7H3SF (Hercules)	0.450
Maple Flavor	0.273
Citric Acid	0.075
Sodium Benzoate	0.060
Potassium Sorbate	0.060
Caramel Color	0.045
Sodium Hexametaphosphate	0.040

Procedure

1. Dissolve CMC in water at room temperature, using a dispersator creating a high speed vortex.
2. Once dissolved, dispersate for 15 minutes.
3. Add Stabilite to CMC/water mixture and disperse while increasing the temperature to 120° F.
4. Once this temperature is reached, dispersate for 10 minutes.
5. Add other ingredients to HSH/CMC/water mixture using a propeller mixer at high speed while increasing the temperature to 180°F.
6. Add ingredients in the following order: citric acid, sodium benzoate, potassium sorbate, sodium hexametaphosphate, flavor, color.
7. Mix at 180 °F for 15 minutes.
8. Place in 180° F water bath for 15 minutes.
9. Cool to room temperature.

**NO SUCROSE ADDED ICING**

<u>Ingredients</u>	<u>Percent by weight</u>
Hydrogenated Starch Hydrolysate (HSH)	5.0
Crystalline Maltitol	26.5
Crystalline Sorbitol	26.5
Shortening with emulsifier	8.0
Unsweetened Chocolate	17.2
Flavor	0.4
Water	16.4

Procedure

1. Combine HSH, shortening and water. Bring to a boil.
2. Sift and combine crystalline maltitol and crystalline sorbitol in a Hobart mixer.
3. Using a paddle attachment, mix the crystalline powders on speed #1. While mixing, add heated water mixture.
4. Blend until smooth.
5. Blend in the flavor.
6. Cool to room temperature.

## SUCROSE-FREE HARD CANDY

<u>Ingredients</u>	<u>Percent by weight</u>
Stabilite	98.3
Citric Acid	0.5
Flavor	1.0
Color	0.2

Procedure

1. Cook Stabilite in an open fire cooker to 157 - 160 °C.
2. Pour cooked syrup onto a cooling table.
3. Cool the batch evenly using cool water circulating in the jacket of the cooling table.
4. Continue to cool to 95 - 100°C and then fold in citric acid, flavor and color.
5. While still pliable, form a rope and cut into pieces.
6. Wrap candy and store at room temperature.

APPENDIX C

000307

**Appendix C**

**POTENTIAL PER CAPITA CONSUMPTION OF  
HYDROGENATED STARCH HYDROLYSATE (HSH)**

**POTENTIAL PER CAPITA CONSUMPTION OF HYDROGENATED STARCH  
HYDROLYSATE (HSH)**

Food	HSH level	Per Capita Annual Consumption (lbs)	Annual HSH Consumption (lbs)	Daily HSH Consumption (lbs)	Daily HSH Consumption (gm)
*Confections	10-100%	24.8	2.48-24.8	0.006-0.068	0.45-4.99
**Cookies	0%-25%	12.4	0.00-3.10	0.000-0.009	0.00-2.72
**Cakes	0-10%	8.34	0.00-0.80	0.000-0.002	0.00-1.36
**Sweet goods	0-10%	9.06	0.00-0.90	0.000-0.002	0.00-1.81
**Donuts	0-2%	3.11	0.00-0.06	0.000-0.0002	0.00-4.08
*Carbonated Soft Drinks	0-1%	440	0.00-4.40	0.000-0.012	0.00-4.08
***Ice Cream	0-15%	32	0.00-4.80	0.000-0.013	0.00-5.89

\*USDA/Economic Research Service and U.S Department of Commerce, Percapita consumption '97

\*\* U.S Census Bureau 1997 Economic Census

\*\*\*Prepared Foods July 1998

000309

APPENDIX D

000310

**Appendix D**  
**References on Carcinogenicity and Mutagenicity**

**References on carcinogenicity and mutagenicity of hydrogenated starch hydrolysates.**

1. Wang, Yeu-Ming; van Eys, Jan. Nutritional significance of fructose and sugar alcohols. Annual review of nutrition. p. 437-475. 1981. v. 1
2. Tischler, A. S.; Powers, J. F.; Downing, J. C.; Riseberg, J. C.; Shahsavari, M.; Ziar, J.; McClain, R. M. Vitamin D-3, lactose, and xylitol stimulate chromaffin cell proliferation in the rat adrenal medulla. Toxicology and Applied Pharmacology VOL. 140 NO. 1 1996 PP. 115-123
3. Yoshida, M.; Ishibashi, S.; Nakazawa, M.; Tamura, H.; Uchimoto, H.; Kawaguchi, K.; Yoshikawa, K.; Hamasu, Y.; Sumi, N. The mechanism of lactitol (NS-4) in inducing adrenomedullary proliferative lesion in rats. Journal of Toxicological Sciences VOL. 20 NO. SUPPL. 1 1995 PP. 37-45
4. Yoshikawa, K.; Hamasu, Y.; Yoshida, M.; Ishibashi, S.; Nakazawa, M.; Tamura, H.; Adachi, T.; Kawaguchi, K.; Sumi, N. Study for adrenal medullary hyperplasia induced by lactitol in male SD rats. Journal of Toxicological Sciences VOL. 19 NO. 4 1994 PP. 343
5. Lynch, B. S.; Tischler, A. S.; Capen, C.; Munro, I. C.; McGirr, L. M.; McClain, R. M. Low digestible carbohydrates ( polyols and lactose): significance of adrenal medullary proliferative lesions in the rat. Regulatory, Toxicology, Pharmacology VOL. 23 NO. 3 1996 Jun PP. 256-97
6. World Health Organisation Technical report series 868 – Evaluation of certain food additives and contaminants. Forty sixth report of the Joint FAO/WHO Expert committee on Food Additives. Geneva 1997.
7. World Health Organisation Food Additive Series: 40. Safety evaluation of certain food additives and contaminants. The forty ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) Geneva 1998

Pages 000313 - 000318 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Appendix E

APPENDIX E

000319

APPENDIX E  
EXHIBIT S 1.0  
HYSTAR 6075



# Consumer Product Testing

Company Incorporated

Bldg No. 2-15B  
1275 Bloomfield Avenue  
Fairfield, New Jersey 07006

(201) 575-7688  
(201) 575-7689

## FINAL REPORT

**CLIENT:**

Lonza Inc.  
22-10 Route 208  
Fair Lawn, New Jersey 07410

**ATTENTION:**

Peter J. Schaeufele  
Assistant Corporate Technical Director

**TEST:**

Acute Oral LD<sub>50</sub> in Rats

**TEST  
ARTICLE:**

Compound W-59-5 = Hystar 6075

**EXPERIMENT  
REFERENCE NO.:**

81354-5

\_\_\_\_\_  
Steven Nitka  
Laboratory Director

\_\_\_\_\_  
Allen L. Palanker  
President

Date January 19, 1982  
SN/tmc

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed and neither the report nor the name of these laboratories nor of any member of its staff may be used in connection with the advertising or sale of any product or process without written authorization.

000321

This report details:

an acute oral LD<sub>50</sub> study in albino rats,

performed at the behest of:

Lonza Inc.  
22-10 Route 208  
Fair Lawn, New Jersey 07410

The test article(s), supplied by:

Lonza Inc.

received on:

October 7, 1981

and identified as:

Compound N-59-5

was used as indicated in the Final Report Summaries.

Study Interval: October 21, 1981 to November 30, 1981

(201) 575-7688  
(201) 575-7689



# Consumer Product Testing

Company Incorporated

Bldg No. 2-15B  
1275 Bloomfield Avenue • Fairfield, New Jersey 07006

## QUALITY ASSURANCE UNIT SUMMARY

Study No.: 81354-5

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies as set forth in the Good Laboratory Practice regulations (21 CFR 58). The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date(s) listed below. Studies lasting six months or more are inspected every three months; and studies lasting less than six months are inspected at time intervals to assure the integrity of the study. The findings of these inspections have been reported to management and Study Director. All materials and data pertinent to this study will be stored in the Archives Facility.

Date(s) of inspections:	October 14, 1981	November 11, 1981
	October 21, 1981	November 18, 1981
	October 28, 1981	January 21, 1982
	November 4, 1981	

Professional personnel involved:	Steven Nitka, B.S.	- Laboratory Director (Study Director)
	Sheila Johnson, B.S.	- Technician
	Ellen Lally, B.A.	- Technician
	Barbara Schultz, B.S.	- Technician
	Pam Emerson	- Technician Assistant
	Irene Komrovsky	- Technician Assistant
	Nancy Somer	- Technician Assistant
	Kirk Puryear	- Technician Assistant
	Deborah A. Worman	- Office Manager

The following has been assured by signing below that this study has been performed in accordance with standard operating procedures and the Good Laboratory Practice regulations.

Janet K. Johnson  
Director of Quality Assurance

000323

(201) 575-7688  
(201) 575-7689



# Consumer Product Testing

Company Incorporated

Bldg No. 2-15B  
1275 Bloomfield Avenue • Fairfield, New Jersey 07006

## Final Report Summary

DATE: January 19, 1982  
CLIENT: Lonza Inc.  
STUDY NO.: 81354-5  
REFERENCE: P.J. Schaeufele  
TEST ARTICLE: Compound W-59-5

### Acute Oral LD<sub>50</sub> in Rats

Method: Albino rats, 218-280 g, sexes distributed as indicated below, were dosed singly at range finding levels and in groups of ten (5M:5F) per test level. Each animal received one (1) oral dose of the test article. Animals were observed for pharmacologic activity and drug toxicity at 1, 3, 6, and 24 hours after treatment, and daily thereafter for a total of 14 days. Animals sacrificed at the end of the 14 day observation period, as well as non-survivors, were subjected to gross necropsy, with all findings noted. The test article was used as received (Sp.g. = 1.38).

LD<sub>50</sub> > 40g/kg\*

	Dose Level -- (g/kg)	Sex	No. Dead/No. Dosed (M:F)	Mortality (%)
Range				
Finding:	1.00	1M	0/1	0
	10.00	1M	0/1	0
	20.00	1F	0/1	0
	40.00	1F	0/1	0
Test Dose Levels:	40.00	5M:5F	1/5:1/5	20

\*Maximum dosage.

000324

This test was designed to determine the acute oral LD<sub>50</sub> of the test article in rats. The methods described by Hagan<sup>1</sup> served as a guide.

Wistar-strain albino rats were used for this test. Animals were obtained from a suitably licensed dealer, in equal numbers of each sex and approximately 6 to 9 weeks of age. Upon receipt, the animals were carefully checked for respiratory difficulty, ocular or nasal lacrimation, dehydration, diarrhea, and general thriftiness.

The animals were acclimated for at least 5 days prior to test initiation. They were housed in galvanized cages with indirect bedding, in a temperature controlled room with a 12 hour light/dark cycle. Diet consisted of a growth and maintenance ration from a commercial producer and water ad libitum.

Prior to test initiation, the test article's mass to volume relationship (specific gravity) was determined to facilitate volumetric dosing.

An initial phase of the test, a dosage level range finding, was performed to determine a possible range for the LD<sub>50</sub>. One rat was dosed at each of several dose levels, with a wide spread between successive levels. The lowest dose level at which mortality occurred served as the guide for choosing the first of several graded dose levels used for the LD<sub>50</sub> calculation.

Twenty-four (24) hours prior to dosing, all rats were reexamined for general thriftiness as described above. A group of rats, sexes equally distributed, and of sufficient weight to assure a fasted bodyweight between 200 and 300 grams, was labelled and set aside.

The following day, after approximately 18 hours of fasting, each rat was weighed and marked with an ear clip. Individual doses, calculated on the basis of bodyweight and the dose level being administered, were given using a stainless steel intragastric feeding needle of sufficient bore to allow even passage of the test article in its dosing form. Rats were then returned to their cages, where food and water were available ad libitum. Each cage was uniquely labelled with respect to job number, test article, dose level, sex, animal number(s), and date of dosing.

The animals were observed for signs of pharmacologic activity and drug toxicity at 1, 3, 6, and 24 hours post-dosage. Observations were made at least once daily thereafter for a total of 14 days.

Animals sacrificed at the end of the 14 day observation period, as well as non-survivors, were weighed and subjected to complete gross necropsy, with all findings noted.

The oral LD<sub>50</sub>, including 95% confidence limits, was calculated where possible using the method of Litchfield and Wilcoxon.<sup>2</sup>

<sup>1</sup>E.C. Hagan, "Acute Toxicity", Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics (The Association of Food and Drug Officials of the United States, 1975), pp. 17-25.

<sup>2</sup>J.T. Litchfield and F. Wilcoxon, "A Simplified Method of Evaluating Dose-Effect Experiments", Journal of Pharmacology and Experimental Therapeutics, 96 (1949), pp. 99-107.

Acute Oral LD50 in Rats

Individual results are presented in Tables 1 through 2.

Summaries of all results are found preceding the text.

000326

Table 1

Acute Oral Toxicity

Lonza Inc.  
81354-5  
Page 7

Compound W-59-5

Dose Level: Range Finding (g/kg)

Animal Number: Bodyweight (grams)

and Sex

Hours:

Days:

Animal Number and Sex	Bodyweight (grams)	Hours:						Days:						Bodyweight (grams)						
		1	3	6	24	2	3	4	5	6	7	8	9		10	11	12	13	14	
1 M-	1.00	280	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
2 M-	10.00	266	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
3 F-	20.00	242	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
4 F-	40.00	236	SD	SD	SD	SD	N <sup>5</sup>	N <sup>5</sup>	N <sup>6</sup>	N <sup>6</sup>	N	N	N	N	N	N	N	N	N	N

Raw Data Page 8406

- N = Normal
- D = Depression
- SD = Slight Depression
- XD = Severe Depression
- H = Hyperactivity
- + = Animal Death

- 1 Hair moist and matted
- 2 Hair matted and unkempt
- 3 Probable middle ear infection
- 4 Diarrhea
- 5 Mucooid diarrhea
- 6 Appears dehydrated
- 7 Convulsions
- 8 Muscle tremors

Comments: Animal #1-#4: No gross changes observed.

Table 2  
Acute Oral Toxicity

Lonza Inc.  
81350-5  
Page 8

Compound W-59-5

Dose Level: Animal Number and Sex	40.00 g/kg Bodyweight (grams)	Hours:						Days:						Bodyweight (grams)					
		1	3	6	24	2	3	4	5	6	7	8	9		10	11	12	13	14
1 M	222	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	310
2 M	224	SD	SD	SD	SD	N	N	N	N	N	N	N	N	N	N	N	N	N	278
3 M	230	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	354
4 M	236	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	354
5 M a	260	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	354
6 F	232	SD	XD	+	5	-	-	-	-	-	-	-	-	-	-	-	-	-	226
7 F	226	N	SD	+	5	-	-	-	-	-	-	-	-	-	-	-	-	-	200
8 F	218	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	270
9 F	230	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	300
10 F	220	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	276

Raw Data Page 8426 and 8466

- N = Normal
- D = Depression
- SD = Slight Depression
- XD = Severe Depression
- H = Hyperactivity
- + = Animal Death
- 1 Hair moist and matted
- 2 Hair matted and unkempt
- 3 Probable middle ear infection
- 4 Diarrhea
- 5 Mucoïd diarrhea
- 6 Appears dehydrated
- 7 Convulsions
- 8 Muscle tremors

Comments: Animals #1-#4, #5a, #8-#10: No gross changes observed.  
 #6: Gastrointestinal mucosa severely reddened.  
 #7: No gross changes observed.  
 Original animal #5 replaced: Fibrous tissue encasing heart and limbs.

APPENDIX E

EXHIBIT S 1.2

138



EST. 1975

# Consumer Product Testing Co.

## FINAL REPORT

**CLIENT:** Grain Processing Corporation  
1600 Oregon Street  
Muscatine, Iowa 52761

**ATTENTION:** Rani M. Thomas  
Director of Quality and  
Regulatory Affairs

**TEST:** Acute Oral LD<sub>50</sub> in Rats

**TEST ARTICLE:** Experimental M180

**EXPERIMENT  
REFERENCE NUMBER:** T00-0040

---

Kathleen Alworth, B.A.  
Director of Quality Assurance

Steven Nitka  
Laboratory Director  
Vice President

**000330**

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor any member of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234



# Consumer Product Testing Co.

## QUALITY ASSURANCE UNIT STATEMENT

Study No.: T00-0040

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. These studies have been performed with strict adherence to the Good Laboratory Practice Act (21 CFR 58) and in accordance to standard operating procedures and applicable standard protocols. The study is listed on this facility's Master Schedule. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date(s) listed below. The findings of these inspections have been reported to management and the Study Director. All materials and data pertinent to this study will be stored in the Archive Facility at 70 New Dutch Lane, Fairfield, New Jersey, 07004, unless specified otherwise, in writing by the Sponsor.

### Dates of biophase/data inspection/Report to Management:

March 9, 2000	March 10, 2000	March 13, 2000
March 14, 2000	March 20, 2000	March 21, 2000
March 22, 2000	March 23, 2000	March 27, 2000
March 28, 2000	March 31, 2000	

### Professional personnel involved:

Steven Nitka, B.S.	- Vice President Laboratory Director (Study Director)
Lillian Deniza, B.S.	- Laboratory Supervisor
Melissa Pandorf, B.S.	- Technician
Essam Eldeib, Ph.D.	- Quality Assurance Associate

The representative signature of the Quality Assurance Unit on the front page signifies that this study has been performed in accordance with standard operating procedures and applicable study protocols.

000331



EST. 1975

# Consumer Product Testing Co.

## Final Report Summary

**CLIENT:** Grain Processing Corporation

**STUDY NO.:** T00-0040

**REFERENCE:** R.M Thomas

**TEST ARTICLE:** Experimental M180

**TEST ARTICLE RECEIPT DATE:** February 29, 2000

**EXPERIMENTAL INTERVAL:** March 10, 2000 to March 28, 2000

## Acute Oral LD<sub>50</sub> in Rats

**Method:** Albino rats, 200 - 230 g, sexes as indicated below, were dosed singly at range finding levels and in a test level group of ten (5M:5F). Each animal received a single oral dose of the test article. Animals were observed for pharmacological activity and drug toxicity 1, 3, 6, and 24 hours after treatment, and daily thereafter for a total of 14 days. All animals survived the observation period and were then euthanized and subjected to a gross necropsy with all findings noted. The test article was used as a 25% suspension in corn oil.

Results:	Dose Level	Sex	No. Dead/No. Dosed	Mortality
	(g/kg)		(M:F)	(%)
Range				
Finding:	1.00	1M	0/1	0
	5.00	1F	0/1	0
	10.00	1F	0/1	0
Test Dose				
Level:	10.00	5M:5F	0/5:0/5	0

**Conclusion:** LD<sub>50</sub> > 10 g/kg (Ten (10) grams per kilogram is the maximum feasible dosage at the concentration of 25%).

000332

### Acute Oral LD<sub>50</sub> in Rats

This test was designed to determine the acute oral LD<sub>50</sub> of the test article in rats. The methods described by Hagan<sup>1</sup> served as a guide.

Wistar-strain, albino rats were used for this test. Animals were obtained from Ace Animals in Boyertown, Pennsylvania, in equal numbers of each sex and approximately six to nine (6 to 9) weeks of age. Upon receipt, the animals were carefully checked for respiratory difficulty, ocular or nasal lacrimation, dehydration, diarrhea, and general condition.

The animals were acclimated for at least seven (7) days prior to test initiation. They were housed in stainless steel cages with indirect bedding, in a room with a 12 hour light/dark cycle. The room temperature was controlled, to provide for the health and comfort of the animals with an approximate range of 65° to 75° F. The humidity was also monitored. Diet consisted of Lab Diet Certified Rodent Diet #5002, as well as water, *ad libitum*.

Prior to test initiation, the test article was suspended in corn oil at 25%. Fresh suspensions were made on each dosing day.

An initial phase of the test, a dosage level range finding with initial dosages as chosen by the sponsor, was performed to determine a possible range for the LD<sub>50</sub>. One (1) rat was dosed at each of several dose levels, with a wide spread between successive levels. The dose levels served as the guide for choosing the test dose level used for the LD<sub>50</sub> calculation.

Twenty-four (24) hours prior to dosing, all rats were reexamined for general condition as described above. A group of rats, sexes equally distributed, and of sufficient weight to assure a fasted body weight between 200 and 300 grams, was labeled and set aside.

The following day, after approximately 18 hours of fasting, each rat was weighed and marked with an ear clip. Individual doses, calculated on the basis of body weight and the dose level being administered, were given using a stainless steel intragastric feeding needle of sufficient bore to allow even passage of the test article in its dosing form. Rats were then returned to their cages, where food and water were available *ad libitum*. Each cage was uniquely labeled with respect to job number, test article, dose level, sex, animal number(s), and date of dosing.

The animals were observed for signs of pharmacological activity and drug toxicity at 1, 3, 6, and 24 hours post-dosage. Observations were made at least once daily thereafter for a total of 14 days. All animals survived the observation period and were then euthanized and subjected to a gross necropsy with all findings noted. Sacrificing was accomplished via carbon dioxide asphyxiation.

<sup>1</sup>E.C. Hagan, "Acute Toxicity", *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics*, (The Association of Food and Drug Officials of the United States, 1959), pp. 17 - 25.

**Acute Oral LD<sub>50</sub> in Rats**

The individual test results are presented in Tables 1 and 2.

**Summaries of all results are found preceding the text.**

Table 1  
 Acute Oral Toxicity  
 Experimental M180

Dose Level	RF @ 1.5 + 10 g/kg	Hours:			Days:														Bodyweight (grams)	
		Animal Number and Sex	1	3	6	24	2	3	4	5	6	7	8	9	10	11	12	13		14
1 M	227	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	330
2 F	200	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	235
3 F	201	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	243

Raw Data Page 17287

- N = Normal
  - D = Depression
  - SD = Slight Depression
  - XD = Severe Depression
  - H = Hyperactivity
  - + = Animal Death
- 1 Hair moist and matted
  - 2 Hair matted and unkempt
  - 3 Probable middle ear infection
  - 4 Diarrhea
  - 5 Mucoïd diarrhea
  - 6 Appears dehydrated
  - 7 Convulsions
  - 8 Muscle tremors

Necropsy comments: Animals #1-#3: No gross changes observed.

Table 2  
Acute Oral Toxicity  
Experimental M180

Dose Level	10 g/kg	Hours:			Days:										Bodyweight (grams)					
		1	3	6	24	2	3	4	5	6	7	8	9	10		11	12	13	14	
1 M	220	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	338
2 M	222	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	336
3 M	213	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	326
4 M	230	N	N <sup>5</sup>	N <sup>5</sup>	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	356
5 M	224	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	348
6 F	218	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	276
7 F	216	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	278
8 F	224	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	268
9 F	209	N <sup>5</sup>	N <sup>5</sup>	N <sup>5</sup>	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	262
10 F	217	N	N	N	N <sup>1</sup>	N	N	N	N	N	N	N	N	N	N	N	N	N	N	276

Raw Data Page 17289

- N = Normal
  - D = Depression
  - SD = Slight Depression
  - XD = Severe Depression
  - H = Hyperactivity
  - + = Animal Death
- 000336
- 1 Hair moist and matted
  - 2 Hair matted and unkempt
  - 3 Probable middle ear infection
  - 4 Diarrhea
  - 5 Mucoïd diarrhea
  - 6 Appears dehydrated
  - 7 Convulsions
  - 8 Muscle tremors

Necropsy comments: Animals #1-#10: No gross changes observed.

**APPENDIX E**

**EXHIBIT S 2.0**

**ROQUETTE GRAS AFFIRMATION PETITON #84G-0003 SECTION IV  
INFORMATION TO ESTABLISH SAFETY AND FUNCTIONALITY IN FOOD**

-17-

iv. Information to Establish Safety  
and Functionality in Food

SAFETY\*

SUMMARY

In June 1983, a panel of experts composed of past members of the Select Committee on GRAS Substances of the Federation of American Societies for Experimental Biology, after a review of the reports and documents contained in Sections ii and iv (but not including the functionality data) of this petition, concluded (Report E-51) that:

There is no evidence in the available information on LYCASIN 80/55 that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced or that might reasonably be expected in the future.

Approximately 96 percent of Lycasin 80/55 is ultimately broken down in the digestive tract into sorbitol and glucose. One half of the remaining four percent, in the form of maltitol, is excreted in the feces, the rest enters the blood stream and is excreted intact in the urine.

The LD<sub>50</sub> of Lycasin 80/55 is equal to or higher than sorbitol. In subchronic studies, Lycasin 80/55 produces no significant toxic effects which cannot be accounted for by the

---

\* Reports E-1 through E-51, pertaining to the safety of hydrogenated glucose sirip, are presented in Appendix E.

000338

-18-

presence of sorbitol. Lycasin 80/55 is nonmutagenic, nonclastogenic, and produces no significant toxic effects on reproduction.

Lycasin 80/55 may produce a laxative effect at an intake level of approximately 100g per day. To reach this threshold level, an individual would have to consume considerable quantities of products containing Lycasin 80/55. For example, the 100g per day intake threshold is equivalent to 4-5 rolls of hard candy mints, 50 jelly beans, 111 sticks of chewing gum or 180 miniature marshmallows (these figures are based on data provided in Appendix C).

#### DIGESTION, ABSORPTION, DISTRIBUTION, AND EXCRETION

Within the first two hours after oral administration, Lycasin 80/55 is broken down into two GRAS substances, sorbitol and glucose, and maltitol. Within 7 hours, 95 percent of the maltitol is broken down into sorbitol and glucose. Of the remaining maltitol one-half is excreted in the feces, one-fourth is excreted in the urine and one-fourth remains in the blood stream. After 12 hours, the blood levels of maltitol are practically zero and there is no accumulation in the other tissues or organs of the body.

#### ACUTE TOXICITY

The LD<sub>50</sub> of Lycasin 80/55 is equal to or greater than that of sorbitol and glucose.

000339

-19-

SUBCHRONIC TOXICITY

Lycasin 80/55, when administered orally to rats and dogs in amounts of 5 to 15 grams per kilogram of body weight per day for 90 days, produces no toxicologically meaningful effects which cannot be accounted for by the presence of sorbitol.

The possible treatment-related effects are aggregates in the renal pelvis of some rats, diarrhea in most dogs and minimal ectasia in the renule tubules of some dogs.

GENETIC TOXICITY/CARCINOGENICITY

Lycasin 80/55 is nonmutagenic and nonclastogenic in short term in vivo and in vitro studies. A similar material containing at least 75 percent maltitol, when administered to rats over a 78-week period, produces no carcinogenic effects.

REPRODUCTION TOXICITY

Lycasin 80/55, when administered to rats over a three-generation period, produces no significant effects on reproduction.

DIGESTIVE AND BIOLOGICAL TOLERANCE IN MAN

Lycasin 80/55, at doses up to 180 grams per day, produces no significant variation in the clinical chemical, hematological, or urinary profile, with the exception of serum glucose and insulin peaks which are less than 50 percent of those produced by an equivalent amount of glucose.

The only clinical effects are flatulence and diarrhea, which can be attributed to the presence of free and bound sorbitol. The mean laxative threshold in adult males is

000340

-20-

approximately 180 grams per day, while in females the threshold is approximately 100 grams per day. In children, the threshold is approximately 60 grams per day, about half that of adults.

POTENTIAL HUMAN EXPOSURE

The potential average daily consumption of Lycasin 80/55 by eaters, those who consume candies and chewing gums, is estimated to be 0.5 to 1.1 grams per day, with a 90th percentile (high eaters) consumption level at 1.1 to 2.6 grams per day.

NOTE: LYCASIN 80/55, LYCASIN 80/33 AND LYCASIN 65/63

Although this petition seeks approval of the product, Lycasin 80/55, chemical and biological data are also presented on the prototype products, Lycasin 80/33 and Lycasin 65/63. These data are presented solely for the purpose of providing secondary verification of the Lycasin 80/55 studies, especially in those instances where the original data on Lycasin 80/55 studies were unavailable for post study audit. A comparison of the chemical composition of these products is provided in report E-50.

000341



-22-

- . Within 7 hours, 95 percent of the total maltitol, (free maltitol plus the maltitol moiety of higher saccharide alcohols) is broken down into glucose and sorbitol. Of the remaining 5 percent of maltitol (equivalent to 3.66 percent of the Lycasin 80/55 ingested), 2 percent is found in the digestive tube and fecal contents, less than 1 percent is found in the plasma, and approximately 1 percent is excreted in the urine.
- . There is no accumulation of maltitol in the plasma, liver, kidneys, or spleen of rats fed 13.5 g/kg/day of Lycasin 80/55 for 10 days. This is true whether measurements are made 12 hours or 10 days after cessation of dosing.

#### DIGESTION

- . 50 to 85 percent of the glucose molecules contained in Lycasin 80/55 are released through hydrolysis when the product is incubated in the presence of amylo-glucosidase for 4 to 6 hours (Report E-1, Cf generally Report E-40).
- . When Lycasin 80/55 is incubated in the presence of either  $\alpha$ -glucosidase or homogenates of rat small intestine, it releases approximately 50 percent of the glucose molecules as compared to an equivalent amount of its precursor high maltose corn syrup (Report E-2).

000343

-23-

- When Lycasin 80/55 is incubated in the presence of either rat intestinal mucosa (pylorus to rectum) or human intestinal mucosa (jejunum), it releases both glucose and sorbitol.
  - The hydrolysis of glucose to glucose bonds proceeds rapidly.
  - The hydrolysis of glucose to sorbitol bonds (maltitol) proceeds more slowly (Report E-3).
- The glucose to glucose bonds of Lycasin 80/55 are rapidly hydrolyzed within the first 1 1/2 hours after oral administration to rats. Within 7 hours 95 percent of the glucose to sorbitol bonds (maltitol) are hydrolyzed (Report E-4).
- Lycasin 80/55 and high maltitol syrup are metabolized by man to approximately the same extent as mixtures of glucose and sorbitol in equivalent ratios (Report E-41).
- 80 percent of the glucose moieties in Lycasin 65/63 are readily split off by the digestive enzymes of the rat, the maltitol moieties, in contrast, are split very slowly (Report E-42).
- Maltitol is split into glucose and sorbitol molecules by the mucosal disaccharidases of rat, rabbit and man. This splitting occurs more slowly than with sucrose; the rate of hydrolysis may be compared to that of lactose. Approximately 70% of the ingested

000344

-24-

maltitol is hydrolyzed by the time it has reached the distal portion of the rats intestines (Report E-44).

- Maltitol is hydrolyzed in the stomach into glucose and sorbitol. Maltitol is also subjected to microbial fermentation in the cecum producing volatile fatty acids (Report E-45).
- A comparison between germ-free and conventional rats indicate that approximately 12 percent of ingested maltitol is metabolized by the intestinal microflora of rats (Report E-41).

#### ABSORPTION

- Approximately 9, 5, and 2 percent respectively of Maltitol-U-<sup>14</sup>C is transported across jejunal, ileal and duodenal everted sacs of rat intestine when incubated for 60 minutes at 37°C (Report E-14).
- Approximately 1 percent of the potential maltitol in 200 to 600 mg of Lycasin 80/55 ingested by rats is absorbed in tact into the bloodstream as determined by urinary excretion. Maltitol is detectable in the plasma only sporadically during the 7 hours of observation and always at very low levels (0.2 mg/ml or less) (Report E-4).
- Approximately 1 percent of the potential sorbitol in 200 to 600 mg of Lycasin 80/55 ingested by rats is absorbed into the bloodstream as determined by urinary excretion. Sorbitol is detectable in the plasma

000345

-25-

at levels of 0.15 to 0.90 mg/ml during the 7 hour period of observation. There appears to be no dose/response relationship (Report E-4).

- . Less than 1 percent of orally administered  $^{14}\text{C}$ -maltitol appears in the blood stream of mice within the first 6 hours after oral administration. Chromatographic analysis indicates that the radiolabeled substances in the blood are principally  $^{14}\text{C}$ -glucose and  $^{14}\text{C}$ -sorbitol (Report E-5).
- . Lycasin 80/55 produces a serum glucose peak within 60 minutes after oral administration in rats. This peak is approximately three-fourths that produced by its precursor, high maltose corn syrup (peak at 30 minutes) (Report E-6).
- . Lycasin 80/55 produces serum glucose and insulin peaks within 30 minutes after oral administration in man. These peaks are approximately one-half to one-third of an equivalent amount of glucose (Report E-7).
- . Lycasin 80/55 produces serum glucose and insulin peaks within 30 to 60 minutes after oral administration in normal and diabetic humans. These peaks are approximately 50 percent of those produced by an equivalent volume of glucose and approximately 50 to 90 percent of those produced by sucrose (Report E-8).
- . Lycasin 65/63 produces a serum glucose peak within 30 minutes after oral administration in man. This peak

000346

-26-

is essentially equal to that produced by an equivalent amount of dextrose (Reports E-9 and E-10).

- Lycasin 65/63 produces a rise in the blood glucose level of man equal to that produced by an equivalent amount of sucrose (Report E-43).
- The glucose units of the maltitol molecules and moieties of Lycasin 65/63 largely escape being absorbed in the small intestines of rats. Sorbitol, whether free or bound, is absorbed very slowly (Report E-42).

#### DISTRIBUTION AND EXCRETION

- Lycasin 80/55 does not produce a significant increase in liver glycogen when administered orally to rats maintained on a carbohydrate-deficient diet. Its precursor, high maltose corn syrup, produces a significant increase (16 percent) under the same conditions (Report E-11).
- When administered orally to rats for 28 days, Lycasin 80/55 does not produce significant differences in liver glycogen, carcass fat, ash, moisture, or protein content as determined by proximate analysis when compared to an equivalent amount of its precursor, high maltose corn syrup, or sucrose (Report E-12).
- There is no accumulation (detection limit 0.1 mg per organ or mg per ml of plasma) of maltitol in the plasma, liver, kidneys, or spleen of rats fed 13.5

000347

-27-

g/kg/day of Lycasin 80/55 for 10 days. The maximum rate of excretion of maltitol in the urine over the same period is less than 0.2 percent (15.8 mg/kg/day). There is also no significant difference between the free sorbitol levels in the liver, plasma, and spleen of control and Lycasin-fed animals, nor are there detectable levels in the kidneys of either group (Report E-13).

- . Seven hours after oral administration of 600 mg of Lycasin 80/55 to rats, 55 percent of the material (based on total sorbitol recovered) is found in the digestive tube and fecal contents and less than one percent is found in each of the plasma and urine. The remainder of the material, in the form of glucose and sorbitol, has presumably entered the body's metabolic pathways (Report E-4).
- . Approximately 30 percent of the radiolabeled material appears in the feces of rats 6 hours after oral administration of maltitol-U-<sup>14</sup>C. An additional 3 percent appears in the total respiratory CO<sub>2</sub>. The majority of the remainder of the activity is found in the digestive tube contents (Report E-5).
- . 83 percent of the recovered radiolabeled material appears in the caecal, large intestine and fecal contents of rats 24 hours after oral administration of maltitol-U-<sup>14</sup>C. An additional 3 percent appears in

000348

-28-

the stomach and small intestinal contents. Six percent appears in the urine and 1.6 percent appears in the total respiratory CO<sub>2</sub>. Less than 0.3 percent appears in each of the blood, liver, muscle, brain, and kidney organs. Less than 0.1 percent appears in each of the heart, lung, spleen, pancreas, stomach, large intestines, caecum, testes, and adipose tissue organs (Report E-14).

- 88 percent of the recovered radiolabeled material appears in the urine of rats 24 hours after intravenous administration of maltitol-U-<sup>14</sup>C. An additional 3.5 percent appears in the total respiratory CO<sub>2</sub>. Less than 0.3 percent appears in each of the blood, liver, muscle, heart, and kidney organs (Report E-14 and Report E-41).

-29-

SUMMARY OF  
ACUTE TOXICITY OF LYCASIN 80/55

SUMMARY

The acute, LD<sub>50</sub>, toxicity of Lycasin 80/55 is comparable to that of sorbitol and glucose.

REPORTS

- The LD<sub>50</sub> (14 days) of Lycasin 80/55 in mice is:

Grams per kilogram of body weight

Route	Sex Male	Sex Female
Oral	> 24.0	> 24.0
Intravenous	> 6.4	> 8.2
Intraperitoneal	> 10.6	> 12.4

(Report E-15)

- The LD<sub>50</sub> (14 days) of Lycasin 80/55 in rats is:

Grams per kilogram of body weight

Route	Sex Male	Sex Female
Oral	> 24.4	> 24.4
Intraperitoneal	> 13.0	> 13.0

(Report E-16)

- The oral LD<sub>50</sub> of sorbitol in male and female mice is 23.2 and 25.7 grams per kilogram of body weight respectively. The oral LD<sub>50</sub> in male and female rats is 17.5 and 15.9 grams per kilogram of body weight respectively (cf. Report E-17). The intraperitoneal LD<sub>50</sub> in mice is 15 grams per kilogram of body weight (NIOSH, RTECS).

000350

-30-

- The oral LD<sub>50</sub> of glucose in rats, dogs and rabbits is 25.8, 8 and 20 grams per kilogram of body weight respectively. The intravenous LD<sub>50</sub> in rabbits is 12 grams per kilogram of body weight. The intraperitoneal LD<sub>50</sub> in mice is 18 grams per kilogram of body weight. (NIOSH, RTECS).

000351

-31-

SUMMARY OF THE  
SUBCHRONIC TOXICITY OF LYCASIN 80/55

SUMMARY

Lycasin 80/55, when administered to rats and dogs in the amount of 5 to 15 grams per kilograms of body weight for 90 days, produces no toxicologically meaningful effects which cannot be accounted for by the presence of sorbitol. (See generally reports E-17, E-46, E-47, E-48 and E-49) The possible treatment-related effects are:

- Aggregates in the renal pelvis of some rats
- Diarrhea in most dogs
- Minimal ectasia in the renal tubules of some dogs.

REPORTS

Clinical chemical and hematological examinations and urinalysis on rats fed diets containing 10, 15, and 20 percent of Lycasin 80/55 for 13 weeks revealed no treatment-related effects when compared to an equivalent diet of 20 percent sucrose. Lycasin 80/55 also produces no significant histopathological effects, with the possible exception of aggregates in the renal pelvis (Report E-18). If this effect is treatment-related, it is probably due to the sorbitol content of Lycasin 80/55 (cf. Report E-17).

000352

-32-

- . When fed to rats as 20 percent of the diet for 90 days, Lycasin 80/55 produces no toxicologically meaningful effects on body weight, mortality, clinical manifestation, food consumption, hematological profile, clinical chemical profile, urine profile, relative organ weights, or histopathological appearance when compared to an equivalent amount of sorbitol diet (Report E-19).
- . When fed to rats as 2, 5, and 15 percent of the diet for 90 days, Lycasin 65/63 produces no toxicologically meaningful effects on body weight gain, mortality, clinical manifestations, food consumption, hematological profile, clinical chemical profile, urine profile, or histopathological appearance when compared to rats maintained on a standard laboratory diet (Report E-20).
- . When orally administered to beagle dogs at a level of 5 grams per kilogram of body weight per day for 90 days, Lycasin 80/55 produces no toxicologically meaningful effects on mortality, clinical manifestations, body weight gain, ophthalmological profile, hematological profile, myelographic profile, clinical chemical profile, PAH clearance, urine profile, or histopathological appearance when compared to untreated animals with the following exceptions:
  - Diarrhea

000353

-33-

- Slight increase in plasma triglycerides of females
- Minimal ectasia in the renal tubules.

These observations must be considered as being physiologic, in relation to the high amount of saccharide alcohols provided by the treatment (Report E-21).

Lycasin 65/63, when fed to beagle dogs as 2, 5, and 15 percent of the diet for 90 days, produces no toxicologically meaningful effects on mortality, body weight gain, food consumption, clinical manifestations, hematological profile, clinical chemical profile, urine profile, organ weights, or histopathological appearance when compared to untreated animals (Report E-22).

000354

-34-

SUMMARY OF  
GENETIC TOXICITY OF LYCASIN 80/55

SUMMARY

- . Lycasin 80/55, as demonstrated in an extensive series of 8 in vivo and in vitro genetic toxicology studies, is nonmutagenic and nonclastogenic. From this it is concluded that Lycasin 80/55 is unlikely to have a carcinogenic potential.
- . A similar material containing at least 75 percent maltitol, when administered to rats over a 78 week period, produces no carcinogenic effects.

REPORTS

- . Lycasin 80/55, at concentrations ranging from 0.003 to 40.0 mg/ml of incubation mixture, does not produce any significant increases in cellular toxicity or reversions to histidine prototrophy in the S. typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, or TA 100 either in the presence or absence of s9 metabolic activators (Report E-23).
- . Lycasin 80/55, at concentrations ranging from 4.0 to 280.0 mg/ml of incubation mixture, does not produce any significant increases in reversion to histidine prototrophy in the S. typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 either in the presence or absence of s9 metabolic activator (Report E-24).

000355

-35-

- Lycasin 80/55, when fed to rats at doses ranging from 2.0 to 15.0 grams per kilogram of body weight for 14 days, does not produce urinary metabolites which are active in inducing reversions to histidine prototrophy in S. typhimurium strains, TA 1535, TA 1537, TA 1538, TA 98, and TA 100 either in the presence or absence of s9 metabolic activation (Report E-25).
- Lycasin 80/55, at concentrations of 0.003 to 30.0 mg/ml of incubation mixture, does not produce any significant increase in the inductive capacity of E. coli K-12, strain GY5027 with Lambaphage (2 pgsa) either in the presence or absence of s9 metabolic activation (Report E-26).
- Lycasin 80/55, at doses of 5.0 to 25.0 grams per kilogram body weight, does not significantly increase the number of micronuclei carrying polychromatophilic erythrocytes in mice (Report E-27).
- Lycasin 80/55, at concentrations ranging from 10.0 to 1000.0 ug/ml of incubation mixture, does not significantly increase the frequency of Type III morphologically transformed foci or cytotoxicity in C3H/10T 1/2 (Clone 8) cells either in the presence or absence of s9 metabolic activators (Report E-28).
- Lycasin 80/55, at concentrations ranging from 49.0 to 4900.0 ug/ml of incubation mixture, does not

000356

-36-

significantly increase the frequency of chromosomal aberrations in Chinese Hamster Ovary cells, either in the presence or absence of s9 metabolic activators (Report E-29),

- . Lycasin 80/55, at concentrations ranging from 27.0 to 1000.0 mg/ml of incubation mixture, does not significantly increase the frequency of mouse lymphoma mutations either in the presence or absence of s9 metabolic activators (Report E-30),
- . It is unlikely that Lycasin 80/55, which has been demonstrated to be nonmutagenic and nonclastogenic in an extensive battery of genetic toxicology procedures, has the potential to produce carcinogenic effects (Report E-31),
- . A material consisting of at least 75 percent matitol, when administered to rats at doses of 1.5 to 5.5 grams per kilogram of body weight for 78 weeks, produces no carcinogenic effects (Report E-32).

000357

-37-

SUMMARY OF THE TOXIC EFFECTS  
OF LYCASIN 80/55 ON REPRODUCTION

SUMMARY

Lycasin 80/55, when administered over three generations, produces no significant effects on reproduction.

BASIS

- Lycasin 80/55, when administered to rats over three generations at dose levels of 13.0 to 17.5 grams per kilogram of body weight per day, produces no significant regularly recurring effects on:
  - Male or female fertility
  - The gestation period
  - The occurrence of pup malformations
  - The number of live and stillborn births
  - Postnatal survival
  - Adult survival
  - Adult hematological parameters
  - Postmortem macroscopic observations
  - Gastrointestinal tract.
- Lycasin 80/55 does produce the following effects:
  - Transitory decrease in pre-weanling growth rate
  - Reduced adult male kidney weight
  - Increased adult male fecal weight.

(Report E-33)

000358

-38-

SUMMARY OF THE DIGESTIVE AND  
BIOLOGICAL TOLERANCE OF MAN OF LYCASIN 80/55

SUMMARY

- . Lycasin 80/55, at the dose levels tested, 30 to 180 grams per day, produces no significant variations in the clinical chemical, hematological or urinary profile of man with the exception of glucose and insulin peaks which are less than 50 percent of those produced by equivalent amounts of glucose, and 50 to 90 percent of those produced by sucrose.
- . The only significant clinical effects are flatulence and diarrhea, which can be accounted for by the presence of free and bound sorbital. (See generally reports E-17, E-46, E-47, E-48 and E-49)
- . The mean laxative threshold in adult males is approximately 180 grams per day, while in females the threshold is approximately 100 grams per day. This difference is possibly due to the fact that females digest and absorb Lycasin 80/55 more slowly than males. (Cf Report E-4). With a higher saccharide alcohol content in the lower digestive tract, the osmotic gradient would produce watery stools.
- . The mean laxative threshold in children appears to be around 60 grams per day, approximately half that of

000359

-39-

adults. Therefore Lycasin 80/55 appears to exert its laxative effect on a grams per kilogram body weight basis.

BASIS

- . In adult males the mean laxative threshold for Lycasin 80/55, after repetitive daily consumption, appears to be greater than 180 grams per day, while in adult females it appears to be at or above 100 grams per day. Lycasin 80/55, when administered in doses of 30 to 180 grams per day for 5 to 120 days, produces no significant effects on the clinical chemical profile or urine volume of normal or diabetic subjects other than mild transitory hyperglycemia (Report E-34).
- . The mean laxative threshold for Lycasin 80/55 in men and women is approximately 125 grams per day (Report E-41).
- . Lycasin 80/33, when administered to adult males and females in doses of 45 to 90 grams per day for 30 to 90 days, produces no significant laxative effect. At the doses tested, Lycasin 80/33 produces no significant effect on clinical chemical or hematological profile of normal or diabetic subjects other than a mild transitory hyperglycemia (Report E-35).

000360

000360

-40-

- . Lycasin 80/55, when administered in single doses of 50 to 100 grams, produces peaks in serum glucose and insulin which are approximately one-half to one-third, respectively, of those produced by an equivalent amount of glucose. Subjects given 100 grams occasionally experience abdominal pain and flatulence which disappear overnight (Report E-7).
- . Lycasin 80/55, when administered to adult males and females in the form of 48 to 58 grams of hard boiled candies per day for six days, produces the same number of symptomless days as a similar amount of sucrose candies; however, the number of gastrointestinal symptoms reported per subject day for Lycasin 80/55 are approximately two to five times higher than those for sucrose (Report E-36).
- . Lycasin 80/55, when administered to adult males and females in doses of 70 grams per day for 28 days, produces diarrhea on less than 7 percent and gas pains on less than 20 percent of the subject days. Over this same period Lycasin 80/55 does not produce any significant changes in the clinical chemical, hematological, or urinary profile (Report E-37).
- . After repeated daily consumption of Lycasin 80/55, the human digestive system appears to adapt, resulting in gradual disappearance of diarrhea and flatulence over 4-5 days (Report E-41).

000361

-41-

- . Lycasin 80/55, when administered to children, ages 3 to 14, in doses of 9 to 60 grams per day over a one-hour period, produces gas pains in 14 percent of the subject days at the 20 gram level, 20 percent at the 30 gram level, 50 percent at the 40 gram level, 75 percent at the 60 gram level, while loose stools are produced in 8 percent of the subject days at the 30 to 40 gram level and 50 percent at the 60 gram level (Report E-38).
- . Lycasin 80/55 produces serum glucose and insulin peaks within 30 to 60 minutes after oral administration in normal and diabetic subjects. These peaks are approximately 50 percent of those produced by an equivalent amount of glucose and approximately 50 to 90 percent of those produced by sucrose (Report E-8).

000362

-42-

SUMMARY OF THE  
LYCASIN 80/55 POTENTIAL  
HUMAN EXPOSURE ASSESSMENT

SUMMARY

The potential average daily consumption of Lycasin 80/55 by "eaters", those individuals who consume candies, confections and chewing gum, is estimated to be 0.5 to 1.1 grams per day, with a 90th percentile (high eaters) consumption level at 1.1 to 2.6 grams per day.

BASIS

- The potential average daily per capita consumption of Lycasin 80/55 is estimated to be 45 to 107 milligrams per day (Report E-39).
- The potential average daily consumption of Lycasin 80/55 by "eaters", is estimated to be 0.5 to 1.1 grams per day, with a 90th percentile consumption level at 1.1 to 2.6 grams per day (Report E-39).
- The potential single day (peak) average daily consumption of Lycasin 80/55 by eaters is estimated to be 1.2 to 2.7 grams per day, with a 90th percentile consumption level at 2.4 to 5.9 grams per day (Report E-39).

000363

-43-

## FUNCTIONALITY\*

The functionality of Lycasin 80/55 in candy, chewing gum and confections is due to the following technical effects:

- . Sweetness
- . Hygroscopicity or aw depressing capacity (Humectant)
- . Binding capacity
- . Anticrystallizing capacity
- . Absence of reducing capacity.

Lycasin 80/55 has approximately 75 percent the sweetness of sucrose (Report F-1). Because the sweetness is less than sugar, the acid flavors currently used in confections (e.g., citric acid, lactic acid, etc.) are more easily tasted. It is, therefore, possible to reduce, by about 25 to 30 percent, the quantities of acid normally used in candies (Report F-2). In addition, Lycasin 80/55 contains no sulphur dioxide (SO<sub>2</sub>), a substance which sometimes may cause deterioration of flavors.

Lycasin 80/55 gives finished products with a lower E.R.H. (aw) than that of standard confectionery containing sugar (Reports F-1 and F-2). It is therefore hygroscopic and a humectant, and has very good bacteriological stability. In the case of boiled confectionery, use of Lycasin 80/55 yields hygroscopic sweets which will not recrystallize on the surface if water is absorbed (Report F-2).

000364

---

\* Reports F-1 through F-11, pertaining to the functionality of hydrogenated glucose sirip, are presented in Appendix F.

-44-

Lycasin 80/55 has an average molecular weight nearly twice that of sucrose; 630 versus 342 (Report F-1). The longer the molecules, the higher the cohesive effect. Its relatively high viscosity, 2000 cps at 20°C, enables it to be easily worked. In finished products, it behaves like a high dextrose equivalent glucose syrup (Report F-2). This technical effect is extensively used in confection production; for example, chewing gum, soft coatings and fillings (Report F-1).

Lycasin 80/55 never crystallizes even at low temperatures or when its concentration is increased. Like a glucose syrup, it prevents crystallization of other components which may be present in the formulation such as sorbitol, mannitol and xylitol. This also explains Lycasin's numerous applications in confectionery, since sorbitol, mannitol, xylitol, etc. have a marked tendency to recrystallize, which can therefore bring about an unwanted change in texture of the finished products during storage (Reports F-1, F-2 and F-3).

Lycasin 80/55 contains practically no reducing sugars; less than 0.2 percent. It is therefore very stable, with little tendency to brown on heating. For the same reason, it does not react with other components of confection formulations; i.e., absence of Maillard reaction in particular (Report F-2).

000365

-45-

Sample Recipes

Developmental recipes for sugarless confectionaries containing Lycasin 80/55 are presented in Report F-4.

- . Soft gums
- . Chewy sweets
- . Marshmallows
- . Gelatin jellies
- . Soft jellies
- . Coated chewing gum
- . Chewing gum
- . Wine gums
- . Hardboiled candies

(Cf Report F-5)

Additional information on the use of Lycasin 80/55 in chewing gums is provided in Reports F-6 and F-7. Information on the use of Lycasin 80/55 in sugarless soft coatings for jelly beans is provided in Report F-8.

Lycasin 80/55 hydrogenated glucose sirip remains essentially unchanged during the manufacture of finished candies and confections. High temperature processing and/or addition of citric acid at the end of the manufacturing process does promote a small amount of  $\alpha$ -1-4 bond hydrolysis releasing small quantities of glucose and sorbitol. (Report F-4).

The stability of Lycasin 80/55, when stored for two years under typical warehouse conditions was good (Report F-10), as was the stability of an 18% Lycasin 80/55 solution when stored for 10 days at room temperature (Report F-11). 000366

Submission End  
TRANSMISSION END

000367

## *Reference List for Industry Submission, GRN 000059*

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000313 - 000318	Joint FAO/WHO Expert Committee on Food Additives	Evaluation of Certain Food Additives and Contaminants	1997	WHO Technical Report Series	Report Series 868, pgs 8-12

*NA- Not applicable*

---

**Grain Processing Corporation**

1600 Oregon Street

Muscatine, Iowa 52761-1494 USA

Phone 319-264-4211

AM



March 19, 2001

Dr. Linda S. Kahl  
Regulatory Policy Branch (HFS-206)  
Petition of Product Policy  
Office of Premarket Approval  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C St. S.W,  
Washington, DC 20204

Reference: Gras Notice (GRN) No. 000059

Dear Dr. Kahl:

This is in response to a request from Dr. Rosalie Angeles with regard to a specification change for lead. We have revised the limit for lead to be <0.1ppm. Attached are the revised specifications for the submission of the Self- Gras notification for hydrogenated starch hydrolysate.

Please call me if you have any questions.

Thanking you,

Yours sincerely  
Grain Processing Corporation

Rani M. Thomas  
Director of Quality and Regulatory Affairs

000370

### Specifications for Hydrogenated Starch hydrolysate

The specifications for food-grade hydrogenated starch hydrolysate are as follows:

Total Solids	Not less than 90% for dry product Not less than 50% for liquid product
Sorbitol	Not more than 10% (dry product basis)
Maltitol	<10%
Hydrogenated Tri- to hexasaccharides	Between 5 and 35% (dry product basis)
Hydrogenated saccharides higher than hexa	greater than 50% (dry product basis)
Arsenic (as As)	Not more than 10 ppm
Chloride	Not more than 50 ppm
Heavy metals	Not more than 5 ppm
Lead	Less than 0.1ppm
Reducing sugars	Not more than 1%
Residue on ignition	Not more than 0.1%
Sulfate	Not more than 100 ppm
Total sugars (after Hydrolysis)	Not more than 97% (dry product basis)

000371



REC'D SEP 24 2001

Dr. Linda S. Kahl  
Office of Food Additive Safety (HFS-206)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C St. S.W,  
Washington, DC 20204

September 14, 2001

Reference: Gras Notice (GRN) No. 000059

Dear Dr. Kahl:

This letter is in reference to the submission of the Self- Gras notification for hydrogenated starch hydrolysate submitted by Grain Processing Corporation and SPI Polyols on September 11, 2000. We are writing this letter requesting you to cease evaluation of our submission for the Self- Gras notification for hydrogenated starch hydrolysate.

Please call me if you have any questions. I could be reached at (563) 264-4681 and my email address is [thomasrani@grainprocessing.com](mailto:thomasrani@grainprocessing.com).

Thanking you,

Yours sincerely  
Grain Processing Corporation and  
SPI Polyols

Rani M. Thomas  
Director of Quality and Regulatory Affairs

000444