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ORIGINAL SUBMISSION

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GRAS Exemption Claim

Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)] for Water-Soluble Tomato Concentrate (WSTC)

Prepared for:

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied
Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Prepared by:

Provexis plc
10 Williams House
Manchester Science Park
Lloyd Street North
Manchester
M15 6SE
United Kingdom

August 9, 2006

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9 August 2006

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Sir or Madam:

Re: GRAS Notification

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the notifier, Provexis plc, 10 Williams House, Manchester Science Park, Lloyd Street North, Manchester, M15 6SE, United Kingdom, a GRAS notification of Water-Soluble Tomato Concentrate (WSTC) for use in foods, a GRAS panel report setting forth the basis for the GRAS determination, and *curricula vitae* of the members of the GRAS panel for review by the agency.

Sincerely,

Dr. Stephen J. Franklin
Director of Research

Enclosures

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WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

Water Soluble Tomato Concentrate (WSTC) has been determined to be Generally Recognized As Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of WSTC in food as described below is exempt from the requirement of premarket approval.

Signed,

9 August 2006

Dr. Stephen J. Franklin
Provexis plc
10 Williams House
Manchester Science Park
Lloyd Street North
Manchester
M15 6SE
United Kingdom

Date

B. Name and Address of Notifier

Dr. Stephen J. Franklin
Provexis plc
10 Williams House
Manchester Science Park
Lloyd Street North
Manchester
M15 6SE
United Kingdom

C. Common Name of the Notified Substance

Water Soluble Tomato Concentrate (WSTC)

August 9, 2006

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WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

D. Conditions of Intended Use in Food

Certain constituents in WSTC have been demonstrated to possess anti-platelet activity. Therefore, Provexis intends to market WSTC as a food ingredient in yogurt drinks, fruit juices, and fruit-flavored drinks in the United States for the purposes of inhibiting platelet aggregation. The individual proposed food uses and use levels of WSTC from all proposed food-uses are summarized in Table 1.

Food Category	Proposed Food-Use	Use-Level (g/RACC)	Serving Size (g)	Use-Level (%)
Milk Products	Yogurt Drinks*	3	65 to 250	1.200 to 4.615
Processed Fruits and Fruit Juices	Fruit-Flavored Drinks	3	240	1.250
	Fruit Juices	3	240	1.250

RACC = Reference Amount Customarily Consumed per eating occasion

*Because there are no specific food codes in the USDA food consumption survey for yogurt drinks, surrogate codes for yogurt were used to represent yogurt drinks. In doing so, a conservative approach to WSTC consumption estimates in the U.S. was maintained.

WSTC is intended to be added to fruit juices, fruit-flavored drinks, and yogurt drinks at a level of 3 g/serving. The recommended intake of WSTC is 3 g/day for healthy adults over the age of 45. Products containing WSTC will be clearly labeled with directions indicating that one serving should be consumed per day, and indicating the size of one serving. The mean intake level of WSTC is therefore considered to be 3 g/day.

Although the mean intake is defined by the directions of use on the product, it was considered appropriate to assess consumption of WSTC using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) survey (USDA, 2000) to assess "worst-case" exposure, in the event that the product is not consumed as directed.

The food use-levels of WSTC are based on a level of 3 g/serving. Given that fruit juices and fruit-flavored drinks have a typical serving size that is different from yogurt drinks (240 and 65 to 250 g, respectively), and that the range of serving sizes for yogurt drinks will provide a percentage use-level ranging from 1.2 to 4.615%, intake estimates were obtained for the highest and lowest levels of use for both serving sizes.

Based on a use-level of 1.2% and a serving size of 250 g for yogurt drinks, on an all-user basis, the mean intake of WSTC by the total population from all proposed food-uses was estimated to be 3.94 g/person/day (90.35 mg/kg body weight/day). The heavy consumer (90th percentile) all-user intake of WSTC by the total population from all proposed food-uses was 7.79 g/person/day (209.8 mg /kg body weight/day). On an absolute basis (per person), male teenagers were

WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

determined to have the greatest mean and 90th percentile all-user intakes of WSTC of 5.80 and 11.62 g/person/day, respectively. On a body weight basis, infants were reported to have the greatest intakes of WSTC of any population group, with mean and 90th percentile all-users intakes of WSTC of 291.05 and 583.99 mg/kg body weight/day, respectively.

Based on a use-level of 4.615% and a serving size of 65 g for yogurt drinks, on an all-user basis, the mean intake of WSTC by the total population from all proposed food-uses was estimated to be 4.38 g/person/day (100.16 mg/kg body weight/day). The heavy consumer (90th percentile) all-user intake of WSTC by the total population from all proposed food-uses was 9.08 g/person/day (228.12 mg/kg body weight/day). On an absolute basis (per person), male teenagers were determined to have the greatest mean and 90th percentile all-user intakes of WSTC of 5.99 and 11.63 g/person/day, respectively. On a body weight basis, infants were reported to have the greatest intakes of WSTC of any population group, with mean and 90th percentile all-users intakes of WSTC of 330.59 and 670.83 mg/kg body weight/day, respectively.

In summary, on an all-user basis, the mean intake of WSTC by the total U.S. population from all proposed food-uses was estimated to range from 3.94 to 4.38 g/person/day or 90.35 to 100.16 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of WSTC by the total U.S. population from all proposed food-uses was estimated to range from 7.79 to 9.08 g/person/day or 209.8 to 228.12 mg/kg body weight/day. As discussed previously, this intake estimate establishes the "worst-case" scenario, should products containing WSTC not be consumed as directed. Under the intended conditions of use, the mean intake of WSTC is 3 g/day, for healthy adults over the age of 45.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, WSTC has been determined to be GRAS on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of WSTC as a component of food. The safety of WSTC is based on the history of use of tomato, which has been safely consumed by humans for many years. Comparative analysis of WSTC to tomatoes and other commercially available tomato products demonstrates similar composition. Moreover, the safety of WSTC is substantiated by the composition of the ingredient, containing mainly carbohydrates, with minor amounts of protein and free amino acids, and lesser amounts of flavonoids, phenolics, and organic acids, which all are present in a normal diet and are expected to be metabolized by common metabolic pathways. Furthermore, preclinical data on GM and non-GM tomatoes have demonstrated no significant toxicological effects at doses of up to 40 g tomato powder/kg body weight/day for up to 11 weeks, providing approximately 600 mg WSTC/kg body weight/day under the assumption that the same proportion of CTE that occurs in fresh tomatoes was present in the tomato powder. In addition, clinical trials in which the effects of WSTC on platelet aggregation were assessed have demonstrated no significant adverse effects. This determination is further supported by an expert panel evaluation of the health aspects of WSTC.

WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

(See Appendix A – EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE STATUS OF WATER SOLUBLE TOMATO CONCENTRATE (WSTC) FOR USE IN FOODS).

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Dr. Stephen J. Franklin
Provexis plc
10 Williams House
Manchester Science Park
Lloyd Street North
Manchester
M15 6SE
United Kingdom

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, Provexis plc will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

WSTC is an aqueous concentrate of tomato paste and consists of soluble solids extracted from a commercially available tomato puree. The common tomato, *Lycopersicon esculentum*, is the starting material for the tomato puree. The end product, WSTC, is in the form of a syrup, which may range in color from deep yellow to golden to brown.

WSTC comprises, on a dry weight basis, mainly carbohydrates (~80% w/w), with minor amounts of protein and free amino acids (~6 and ~3% w/w, respectively), and lesser amounts of flavonoids, simple phenolics (0.2% w/w), and low-molecular weight organic acids (0.7% w/w), including citric acid, malic acid, ascorbic acid, and dehydroascorbic acid, and their derivatives. Other constituents account for approximately 8.2% (w/w) of WSTC.

Common or Usual Name:	Water Soluble Tomato Concentrate (WSTC)
Chemical Name:	Not applicable
Chemical Abstracts Service (CAS) Number:	Not applicable

WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

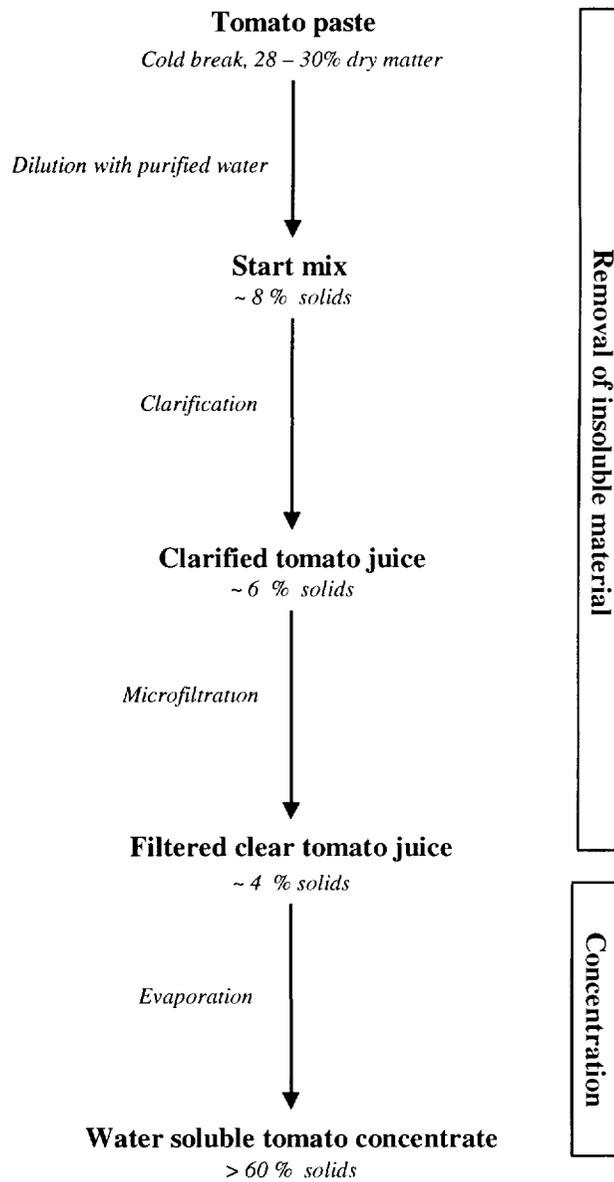
Empirical Formula and Formula Weight:	Not applicable
Molecular weight:	Not applicable
Structural Formula:	Not applicable

B. Method of Manufacture

WSTC is produced in a process utilizing physical means (centrifugal separation, membrane filtration) to concentrate the water-soluble tomato compounds of interest from cold-break tomato paste, while removing unwanted suspended solids. The resulting straw-colored aqueous solution is then pH-adjusted by addition of food-grade citric acid, and concentrated by evaporation at low temperature. The final WSTC product is packaged using bag-in-box technology and stored at 4°C prior to shipping. All raw materials and processing aids used in the manufacture of WSTC meet food-grade specifications and any additional requirements or limitations outlined in the Code of Federal Regulations. A schematic overview of the manufacturing process of WSTC is presented in Figure 1.

WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

Figure 1 Schematic Overview of the Manufacturing Process for WSTC



WATER SOLUBLE TOMATO CONCENTRATE NOTIFICATION

C. Specifications for Food Grade Material

Table 2 Chemical and Microbiological Specifications for WSTC		
Specification Parameter	Specification	Method
Dry Matter (°Brix)	60 to 63	AOAC 985.26
Density (g/cm ³)	1.15 to 1.22	Gravimetric / volumetric
pH (at 10°Brix)	3.90 to 4.15	Standardized pH electrode
Browning index (at 10°Brix)	<0.70	Absorbance of solution diluted to 10°Brix, at 420 nm [as referenced in Meydav <i>et al.</i> (1977)]
Total Carbohydrates (g/100g)	58 to 70	Colorimetric assay: phenol-sulfuric acid method with a modification for use with microplate formats
Pectin (g/100 g)	33 to 40	Colorimetric assay: modified sulfamate / m-hydroxydiphenyl method for analysis of uronic acid in the presence of neutral sugars
Reducing Sugars (g/100 g)	22 to 30	Colorimetric assay: oxidation of free carbonyl group using the 3,5-dinitrosalicylic acid method
Protein (g/100 g)	4 to 5	Colorimetric assay: Bradford assay in a microtiter plate format, using Bradford reagent from BioRad
Free Amino Acids (g/100 g)	2 to 3.5	Measured by HPLC: derivatisation of amino acids using α -phthalaldehyde after sample deproteinisation with β -mercaptoethanol, followed by quantification using HPLC with fluorescence detection
Ash (g/100 g)	<3.0	AOAC 940.26 A
Lead (ppm)	<0.9	AOAC 979.17
Microbiological Parameters		
Total viable count (CFU/mL)	<1,000	ISO 4833 2003
<i>Salmonella</i> (CFU/25 mL)	Absent	ISO 6579 2002
<i>Listeria monocytogenes</i> (CFU/25 mL)	Absent	Consult-Us Method of Analysis
<i>Staphylococcus aureus</i> (CFU/mL)	Absent	ISO 6888-1 1999
<i>Enterobacteria</i> (CFU/mL)	<1	ISO 7402 1993
Yeasts and molds (CFU/mL)	<100	ISO 7954 1987

AOAC = Association of Analytical Communities; Consult-Us = Consult-Us Laboratories, Fermoy, Co. Cork, EIRE; accredited microbiological analysts; ISO = International Organization for Standardization

III. Self-Limiting Levels of Use

There are no physical or chemical characteristics that will limit the levels of use. However, WSTC is added to beverage products at a very specific level of use, and there is no benefit to increasing the level of WSTC (*i.e.*, there is no increase in the inhibition of platelet aggregation at higher levels).

IV. Basis for GRAS Determination

The determination that Water Soluble Tomato Concentrate is GRAS is on the basis of scientific procedures. (See Appendix A – EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE STATUS OF WATER SOLUBLE TOMATO CONCENTRATE (WSTC) FOR USE IN FOODS).

Appendix A

**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS
SAFE (GRAS) STATUS OF WATER-SOLUBLE TOMATO CONCENTRATE (WSTC)
FOR USE IN FOODS**

July 26, 2006

INTRODUCTION

At the request of Provoxis plc (Provoxis), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use as a nutrient in traditional foods, Water-Soluble Tomato Concentrate (WSTC) would be "generally recognized as safe" (GRAS), based on scientific procedures. The Panel consisted of the below-signed qualified scientific experts: John Doull, Ph.D., M.D. (University of Kansas Medical Center) and Ian C. Munro, Ph.D (CANTOX Health Sciences International). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of data and information provided by Provoxis. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, consumption estimates for all intended uses, and literature supporting the safety of tomatoes, WSTC, and its individual components.

Following independent, critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, Water-Soluble Tomato Concentrate, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practice, is GRAS based on scientific procedures and its compositional similarity to tomatoes. A summary of the basis for the Panel's conclusion, excluding confidential data and information, is provided below.

COMPOSITION, MANUFACTURING AND SPECIFICATIONS

WSTC is an aqueous concentrate of tomato paste and consists of soluble solids concentrated from a commercially available tomato puree. The common tomato, *Lycopersicon esculentum*, is the starting material for the tomato puree. The end product, WSTC, is in the form of a syrup, which may range in color from deep yellow to golden to brown.

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WSTC comprises, on a dry weight basis, mainly carbohydrates (~80% w/w), with minor amounts of protein and free amino acids (~6 and ~3% w/w, respectively), and lesser amounts of flavonoids, simple phenolics (0.2% w/w), and low-molecular weight organic acids (0.7% w/w), including citric acid, malic acid, ascorbic acid, and dehydroascorbic acid, and their derivatives. Other constituents account for approximately 8.2% (w/w) of WSTC. All constituents occur naturally in tomatoes, with a 3 g serving of WSTC providing levels of constituents that are comparable to levels derived from 2.5 tomatoes. Based on 3 g WSTC being equivalent to the level in 2.5 tomatoes, and an average tomato weight of 80 g, a level of 1.5% WSTC in tomatoes was calculated.

WSTC is produced in a 5-step process. The first step involves the addition of purified water to tomato paste, followed by the second step, which utilizes physical means (centrifugal separation, membrane filtration) to concentrate the water-soluble tomato compounds of interest from the cold-break tomato paste, and removes unwanted suspended solids. The resulting straw-colored aqueous concentrate is then pH-adjusted by addition of food-grade citric acid, and concentrated by evaporation at low temperature. The final WSTC product is packaged using bag-in-box technology and stored at 4°C prior to shipping. All of the raw materials used in the manufacture of WSTC (*i.e.*, tomato paste, water, citric acid, and ceramic filtration membranes) meet food-grade specifications and any additional requirements or limitations outlined in the Code of Federal Regulations.

In order to ensure a consistent product, Provoxis has established chemical and microbiological specification parameters for WSTC, which are presented in Table 1. Analyses of representative lots of WSTC have demonstrated compliance with final product specifications.

Additionally, analytical results of the long-term stability (up to 336 days) of WSTC under the normal storage conditions (at pH 4.2 and 4°C) demonstrate that the product is stable.

Table 1 Chemical and Microbiological Specifications for WSTC		
Specification Parameter	Specification	Method
Dry Matter (°Brix)	60 to 63	AOAC 985.26
Density (g/cm ³)	1.15 to 1.22	Gravimetric / volumetric
pH (at 10°Brix)	3.90 to 4.15	Standardized pH electrode
Browning index (at 10°Brix)	<0.70	Absorbance of solution diluted to 10°Brix, at 420 nm [as referenced in Meydav <i>et al.</i> (1977)]
Total Carbohydrates (g/100g)	58 to 70	Colorimetric assay: phenol-sulfuric acid method with a modification for use with microplate formats
Pectin (g/100 g)	33 to 40	Colorimetric assay: modified sulfamate / m-hydroxydiphenyl method for analysis of uronic acid in the presence of neutral sugars
Reducing Sugars (g/100 g)	22 to 30	Colorimetric assay: oxidation of free carbonyl group using the 3,5-dinitrosalicylic acid method
Protein (g/100 g)	4 to 6	Colorimetric assay: Bradford assay in a microtiter plate

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Table 1 Chemical and Microbiological Specifications for WSTC		
Specification Parameter	Specification	Method
		format, using Bradford reagent from BioRad
Free Amino Acids (g/100 g)	2 to 3.5	Measured by HPLC: derivatisation of amino acids using α -phthalaldehyde after sample deproteinisation with β -mercaptoethanol, followed by quantification using HPLC with fluorescence detection
Ash (g/100 g)	<3.0	AOAC 940.26 A
Lead (ppm)	<0.9	AOAC 979.17
Microbiological Parameters		
Total viable count (CFU/mL)	<1,000	ISO 4833 2003
<i>Salmonella</i> (CFU/25 mL)	Absent	ISO 6579 2002
<i>Listeria monocytogenes</i> (CFU/25 mL)	Absent	Consult-Us Method of Analysis
<i>Staphylococcus aureus</i> (CFU/mL)	Absent	ISO 6888-1 1999
<i>Enterobacteria</i> (CFU/mL)	<10	ISO 7402 1993
Yeasts and molds (CFU/mL)	<1,000	ISO 7954 1987

AOAC = Association of Analytical Communities; Consult-Us = Consult-Us Laboratories, Fermoy, Co. Cork, EIRE; accredited microbiological analysts; ISO = International Organization for Standardization

INTENDED USE AND ESTIMATED EXPOSURE

Provexis intends to market WSTC as a food ingredient in yogurt drinks, fruit juices, and fruit-flavored drinks in the United States. The individual proposed food uses and use levels of WSTC from all proposed food-uses are summarized in Table 2.

Table 2 Summary of the Individual Proposed Food-Uses and Use-Levels for WSTC in the United States				
Food Category	Proposed Food-Use	Use-Level (g/RACC)	Serving Size (g)	Use-Level (%)
Milk Products	Yogurt Drinks*	3	65 to 250	1.200 to 4.615
Processed Fruits and Fruit Juices	Fruit-Flavored Drinks	3	240	1.250
	Fruit Juices	3	240	1.250

RACC = Reference Amount Customarily Consumed per eating occasion

*Because there are no specific food codes in the USDA food consumption survey for yogurt drinks, surrogate codes for yogurt were used to represent yogurt drinks. In doing so, a conservative approach to WSTC consumption estimates in the U.S. was maintained.

WSTC is intended to be added to fruit juices, fruit-flavored drinks, and yogurt drinks at a level of 3 g/serving. The recommended intake of WSTC is 3 g/day for healthy adults over the age of 45. Products containing WSTC will be clearly labeled with directions indicating that one serving

should be consumed per day, and indicating the size of one serving. The mean intake level of WSTC is therefore considered to be 3 g/day.

Although the mean intake is defined by the directions of use on the product, it was considered appropriate to estimate consumption of WSTC using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) survey (USDA, 2000) to assess "worst-case" exposure, in the event that the product is not consumed as directed.

The food use-levels of WSTC are based on a level of 3 g/serving. Given that fruit juices and fruit-flavored drinks have a typical serving size that is different from yogurt drinks (240 and 65 to 250 g, respectively), and that the range of serving sizes for yogurt drinks will provide a percentage use-level ranging from 1.2 to 4.615%, intake estimates were obtained for the highest and lowest levels of use for both serving sizes. Estimates for the total daily intakes from all proposed food-uses of WSTC, assuming a use-level of 1.2 % for yogurt drinks (serving size 250 g) are presented in Tables 3 and 4 on a per person (g/person/day) and per kilogram body weight basis (mg/kg body weight/day), respectively. Estimates for the total daily intakes from all proposed food-uses of WSTC, assuming a use-level of 4.615% for yogurt drinks (serving size 65 g) are presented in Tables 5 and 6 on a per person (g/person/day) and per kilogram body weight basis (mg/kg body weight/day), respectively.

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90 th Percentile (g)	Mean (g)	90 th Percentile (g)
Infant	0-2	60.9	2,180	2.44	6.22	3.62	7.37
Children	3-11	84.2	5,309	3.19	7.00	3.99	7.54
Female Teenager	12-19	67.0	470	2.98	7.66	4.44	9.30
Male Teenager	12-19	65.9	459	3.85	9.38	5.80	11.62
Female Adult	20 and Up	52.8	2,416	1.71	4.67	3.18	6.25
Male Adult	20 and Up	48.3	2,297	2.13	6.20	4.33	8.81
Total Population	All Ages	63.7	13,131	2.28	6.20	3.94	7.79

^a Based on a use-level of 1.2% in yogurt drinks (serving size 250 g)

Table 4 Summary of the Estimated Daily Per Kilogram Body Weight Intake of WSTC in the United States by Population Group (1994-1996, 1998 USDA CSFII Data)^a							
Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90 th Percentile (mg/kg)	Mean (mg/kg)	90 th Percentile (mg/kg)
Infant	0-2	60.6	2,070	195.61	498.48	291.05	583.99
Children	3-11	84.1	4,958	135.27	312.16	169.77	339.94
Female Teenager	12-19	66.8	458	54.52	138.39	81.46	162.08
Male Teenager	12-19	65.6	451	61.33	161.75	92.63	182.68
Female Adult	20 and Up	52.9	2,346	26.42	73.35	49.20	102.21
Male Adult	20 and Up	48.4	2,285	26.55	75.19	54.02	112.85
Total Population	All Ages	63.3	12,568	52.08	143.49	90.35	209.80

^a Based on a use-level of 1.2% in yogurt drinks (serving size 250 g)

Table 5 Summary of the Estimated Daily Intake of WSTC in the United States by Population Group (1994-1996, 1998 USDA CSFII Data)^a							
Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (g)	90 th Percentile (g)	Mean (g)	90 th Percentile (g)
Infant	0-2	60.9	2,180	2.74	7.03	4.07	8.16
Children	3-11	84.2	5,309	3.41	7.66	4.27	8.25
Female Teenager	12-19	67.0	470	3.11	8.31	4.63	9.71
Male Teenager	12-19	65.9	459	3.98	9.70	5.99	11.63
Female Adult	20 and Up	52.8	2,415	2.05	5.86	3.83	8.15
Male Adult	20 and Up	48.3	2,296	2.33	6.45	4.75	10.12
Total Population	All Ages	63.7	13,129	2.53	6.93	4.38	9.08

^a Based on a use-level of 4.615% in yogurt drinks (serving size 65 g)

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Table 6 Summary of the Estimated Daily Per Kilogram Body Weight Intake of WSTC in the United States by Population Group (1994-1996, 1998 USDA CSFII Data)^a

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90 th Percentile (mg/kg)	Mean (mg/kg)	90 th Percentile (mg/kg)
Infant	0-2	60.6	2,070	222.18	584.79	330.59	670.83
Children	3-11	84.1	4,958	145.85	336.41	183.04	367.47
Female Teenager	12-19	66.8	458	56.83	142.92	84.91	168.23
Male Teenager	12-19	65.6	451	63.39	163.17	95.74	190.78
Female Adult	20 and Up	52.9	2,346	31.73	92.85	59.12	123.75
Male Adult	20 and Up	48.3	2,285	29.04	81.85	59.11	129.17
Total Population	All Ages	63.3	12,568	57.72	158.96	100.16	228.12

^a Based on a use-level of 4.615% in yogurt drinks (serving size 65 g)

Based on a use-level of 1.2% and a serving size of 250 g for yogurt drinks, on an all-user basis, the mean intake of WSTC by the total population from all proposed food-uses was estimated to be 3.94 g/person/day (90.35 mg/kg body weight/day). The heavy consumer (90th percentile) all-user intake of WSTC by the total population from all proposed food-uses was 7.79 g/person/day (209.8 mg/kg body weight/day). On an absolute basis (per person), male teenagers were determined to have the greatest mean and 90th percentile all-user intakes of WSTC of 5.80 and 11.62 g/person/day, respectively. On a body weight basis, infants were reported to have the greatest intakes of WSTC of any population group, with mean and 90th percentile all-users intakes of WSTC of 291.05 and 583.99 mg/kg body weight/day, respectively.

Based on a use-level of 4.615% and a serving size of 65 g for yogurt drinks, on an all-user basis, the mean intake of WSTC by the total population from all proposed food-uses was estimated to be 4.38 g/person/day (100.16 mg/kg body weight/day). The heavy consumer (90th percentile) all-user intake of WSTC by the total population from all proposed food-uses was 9.08 g/person/day (228.12 mg/kg body weight/day). On an absolute basis (per person), male teenagers were determined to have the greatest mean and 90th percentile all-user intakes of WSTC of 5.99 and 11.63 g/person/day, respectively. On a body weight basis, infants were reported to have the greatest intakes of WSTC of any population group, with mean and 90th percentile all-users intakes of WSTC of 330.59 and 670.83 mg/kg body weight/day, respectively.

This type of intake methodology is generally considered to be "worst case" as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or

3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently.

In summary, on an all-user basis, the mean intake of WSTC by the total U.S. population from all proposed food-uses was estimated to range from 3.94 to 4.38 g/person/day or 90.35 to 100.16 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of WSTC by the total U.S. population from all proposed food-uses was estimated to range from 7.79 to 9.08 g/person/day or 209.8 to 228.12 mg/kg body weight/day.

As discussed previously, this intake estimate establishes the "worst-case" scenario, should products containing WSTC not be consumed as directed. Under the intended conditions of use, the mean intake of WSTC is 3 g/day, for healthy adults over the age of 45.

DATA PERTAINING TO SAFETY

The assessment of the safety of WSTC is based on the history of use of tomato, which has been safely consumed by humans for many years. Comparative analysis of WSTC to tomatoes and other commercially-available tomato products demonstrates similar composition. Moreover, the safety of WSTC is substantiated by the composition of the ingredient, containing mainly carbohydrates, with minor amounts of protein and free amino acids, and lesser amounts of flavonoids, phenolics, and organic acids, which all are present in a normal diet and are expected to be metabolized by common metabolic pathways. Furthermore, clinical trials in which the effects of WSTC on platelet aggregation were assessed have demonstrated no significant adverse effects.

COMPARATIVE ANALYSIS OF WSTC TO TOMATO-BASED PRODUCTS

The main constituents of WSTC (on a weight/weight basis) are carbohydrates, protein, and amino acids, accounting for approximately 80, 6, and 3% of WSTC soluble solids, respectively. Constituents present in lower amounts include flavonoids and simple phenolics (0.2%) and low molecular-weight organic acids (0.7%). Other constituents account for a further 8.2% (3% identified, 5.2% unidentified). No carotenoids or long-chain fatty acids are detectable. In addition, certain constituents in WSTC have been demonstrated to possess anti-platelet activity. These constituents can be divided into 3 broad groups (fractions), labeled 'f1', 'f2', and 'f3' in order of decreasing polarity. These 3 fractions contain 7, 16, and 14 constituents, respectively.

As WSTC is derived from tomatoes, its constituents are present in a wide variety of tomato-based food products. The levels of constituents present in the f1, f2, and f3 fractions of WSTC were analyzed in a total of 20 commercially available tomato-based food products, including tomato juice (3 products), passata (sieved tomato pulp) (2 products), baby food (1 product), tomato puree/paste (4 products), tomato sauce (4 products), and tomato soup (6 products). The results indicate that the level of these constituents present in one 3 g serving of WSTC is within

the range of constituents present in a standard serving of tomato-based products. The levels of constituents present in the f1, f2, and f3 fractions of WSTC, as well as the range (minimum and maximum) and the mean levels of constituents identified in 20 tomato products, are summarized in Table 7.

Component		WSTC Composition (mg/3 g serving)	Summary of Exposure Levels in 20 Tomato-Based Products		
			Minimum Value (mg/serving)	Maximum Value (mg/serving)	Mean Value (mg/serving)
f1 constituents	Adenosine-5'-monophosphate	25.887	0.752	39.818	15.826
	Cytidine	5.794	0.467	15.955	6.616
	Uridine	7.304	1.048	13.593	6.359
	2-Deoxycytidine	0.685	0.182	8.852	2.773
	Adenosine	5.182	1.342	14.276	6.429
	Inosine	-	0.458	3.933	2.196
	Guanosine	4.021	0.211	6.763	2.936
	GMP	3.799	-	-	-
	quantified f1	53.175	4.002	90.776	40.873
	unidentified f1	15.733	1.544	65.405	13.184
f2 constituents	Deoxyadenosine	0.118	0.014	0.158	0.082
	Deoxyguanosine	0.269	0.061	0.659	0.334
	Unknown	0.172	-	-	-
	Peak @ 2.923 Minutes	0.068	0.001	0.015	0.007
	Peak @ 3.853 Minutes	0.015	0.000040	0.025	0.011
	Peak @ 4.605 Minutes	0.244	0.000418	0.012	0.005
	Hydroxymethylfurfural	0.096	0.009	3.975	0.870
	Furaneol	0.350	0.019	0.596	0.240
	quantified f2	1.344	0.147	4.362	1.444
	unidentified f2	3.054	0.086	5.352	1.638
f3 constituents	3-O-methyl adenosine	4.139	0.230	4.537	1.670
	Caffeoyl-3-O-glucoside	1.105	0.112	2.134	0.738
	Feruloyl derivative, possibly a glucoside	1.331	0.069	1.802	0.682
	4-hydroxybenzoic acid	0.337	0.000002	0.001	0.000
	Feruloyl tyramine	0.318	0.003	4.957	1.184
	Peak @ 12.118 Minutes	2.367	0.212	3.360	1.364
	Peak @ 12.657 Minutes	2.397	0.031	3.439	1.063
	Chlorogenic acid	2.927	0.035	2.176	0.650
	Caffeic acid	0.020	0.000002	0.000285	0.000047

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Component	WSTC Composition (mg/3 g serving)	Summary of Exposure Levels in 20 Tomato-Based Products		
		Minimum Value (mg/serving)	Maximum Value (mg/serving)	Mean Value (mg/serving)
Vanillin	0.076	0.000008	0.000136	0.000047
Coumaric acid	0.221	0.000009	0.000427	0.000203
Ferulic acid	0.370	0.005	0.311	0.068
Benzoic acid	1.177	0.028	12.414	1.250
Rutin	0.287	0.000217	0.007	0.002
Myricetin	0.562	0.010	0.363	0.094
Quercetin	0.338	0.008	0.398	0.148
Luteolin	0.509	0.003	0.101	0.032
quantified f3	18.652	0.898	18.952	8.809
unidentified f3	102.089	7.630	210.512	63.682
total f1, f2 and f3 constituents quantified	73.171	5.402	110.475	51.126
total fraction including unknown constituents	192.223	19.599	390.452	129.630

COMPARISON OF EXPOSURE TO WSTC CONSTITUENTS TO BACKGROUND CONSUMPTION LEVELS

In order to examine the potential dietary impact of consuming WSTC daily at defined levels, Toxicology Advice and Consulting Ltd. (TAC), an independent consulting firm, performed a relative risk assessment to evaluate the intake of the constituents of WSTC (referred to as CardioFlow®) from proposed food uses in comparison to typical exposures from a normal diet (TAC, unpublished). TAC conducted the relative risk assessment based on a WSTC exposure level of 8.5 g/day. Taking into account the exposure level of 8.5 g WSTC/day, the composition of WSTC, and the typical exposures of each constituent within WSTC from the diet, TAC concluded that an intake of 8.5 g WSTC/day "would not result in any increased health risk over and above any risks posed by consumption of other commonly-consumed, tomato-based products."

TAC conducted the WSTC risk assessment using analytical data from a pilot batch of WSTC. The concentration process in the manufacture of WSTC has subsequently been refined, producing higher concentrations of soluble solids. The pilot batch of WSTC analyzed by TAC was similar in composition to batches of WSTC currently produced, with the exception of the level of constituents present in the f1, f2, and f3 fractions. The pilot WSTC batch analyzed by

TAC was composed of 2.9% of Fraction constituents (1% identified, 1.9% unidentified), while an average of 4 WSTC batches currently produced demonstrates a composition of approximately 7.6% Fraction constituents (2.9% identified, 4.7% unidentified). In order to provide an accurate assessment of the exposure to the individual constituents of WSTC, the exposure level to each constituent of WSTC was calculated based on a mean intake of 3.0 g WSTC/day, and the "worst-case" 90th percentile intake estimate of 9.08 g WSTC/day. These levels of intake were then compared to the normal dietary intake levels for each constituent reported by TAC (unpublished). Table 8 summarizes the exposure to the individual constituents of WSTC based on daily intakes of 3 g (intended use) and 9.08 g (worst-case exposure estimate), as well as the exposure to WSTC based on a daily intake of 8.5 g WSTC, as calculated by TAC, and the estimated daily intake of the constituents from a normal diet.

As demonstrated in Table 8, the exposure to the individual constituents of WSTC from consumption of 3 g WSTC/day is well within the range of exposure to these constituents following the consumption of a normal daily diet. WSTC intake at the 90th percentile ("worst-case" estimate) of 9.08 g/day (3 servings of WSTC) provides levels of some constituents that would be present in 2 to 4 servings of tomato-based food products. It is therefore apparent that the level of constituents in one 3 g serving of WSTC are equivalent to those present in one serving of tomato-based food products, and would therefore not result in any health risks under the conditions of intended use.

	Component	Calculated Exposure (mg/day)			Estimated Dietary Intakes from a Normal Diet
		Per 3.0 g CTE ^a	Per 9.08 g CTE ^a	Per 8.5 g CTE ^b	
Carbohydrates	Pectin	1,106.226	3,348.177	3,841	-
	Starch	4.961	15.016	80	-
	Uronic acid	54.770	165.771	55	-
	Glucose	413.374	1,251.146	1,488	-
	Fructose	424.435	1,284.622	1,354	-
	Other simple sugars	54.511	164.987	372	-
	Total carbohydrates	2,077.755	6,288.673	7,191	100 to 130 g/day ^c
Protein	Total protein	142.347	430.838	592	46 to 56 g/day ^c
Amino Acids	Aspartic acid	7.616	23.051	24.5	6,520 mg/day ^d
	Glutamic acid	34.165	103.405	106	15,220 mg/day ^d
	Serine	3.506	10.610	6.8	3,510 mg/day ^d
	Glycine	1.277	3.866	1.7	3,200 mg/day ^d
	Glutamine	3.826	11.580	5.9	-
	Histidine	11.223	33.969	49	2,190 mg/day ^d
	GABA	0.000	0.000	35.5	-
	Threonine	1.596	4.830	5	3,010 mg/day ^d

	Component	Calculated Exposure (mg/day)			Estimated Dietary Intakes from a Normal Diet
		Per 3.0 g CTE ^a	Per 9.08 g CTE ^a	Per 8.5 g CTE ^b	
	Alanine	7.732	23.402	21.2	3,630 mg/day ^d
	Arginine	0.962	2.913	3.4	4,170 mg/day ^d
	Proline	0.200	0.604	0.9	5,190 mg/day ^d
	Tyrosine	1.390	4.208	2.5	2,780 mg/day ^d
	Valine	1.116	3.379	2.5	3,980 mg/day ^d
	Methionine	0.242	0.733	0.9	1,760 mg/day ^d
	Isoleucine	0.472	1.428	2.5	3,550 mg/day ^d
	Leucine	0.786	2.379	2.5	6,080 mg/day ^d
	Phenylalanine	3.553	10.753	10.2	3,390 mg/day ^d
	Lysine	2.067	6.257	4.2	5,260 mg/day ^d
	Total amino acids	82.516	249.748	285	-
Phenolics	Flavonoids and derivatives	4.186	12.669	6.5	-
	Simple phenolics and derivatives	1.778	5.381	1.1	-
	Other*	1.925	5.826	1.8	-
	Total phenolics	7.971	24.125	9.5	1 to 2 g/day ^e
Low molecular weight organic acids	Total low MW organic acids ^f	18.116	54.832	55	2.1 g/day (citric acid) ^g 1.7 g/day (malic acid) ^g 75 to 90 mg/day (ascorbic acid) ^h
Fraction f1	Total f1	68.260	206.601	-	-
	Adenosine-5'-monophosphate	25.887	78.350	34.373	1 to 54 mg/serving ⁱ
	Cytidine	5.794	17.537	10.554	0.5 to 16 mg/serving ⁱ
	Uridine	7.304	22.107	8.633	1 to 14 mg/serving ⁱ
	2-Deoxycytidine	0.685	2.075	0.796	0.2 to 9 mg/serving ⁱ
	Adenosine	5.182	15.683	7.778	1.3 to 14 mg/serving ⁱ
	Inosine	-	-	-	0.5 to 4 mg/serving ⁱ
	Guanosine	4.021	12.171	4.486	0.2 to 6.8 mg/serving ⁱ
	GMP	3.799	11.499	-	-
	Monitored f1	44.683	135.240	-	-
	Unmonitored f1	23.577	71.361	-	-
	Total identified f1	53.175	160.943	66.619	-
	Unidentified f1	15.733	47.618	23.624	2 to 65 mg/serving ⁱ
Fraction f2	Total f2	4.352	13.173	-	-
	deoxyadenosine	0.118	0.357	0.039	0.014 to 0.158 mg/serving ⁱ
	deoxyguanosine	0.269	0.813	0.319	0.06 to 0.66 mg/serving ⁱ
	unknown	0.172	0.519	-	-

Table 8 Comparison of Intakes of Constituents of WSTC to Exposure from a Normal Diet					
	Component	Calculated Exposure (mg/day)			Estimated Dietary Intakes from a Normal Diet
		Per 3.0 g CTE ^a	Per 9.08 g CTE ^a	Per 8.5 g CTE ^b	
	Peak @ 2.923 Minutes	0.068	0.205	0.015	0.001 to 0.015 mg/serving ¹
	Peak @ 3.853 Minutes	0.015	0.045	0.018	<0.001 to 0.025 mg/serving ¹
	Peak @ 4.605 Minutes	0.244	0.739	0.013	<0.001 to 0.012 mg/serving ¹
	hydroxymethylfurfural	0.096	0.289	0.138	0.01 to 4 mg/serving ¹
	furaneol	0.350	1.061	0.891	0.09 to 0.6 mg/serving ¹
	Monitored f2	1.004	3.039	-	-
	Unmonitored f2	3.348	10.134	-	-
	Total identified f2	1.344	4.067	1.432	-
	Unidentified f2	3.054	9.242	2.411	0.09 to 5.4 mg/serving ¹
Fraction f3	Total f3	119.611	362.021	-	-
	3-O-methyl adenosine	4.139	12.526	4.06	0.2 to 4.5 mg/serving ¹
	Caffeoyl-3-O-glucoside	1.105	3.345	1.371	0.1 to 2.1 mg/serving ¹
	Feruloyl derivative, possibly a glucoside	1.331	4.028	2.023	0.07 to 1.8 mg/serving ¹
	4-hydroxybenzoic acid	0.337	1.021	<0.001	<0.001 to 0.001 mg/serving ¹
	Feruloyl tyramine	0.318	0.962	0.015	0.003 to 5 mg/serving ¹
	Peak @ 12.118 Minutes	2.367	7.163	3.453	0.2 to 3.4 mg/serving ¹
	Peak @ 12.657 Minutes	2.397	7.256	3.067	0.03 to 3.4 mg/serving ¹
	chlorogenic acid	2.927	8.860	1.922	0.04 to 2.2 mg/serving ¹
	caffeic acid	0.020	0.060	<0.001	<0.001 mg/serving ¹
	vanillin	0.076	0.230	<0.001	<0.001 mg/serving ¹
	coumaric acid	0.221	0.670	<0.001	<0.001 mg/serving ¹
	ferulic acid	0.370	1.119	<0.001	0.005 to 0.03 mg/serving ¹
	benzoic acid	1.177	3.562	0.944	0.03 to 12 mg/serving ¹
	rutin	0.287	0.868	0.011	<0.001 to 0.007 mg/serving ¹
	myricetin	0.562	1.701	0.57	0.01 to 0.36 mg/serving ¹
	quercetin	0.338	1.024	0.086	0.008 to 0.4 mg/serving ¹
	luteolin	0.509	1.540	0.591	0.003 to 0.1 mg/serving ¹
	Monitored f3	12.802	38.747	-	-
	Unmonitored f3	106.809	323.274	-	-
Total identified f3	18.652	56.455	18.116	-	
Unidentified f3	102.089	308.988	132.049	8 to 211 mg/serving ¹	
	Total of Fractions f1, f2, and f3	192.223	581.795	240	-
	Total other unidentified	32.819	99.333	102	-

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	Component	Calculated Exposure (mg/day)			Estimated Dietary Intakes from a Normal Diet
		Per 3.0 g CTE ^a	Per 9.08 g CTE ^a	Per 8.5 g CTE ^b	
	Total constituents	2,533.401	7,667.760	-	-

^a Calculations based on average values from 4 batches of WSTC using current concentration processes

^b Adapted from TAC (unpublished). Calculations made by TAC based on a pilot batch of WSTC

^c Based on recommended daily allowance values published in IOM, 2002, cited by TAC (unpublished)

^d Based on intake data from NHANES III survey, published in IOM, 2002, cited by TAC (unpublished)

^e Based on data reported by Hertog *et al.* (1993), cited by TAC (unpublished)

^f Primarily citric acid, malic acid, ascorbic acid, hydroascorbic acid, and their derivatives

^g Based on intake data from the Japanese Ministry of Welfare (Anonymous, 2000), cited by TAC (unpublished)

^h Based on the U.S. recommended daily allowance for vitamin C (Jacob and Soutoudeh, 2002), cited by TAC (unpublished)

ⁱ Based on analysis of 20 commercially-available tomato products (see Section 5.1), cited by TAC (unpublished)

TOXICOLOGICAL STUDIES

In a study designed to evaluate the effect of tomato powder consumption on antioxidant status, Moreira *et al.* (2005) reported no significant effects on the growth of male Wistar rats fed diets containing tomato powder at a level of 25% in the diet (25 g/kg body weight/day) for a period of 28 days. Based on a level of 1.5% WSTC in tomatoes, the dose of 25% in the diet provided 375 mg WSTC/kg body weight/day (22.5 g/day for a 60 kg human). In a 30-day toxicity study, Chen *et al.* (2003) reported no significant hematological, biochemical, or histopathological effects in male and female Wistar rats fed lyophilized tomato cultivars from either genetically-modified (GM) or non-GM tomatoes at levels of 0, 83.3, 416, or 833 g/kg body weight/day.

In another study evaluating the effects of a genetically-modified tomato, Stoewsand *et al.* (1996) investigated the effects of a nematode-resistant tomato in an 11-week study in male F344 rats. Groups of 6 rats were fed a basal diet (control) or diets containing a nematode-resistant tomato cultivar (VFN8) or a nematode-susceptible cultivar ("New Yorker" tomato). The tomato cultivars were freeze-dried prior to addition to the semipurified rat diets. The tomato preparations were added to the diets at a level of 10% for the first 7 days, 20% for the following 3 days, and increased to 40% (approximately 40 g/kg body weight/day) for the remainder of the 11-week study. Hematological parameters were measured at 5 and 11 weeks, and all animals were necropsied at the end of the study period, at which time organ weights were measured and organs and tissues were examined. There were no significant differences between groups in body weight gain, food consumption, or relative liver weights. There were no significant differences between groups in hematological parameters, which were all within the range of normal reference values. Examination of the organs and tissues also revealed no significant differences between groups. The 40% dietary level is equivalent to 40 g/kg body weight/day of tomato cultivar, which is considered to be the no-observed-adverse-effect level (NOAEL).

Based on a level of 1.5% WSTC in tomatoes, this NOAEL provides a dose of 600 mg WSTC/kg body weight/day, or 36 g/day for a 60 kg human.

In vitro and *in vivo* mutagenicity and genotoxicity studies have revealed a lack of significant effects of various tomato cultivars. Chen *et al.* (2003) reported a genetically-modified (GM) tomato cultivar (*Lycopersicon esculentum* Su 8805) not to be mutagenic to *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA102 at concentrations of 0.1 to 5.0 mg/plate. In an *in vivo* sperm aberration test, Chen *et al.* (2003) reported no significant differences in the number of aberrant sperm in groups of male Kunming mice administered GM and non-GM tomato powders at doses of 0.625, 2.5, or 5.0 g/kg body weight by gavage for 5 days, relative to each other and relative to the negative control. The same authors also reported no significant differences in micronucleus incidence ratios between GM, non-GM, and negative control groups in male Kunming mice administered 0.625, 2.5, or 5.0 g/kg body weight by gavage for 2 days (Chen *et al.*, 2003).

CLINICAL TRIALS

A number of unpublished clinical trials supported by Provexis have been conducted to investigate the anti-platelet activity of WSTC, and are summarized below. Although safety-related endpoints were not evaluated, these studies demonstrate that consumption of WSTC at high doses (up to 18 g) is well-tolerated and without adverse effects.

In one *ex vivo* cannulation study, 18 g of WSTC in orange juice was administered to healthy adult volunteers with high platelet function (O'Kennedy *et al.*, 2005a). Analysis of blood samples taken at 1.5, 3, and 6 hours post-consumption revealed significantly decreased adenosine diphosphate (ADP)-induced platelet aggregation at the 3-hour time point (compared to a placebo drink), with a return to normal platelet function 18 hours post-consumption. There were no significant effects on clotting time. In a crossover study, a placebo drink and drinks containing 6 and 18 g of WSTC (in orange juice) were given to healthy adult volunteers (with normal platelet function) for a treatment period of 3 days, with a 1 week washout period between each treatment period (O'Kennedy *et al.*, 2005b). WSTC was reported to significantly reduce both ADP- and collagen-induced platelet aggregation 3 hours post-consumption in comparison to baseline measurements and the placebo drink. This effect was reported to be dose-dependent and to invoke a more pronounced response in male subjects. Consumption of WSTC-supplemented drinks had no significant effects on thrombin- or prothrombin-mediated clotting time in comparison to placebo or baseline measurements.

The effects of longer-term WSTC consumption, including the anti-platelet effects of WSTC and any potential adverse effects, have been investigated in 2 further studies (summarized below). The details of these studies are unpublished, and currently only preliminary results are available.

The information related to these studies was provided by Provexis in a personal communication, and is available in abstract form.

In a 9-week single-blind, crossover study, a total of 23 subjects (male and female, aged 40 to 65 years) were randomized to receive 1 of 3 treatments: capsules containing WSTC in an amount equivalent to that present in 2 or 4 fresh tomatoes (approximately 2.4 or 4.8 g), or the placebo treatment (treacle capsules). Each 14-day intervention period was preceded by a 7-day washout period. Blood samples were taken at baseline (at the end of each washout period), and at days 7 and 14 of the intervention periods. Platelet function was assessed using 10, 7.5, and 5 $\mu\text{mol/L}$ of ADP agonist, and the percentage change in platelet function from baseline was calculated for each time point. Results for only 15 subjects were analyzed, as 2 subjects discontinued the trial following phlebotomy difficulties, and data on 6 other subjects were discarded due to low platelet counts ($<170 \times 10^6/\text{L}$) or technical difficulties. There were no significant differences between the 2 WSTC groups; however, platelet activity was significantly different (*i.e.*, decreased) in both WSTC groups in comparison to the placebo group. There were no differences in platelet function between the 7- and 14-day time points measured within any group. High intra-subject variability in response was reported, and was thought to be due to a lack of standardization of some study variables, such as time between supplementation and blood sampling, volumes of liquid drunk with supplement capsules, and poor control of subject behavior during the intervention periods. No adverse effects were reported.

In a later, 42-day double-blind, crossover study, a total of 22 subjects (male and female, aged 45 to 70 years) were randomized to receive orange juice supplemented with WSTC in an amount equivalent to 2 tomatoes (approximately 2.4 g), for a 28-day intervention period, and placebo orange juice, for a period of 14 days. Subjects were randomly assigned to one of 2 groups, with group A beginning with the WSTC supplementation, followed by placebo, and group B beginning with the placebo, followed by WSTC supplementation. The supplement drink provided was the same as the 2TE supplement used in the 90-subject crossover study previously described (O'Kennedy *et al.*, 2005b), which had focused on the acute anti-platelet effect. A 10-day washout period was observed prior to study initiation, at the end of which blood samples were taken to assess baseline platelet function, blood coagulation, plasma lipids, glucose, homocysteine, and C-reactive protein. Blood samples were then taken at 14-day intervals thereafter. WSTC consumption was reported to result in a 15% decrease in platelet function (from baseline) on Day 14 of the WSTC treatment period, which persisted at this magnitude on Day 28 in male subjects, but had decreased slightly to a 10% reduction in female subjects on Day 28. The decrease in platelet function in the WSTC group was significantly different from placebo. The reduction in platelet function was reported not to persist once supplementation with WSTC had been discontinued. There were no effects on blood coagulation; however, a small but significant decrease in plasma triglycerides was reported. No adverse effects, assessed by subject questionnaires, were reported.

The primary adverse effect that would be expected to occur in clinical trials using WSTC (as a result of reduced platelet function) is prolonged bleeding time. As demonstrated in all the studies described, no adverse effects on blood clotting time were observed either over the time course of the acute effect (up to 18 hours after consumption of WSTC), or in the longer term

studies after a continuous period of daily WSTC consumption. Thus the consumption of WSTC has no adverse effects on bleeding time.

SUMMARY

Provexis plc. (Provexis) intends to market Water-Soluble Tomato Concentrate (WSTC) as a food ingredient in the United States in food products such as yogurt drinks, fruit juices, and fruit-flavored drinks. WSTC is an aqueous concentrate of tomato paste and consists of soluble solids concentrate from a commercially available tomato puree derived from the common tomato, *Lycopersicon esculentum*. WSTC is intended to be added to food at a level of 3 g/serving. Products containing WSTC are to be labeled with directions indicating that only one serving per day is to be consumed by healthy adults over the age of 45. The mean intake level of WSTC is therefore 3 g/day. "Worst-case" estimates of exposure also were determined in the event that the product is not consumed as directed. On an all-user basis, the mean intake of WSTC by the total U.S. population from all proposed food-uses was estimated to range from 3.94 to 4.38 g/person/day (90.35 to 100.16 mg/kg body weight/day), while the 90th percentile intake of WSTC was estimated to range from 7.79 to 9.08 g/person/day (209.8 to 228.12 mg/kg body weight/day).

The assessment of the safety of WSTC is based on the history of use of tomato, which has been safely consumed by humans for many years. Moreover, the safety of WSTC is substantiated by the composition of the ingredient, of which >90% consists of carbohydrates, protein, free amino acids, flavonoids, phenolics, and organic acids, which all are present in a normal diet and are expected to be metabolized by common metabolic pathways. Detailed analytical data have demonstrated that the levels of other constituents present in the f1, f2, and f3 fractions of one 3 g serving WSTC are comparable to the levels present in one standard serving of commercially available tomato-based products. Furthermore, preclinical data on GM and non-GM tomatoes have demonstrated no significant toxicological effects at doses of up to 40 g tomato powder/kg body weight/day for up to 11 weeks, providing approximately 600 mg WSTC/kg body weight/day under the assumption that the same proportion of WSTC that occurs in fresh tomatoes was present in the tomato powder. This level is equivalent to 36 g/day for a 60 kg human. In addition, clinical trials in which the effects of WSTC on platelet aggregation were assessed at WSTC levels of up to 18 g have demonstrated no significant adverse effects, including no effects on bleeding time.

In summary, the safety of WSTC is supported by the fact that all constituents of WSTC have a long history of consumption as part of the normal diet and would be consumed at levels of exposure that are comparable to those from consumption of other tomato-based food products. Furthermore, clinical studies have demonstrated that exposure to WSTC is well-tolerated and without adverse effects. The data and information summarized in this report demonstrate that WSTC, meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practice, is GRAS based on scientific procedures and on the

compositional similarity to tomatoes, under the conditions of intended use in foods described herein.

CONCLUSION

We, the Expert Panel, have, independently and collectively, critically evaluated the data and information summarized above and conclude that Water-Soluble Tomato Concentrate, meeting appropriate food grade specifications and produced in accordance with current good manufacturing practice, is Generally Recognized As Safe (GRAS) based on scientific procedures and on the compositional similarity to tomatoes under the conditions of intended use in foods specified herein.

John Doull, Ph.D., M.D.
University of Kansas Medical Center

7/28/2006

Date

Ian C. Munro, Ph.D, FRCPath
President
CANTOX Health Sciences
International

Date

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CONCLUSION

We, the Expert Panel, have, independently and collectively, critically evaluated the data and information summarized above and conclude that Water-Soluble Tomato Concentrate, meeting appropriate food grade specifications and produced in accordance with current good manufacturing practice, is Generally Recognized As Safe (GRAS) based on scientific procedures and on the compositional similarity to tomatoes under the conditions of intended use in foods specified herein.

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ATTACHMENT 1

CURRICULA VITAE OF EXPERT PANEL MEMBERS

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CURRICULUM VITAE

John Doull, Ph.D., M.D

1/30/2004

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HOME:

DATE/PLACE OF BIRTH: :

MARITAL STATUS:

CHILDREN:

EDUCATION:

B.S., Chemistry, Montana State College, Bozeman, Mont., 1944

US Navy, Electronics, 1944-1946

Ph.D., Pharmacology, Univ. of Chicago, Chicago, Ill., 1950

M.D., School of Medicine, Univ. of Chicago, Chicago, Ill., 1953

PROFESSIONAL EXPERIENCE:

University of Chicago Medical School

Research Assistant, Univ. of Chicago Toxicity Laboratory, 1946-1950

**Research Associate, US Air Force Radiation Laboratory and Univ. of
Chicago Toxicity Laboratory, 1951-1953**

**Assistant Director, US Air Force Radiation Laboratory & Univ. of
Chicago Toxicity Laboratory, 1954-1967**

Assistant Professor, Department of Pharmacology, 1956-1957

Associate Professor, Department of Pharmacology, 1957-1967

University of Kansas Medical Center

**Professor of Pharmacology and Toxicology, Department of Pharmacology,
Toxicology and Therapeutics, 1967-1994**

Co-Director Clinical Pharmacology Toxicology Center, 1967-1978
Director, Univ. of Kansas Medical Center Safety Office, 1978-1985
Director, Center for Environmental and Occupational Health, 1986-1989
Professor Emeritus of Pharmacology and Toxicology, Department of
Pharmacology, Toxicology and Therapeutics 1995-

PROFESSIONAL SOCIETY MEMBERSHIPS:

American Chemical Society, 1949-1996
Kansas City Regional Chapter, 1967-1996
American Industrial Hygiene Association, 1950-1996
Radiation Research Society, 1953-1980
American Society for Pharmacology & Experimental Therapeutics, 1953-1996
Environmental Pharmacology Committee, 1975-1978
Society for Experimental Biology and Medicine, 1954-1995
New York Academy of Sciences, 1954-1975
American Ass. for the Advancement of Science, 1954- (Fellow, 1958-)
Society of Toxicology (Charter Member), 1961-
Technical Committee, 1967-1968
Education Committee, 1974-1976
Membership Requirement Revision Committee, 1975-1976
Biomed Research Oversight Committee, 1977-1978
Central States Regional Chapter, 1986-
Program Committee (Chairman), 1985-1986
Finance Committee, 1986-1987
Awards Committee (Chairman), 1987-1988
Nominating Committee (Chairman), 1988-1989
Council Member, 1981-1988
Vice President Elect, 1984-1985
Vice President, 1985-1986
President, 1986-1987
Past-President, 1987-1988
Toxicology Education Foundation (Trustee, President) 1997-1999
American Academy of Clinical Toxicology, 1970-1996
Board of Trustees, 1972-1977
Canadian Academy of Clinical Toxicology, 1976-1989
Program Committee, 1976-1977
The Toxicology Forum, 1979-1998
Board of Directors, 1981-1982

American Board of Toxicology, 1979-1983
Chairman Examination Committee, 1979-1982
Vice President, 1981-1982
President, 1982-1983
American Water Works Association, 1983-1995
Kansas Regional Section, 1983-1995
American Conference of Governmental Industrial Hygienists, 1989-
Chairman, TLV Committee, 1989-1997
The Academy of Toxicological Sciences (Fellow), 1999

EDITORIAL BOARDS:

Toxicology and Applied Pharmacology, 1970-1982
Forum for the Advancement of Toxicology, 1973-1983
AACTION (American Academy of Clinical Toxicology), 1974-1977
Environmental Health Sciences, 1976-1989
Archives Internationales de Pharmacodynamie et de Therapie, 1976-1989
Journal of Environmental Pathology and Toxicology, 1977-1989
Health & Environment Digest, 1987-1997
Toxicological Reviews 2003-
Therapeutics and Clinical Risk Management 2004-

CONSULTANTSHIPS

Walter Reed Army Institute for Research, 1960-1963
Radiation Protection Panel, 1962-1963
Atomic Defense Support Agency, Group N-3, 1961-1962
White House Evaluation Study (Woolridge Report), 1962-1963
NIH Special Grants Program Advisory Panel, 1962
NIH Toxicology Study Section, 1965-1970
HEW Secretary's Commission on Pesticides (Mrak Report), 1968-1969
Subcommittee on Interactions, 1968-1969
Midwest Research Institute, 1969-1990
Institute for Clinical Toxicology, Houston, Texas, 1969-1973
National Academy of Sciences, National Research Council
Toxicology Information Program (Chairman), 1970-1975
Food Protection Committee, 1974-1979
Committee on Non-nutritive Sweeteners, 1974-1975
Safe Drinking Water Committee, 1975-1978 (Chairman, 1976-1978)
Pesticides Subcommittee (Chairman), 1975-1977

Committee to Revise Publication 1138, 1976-1977
Chronic Toxicity Subcommittee (Chairman), 1976-1977
Board on Toxicology and Environmental Health Hazards, 1978-1986
Board on Environmental Sciences and Toxicology, 1986-1989
IOM Food Safety Policy Subcommittee, 1978-1979
Committee to study Saccharin and Food Safety Policy, 1978-1979
IOM Advisory Committee on CDC's Study of Vietnam Veteran Health, 1985-1988
Committee on Toxicity Testing Strategies (Chairman), 1982-1984
Committee on Mixtures (Chairman), 1986-1988
Committee on Toxicology (Chairman), 1987-1993
Committee on Risk Assessment of Hazardous Air Pollutants, 1990-1993
Committee to Study the Interactions of Drugs, Biologics and Chemicals in Deployed U. S. Military Forces, 1995-1996
Subcommittee on Acute Exposure Guideline Levels, 1997-2003
Board on on Environmental Studies and Toxicology (Vice Chair)1999-2003
Committee on the Use of Third Party Toxicity Research with Human Participants, Science Technology and Law Program, 2002-2004
Subcommittee on Fluoride in Drinking Water (chair) 2003-Environmental Protection Agency, Washington, D.C., 1976-1995
FIFRA Science Advisory Panel, 1976-1980
Worker Re-entry Protocol Group, 1977-1978
Committee on Tolerances, 1978-1979
Science Advisory Board, Environmental Health Committee, 1980-1989
Organics Subcommittee (Chairman), 1986-1989
Estimating Risks from Dioxins/Dibenzofurans, 1986-1987
Severity of Effects Ranking Schemes, 1985-1986
Acute Toxics Committee, 1986-1987
Hazard Ranking System Committee, 1987-1988
Dioxin Reassessment Review Committee 1995
Science Advisory Board, Environmental Health Committee, 1997-2001
National Institute of Environmental Health Sciences, 1975-1978
NIEHS Advisory Council, 1975-1978
University-Based Centers Subcommittee (Chairman), 1975-1978
Second Task Force on Human Health and the Environment, 1976-1977
Biologic Mechanisms and Toxicity Subcommittee, 1976-1977
F.E.M.A., Washington, D.C., Expert Panel Member, 1977-2003
National Advisory Committee, California Primate Center, Davis, 1977-1980

OTA, Wash., Panel on Assessment of Environmental Contaminants, 1978
National Toxicology Program, Board of Scientific Counselors Ad Hoc
Panel on Chemical Carcinogenesis Testing & Evaluation, 1982-1984
DHHS Advisory Committee on Long-term Health Effects of Phenoxy
Herbicides and Contaminants, 1982-1985
UAREP Panel on Health Aspects of Waste Chemical Disposal, 1983-1984
Nutrition Foundation, Washington Committee, 1982-1983, DC
Predictive Role of Mouse Liver Tumors
National Sanitation Foundation, Ann Arbor, 1983-1989
Council of Public Health Consultants, 1983-1989
Health Advisory Board, 1983-1989
Drinking Water Additives Peer Review Group, 1987-1989
Kansas Dept. Health and Environment, Topeka, 1983-1987
Toxicology Advisory Committee, 1983-1987
Governors Advisory Committee on Radon (Chairman), 1987-1988
Governors Surface Water Quality Commission 1997-1999
National Institute of Occupational Safety and Health, 1984-1987
Board of Scientific Counselors, 1984-1987
White House Advisory Panel on Ranchhand Veterans, 1984-1986
Clean Sites Inc., Alexandria, Technical Advisory Panel, 1984-1993
Naylor Dana Institute, Advisory Panel on Acetaminophen, 1986-1987
Denver Water Dept. Reuse Demo. Project Advisory Committee, 1986-1992
Scientific Advisory Panel on Ground Water Recharge (California), 1987
Water Resource Recovery Pilot Plant Project (Tampa, FL), 1987-1992
Health Effects Group (Chairman), 1987-1992
International Life Sciences Institute, Risk Science Institute, 1988-
Armed Forces Epidemiological Board, 1988-1991
Lovelace Biomedical & Environmental Res. Inst. Board of Directors, 1988
Presidential Risk Assessment & Management Commission, 1990-1998
Food and Drug Administration, CFSAN Review Panel 1999
Food and Drug Administration, OPS Advisory Committee, 1999-2002
FDA, OPS Adv Com: Non-clinical studies subcommittee (chair), 1999-2003

LOCAL COMMITTEES:

Poison Control Center Committee (Chairman), 1968-1980
Pharmacy and Therapy Committee (Chairman), 1969-1984
Basic Science Lectureship Committee, 1970-1972
Health Care Delivery Systems Committee, 1971-1972

Research Committee, 1971-1973
Animal Care Committee, 1972-1974
Computer Committee (Chairman), 1972-1974
Search Committee for Chair of Biochemistry, 1975
Search Committee for Dean of School of Nursing (Chairman), 1975
Education Committee, 1976-1977
Faculty Promotion and Tenure Committee, 1976-1977
Curriculum Implementation Committee, 1976
Ad Hoc Ethics Committee, 1976
Long Range Planning Committee, 1976
Information Systems Advisory Committee, 1977
Medical Center Safety Committee (Chairman), 1978-1983
 Radiation Safety Committee, 1978-1983
 Biohazards Committee, 1978-1983
 Engineering Safety Committee, 1978-1983
Committee for Intercampus Liaison (Chairman), 1978-1980
Search Committee for Director of Biomed. Engineering (Chairman), 1980
Search Committee for Graduate School Dean (Chairman), 1980
Task Force on Need for School of Public Health, 1980
Education and Curriculum Committee, 1984-1987
Center for Environmental and Occupational Health (Director 1986-1989)
 Executive Advisory Committee, 1986-1989
 External Advisory Committee, 1986-1989

HONORS/AWARDS:

Sigma Xi (Univ. of Chicago), 1960
Alpha Omega Alpha (Univ. of Kansas), 1973
The Kenneth P. DuBois Award (Midwest Chapter SOT), 1985
Samuel Kuna Award (Rutgers Univ.), 1989
Commander's Award for Public Service (Armed Forces Epidemiological Board), 1990
International Achievement Award (International Society of Regulatory Toxicology), 1990
Ambassador of Toxicology Award (Mid-Atlantic Chapter Society of Toxicology), 1991
Distinguished Medical Alumnus Award (Univ. of Chicago), 1991
Stokinger Award (Amer. Cont. Governmental Industrial Hygienists), 1992
John Doull Award (Mid-America Chapter Society of Toxicology), 1992

Special Recognition Award (University of Kansas Medical Center), 1992
Merit Award (Society of Toxicology), 1993
Snider Award (University of Arkansas Toxicology Symposium Series), 1994
Founders Award (Chemical Industry Institute of Toxicology), 1996
Distinguished Service Award, (American College of Toxicology), 1996
The Meritorious Service Award (Amer. Conf. Gov. Ind. Hygienists), 1996
Honorary Doctor of Pharmacy (The University of Kuopio, Finland), 1996

BOOKS/BOOK CHAPTERS:

Essays in Toxicology (F. Blood, ed.), Academic Press, New York, Effect of Physical Environmental Factors on Drug Response, 1972.
Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co., Inc., New York.
First Edition (L. J. Casarett and J. Doull, eds.), 1975
Second Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1980
Third Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1986
Fourth Edition (M. O. Amdur, J. Doull and C. D. Klaassen, eds.), 1991
Fifth Edition (C. D. Klaassen ed., M. O. Amdur and J. Doull, emeritus eds.) 1995
Insecticide Biochemistry and Physiology (C. Wilkinson, ed.), Plenum Press, NY, The Treatment of Insecticide Poisoning, 1976.
Information Technology in Health Science Education (E. Deland, ed.), Plenum Pub. Co., Use of CATS in Pharmacology, 1978.
Food Safety (H. Roberts, ed.), Wiley & Sons, New York, Chapter 7, Food Safety and Toxicology, 1981.
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Environmental Toxicology, Current Developments (J. Rose Ed.), Chapter 1, General Principles of Toxicology, Gordon and Breach, Amsterdam , 1998
Acute Exposure Guideline Levels for Selected Airborne Chemicals, National Academy Press, Washington, D.C., 2000, 2001, 2002, 2003
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Vol 1, Chapter 1, Dose Time and Other Factors Influencing Toxicity.

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19. Doull, J. Studies on the cholinesterase activity of tissues of irradiated animals. *J. Pharmacol. Exp. Ther.* 110: 14 (1954).
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33. Noble, J. F., Hasegawa, A. T., Landahl, H. D., and Doull, J. Effect of fractionation on survival of mice following chronic exposure to x-irradiation. *Radiat. Res.* 11: 457 (1959).
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Ottawa, Canada. Section Head, The Division of Toxicology.
- 1963-1974 **Health and Welfare, Canada**, Health Protection Branch,
Ottawa, Canada. Research Scientist.

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COMMITTEE MEMBERSHIPS

- 2006-Present** Chair, Faculty of Agriculture and Environmental Sciences Advisory Board, McGill University
- 2005-Present** Member at Large, Executive Committee, Toxicology and Safety Evaluation Division, Institute of Food Technologists
- 2004** Chairman, Panel Member, The Tooth Whitening Products Task Force of COLIPA, The European Cosmetics Industry Association
- 2002-2006** Technical Advisory Committee, World Food Program (WFP), The Food Aid Organization of the United Nations
- 2001** Chairman, Safety Assessment of Foods Derived from Genetically Modified Microorganisms. World Health Organization, Headquarters, Geneva, Switzerland – September 2001
- 2000-Present** Member, Georgetown Dialogue Science Council, Georgetown University Center for Food and Nutrition Policy (CFNP)
- 2000-Present** Consultant, FEMA Expert Panel
- 1999** Center for Food Safety and Applied Nutrition (CFSAN) Research Program Committee, Food and Drug Administration
- 1998-2001** Member, Minister's Advisory Board, Canadian Food Inspection Agency
- 1996-2002** Chairman, Institute of Medicine, Subcommittee on Upper Safe Reference Levels of Nutrients
- 1996** Member, Ad Hoc Expert Panel, Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB)
- 1993-Present** Member FAO/WHO Expert Committee on Food Additives
- 1989** Chairman, Expert Group to Develop a Threshold of Regulation for Indirect Food Additives
- 1989-1991** Member, Scientific Committee, International Food Biotechnology Council
- 1985-2000** Member, FEMA Expert Panel
- 1985** Member ILSI-NF, Nutrition and Safety Committee (FNSC)
- 1985** Member, NAS, Committee on Carcinogenicity of Cyclamates.
- 1984** Member, Committee on Food Chemicals Codex.
- 1983-1984** Member, Panel of Chemical Carcinogenesis Testing and Evaluation (National Toxicology Program)
- 1983** Member, The Nutrition Foundation Project on the Use of Mouse Hepatoma Data.
- 1981-1983** Expert Committee on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, The Nutrition Foundation, Inc.
- 1981-1982** Expert Advisory Committee to The Nutrition Foundation, Inc., on the Assessment of the Safety of Lead and Lead Salts in Foods.
- 1981** Chairman, International Committee on Hazards Associated with Dioxin in the Great Lakes.
- 1981** Chairman, WHO Ad Hoc Meeting on the Future of Joint Expert Committees in the Context of the International Program on Chemical Safety, Geneva.
- 1980-1983** Chairman, Health Protection Branch/Food Industry Liaison Committee.
- 1980-1983** Chairman, Interdepartmental Committee on Canning Regulations.
- 1980** Member, Federal Interdepartmental Salmonella Committee.
- 1980** Member, Senior Level Committee (U.S., U.K., Canada).
- 1980** Member, International Life Sciences Institute Experts in Pathology and Toxicology.
- 1980** Member, Technical Committee: WHO International Program on Chemical Safety.
- 1978-1980** Expert Committee on Food Safety - Agriculture Canada
- 1978-1980** Food Safety Council, Social and Economic Committee.
- 1978-1979** U.S. National Academy of Sciences, Subcommittee on Risk Assessment - Safe Drinking Water Committee.
- 1978** Chairman, Tripartite Toxicology Committee (U.S., U.K., Canada).
- 1977-1981** International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC), subcommittee 3.
- 1977-1979** U.S. National Cancer Institute, Cause and Prevention Scientific Review Committee.
- 1976-1984** WHO/FAO Joint Expert Committee on Food Additives.
- 1976-1980** Food Safety Council, Toxicology Committee.

1976-1979 Canadian Council on Animal Care.
1976-1979 Interdepartmental Committee on Toxicology Needs in Canada.
1976-1978 National Research Council Task Force on Mercury and Captan.
1975-1976 U.S. National Academy of Sciences Committee on Toxicology
1975-1976 WHO/FAO Committee on Criterion Documents on the Toxicology of Environmental Chemicals.

EDITORIAL RESPONSIBILITIES

1982-1996 Editorial Board Journal of the American College of Toxicology
1979-1991 Advisory Board Neurotoxicology
1978-1989 Editorial Board Journal of Environmental Pathology and Toxicology

PROFESSIONAL AFFILIATIONS

Professional Society Memberships:

Member, Society of Toxicology
 Member, Toxicology Forum
 Member, Society of Toxicology of Canada
 Member, American College of Toxicology
 Member, Institute for Risk Research
 Member, International Society of Regulatory Toxicology and Pharmacology
 Member, Institute of Food Technologists

Contributions to Professional Societies:

2004-Present The Academy of Toxicological Sciences, Board of Directors
1981 Professional Standards Evaluation Board in General Toxicology, Academy of Toxicological Sciences
1978-1979 Society of Toxicology, Nominating Committee
1978-1979 Society of Toxicology, Finance Committee
1976-2006 Toxicology Forum, Inc., Board of Directors

AWARDS

2006 Joint FAO/ WHO Committee on Food Additives (JECFA) – on the 50th Anniversary of the Committee for his long service as an Expert Advisor to the Secretariat.
2005 Institute of Food Technologists “Bernard L. Oser Food Ingredient Safety Award” for his contributions to the scientific knowledge of food ingredient safety or leadership in establishing principles for food ingredient safety evaluation or regulation.
1998 International Society of Regulatory Toxicology and Pharmacology’s International Achievement Award for his guiding role as Chairman of the Expert Panel of Members – An Interpretive Review of the Effects of Chlorinated Organic Chemicals.
1975 Society of Toxicology "Achievement Award" for outstanding contributions to the science of toxicology by an individual 35 years of age or younger.

SCIENTIFIC PUBLICATIONS AND MONOGRAPHS

Young, K.W.H., Danielewska-Nikiel, B., and Munro, I.C. 2006. An Evaluation of the Maximized Survey-Derived Intake (MSDI) as a Practical Method to Estimate Intake of Flavouring Substances. Food Chem Toxicol. In press.

Munro, I.C., and Renwick, A.G. 2006. The Fifth Workshop on the Assessment of Adequate Intake of Dietary Amino Acids: General Discussion. *J Nutr* 136(6 Suppl):1755S-1757S.

Munro, I.C., Williams, G.M., Heymann, H.O., and Kroes, R. 2006. Use of Hydrogen Peroxide-Based Tooth Whitening Products and its Relationship to Oral Cancer. *J Esthet Restor Dent* 18:119-125.

Munro, I.C. 2006. Setting Tolerable Upper Intake Levels for Nutrients. *J Nutr* 136(2):490S-492S.

Munro, I.C., and Danielewska-Nikiel, B. 2006. Comparison of Estimated Daily Intakes of Flavouring Substances with No-Observed-Adverse-Effect Levels. *Food Chem Toxicol* 44(2006):758-809.

Munro, I.C., Williams, G.M., Heymann, H.O., and Kroes, R. 2006. Tooth Whitening Products and the Risk of Oral Cancer. *Food Chem Toxicol* 44:301-315.

Munro, I.C., Newberne, P.M., Young, V.R., and Bär, A. 2004. Safety Assessment of γ -Cyclodextrin. *Reg Toxicol Pharmacol* 39:S3-S13.

Adams, T.B., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., and Wagner, B.M. 2004. The FEMA GRAS Assessment of Cinnamyl Derivatives Used as Flavor Ingredients. *Food Chem Toxicol* 42:157-185.

Feron, V.J., Adams, T.B., Doull, J., Goodman, J.I., Hall, R.L., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., and Wagner, B.M. 2004. Safety Evaluation of Natural Flavour Complexes. *Toxicol Lett* 144(Suppl. 1):S16.

Munro, I.C. et al. 2003. Guidance for the Safety Assessment of Botanicals and Botanical Preparations for Use in Food Supplements. Expert Group Report reviewed at a Workshop held in May 2002, Marseille, France. Organized by the International Life Science Institute (ILSI) Europe Natural Toxin Task Force. *Food Chem Toxicol* 41:1625-1649.

Hlywka, J.J., Reid, J.E., and Munro, I.C. 2003. Review: The Use of Consumption Data to Assess Exposure to Biotechnology-Derived Foods and the Feasibility of Identifying Effects on Human Health Through Post-Marketing Monitoring. *Food Chem Toxicol* 41:1273-1282.

Munro, I.C., Haighton, L.A., Lynch, B.S., Hlywka, J.J., Doull, J., and Kroes, R. 2003. Letter to the Editor – Response to “Does Exposure to Bisphenol A Represent a Human Health Risk?” *Reg Toxicol Pharmacol* 37:409-410.

Munro, I.C., Harwood, M., Hlywka, J.J., Stephen, A.M., Doull, J., Flamm, W.G., and Adlercreutz, H. 2003. Soy Isoflavones: A Safety Review. *Nutr Rev* 61(1):1-33.

Munro, I.C., Haighton, L.A., Hlywka, J.J., Lynch, B.S., Doull, J., and Kroes, R. 2002. Reply to Letter to the Editor – Carcinogenicity Bioassay of Bisphenol A. *Toxicol Sci* 70:283-284.

Munro, I.C. 2002. The Precautionary Principle and the Scientific Risk Assessment Process. Submitted to *Regul Toxicol Pharmacol* July 31, 2002.

Butchko, H.H., Stargel, W.W., Comer, C.P., Mayhew, D.A., Benninger, C., Blackburn, G.L., de Sonneville, L.M.J. Geha, R.S., Hertelendy, Z., Koestner, A., Leon, A.S., Liepa, G.U., McMartin, K.E., Mendenhal, C.L., Munro, I.C., Novotny, E.J., Renwick, A.G., Schiffman, S.S., Schomer, D.L., Shaywitz, B.A., Spiers, P.A., Tephly, T.R., Thomas, J.A., and Trefz, F.K. 2002. Aspartame: Review of Safety. *Reg Toxicol Pharmacol* 35(No.2) Part 2 of 2.

Munro, I.C., et al. 2002. Exposure From Food Contact Materials: Summary Report of a Workshop Held in October 2001 in Ispra, Italy. ILSI Europe Packaging Material Task Force in Collaboration with the European Commission's Joint Research Centre (JRC). International Life Science Institute (ILSI) Press; Washington, DC.

Adams, T.B., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Newberne, P.M., Portoghese, P.S., Smith, R.L., Waddell, W.J., and Wagner, B.M. 2002. The FEMA GRAS Assessment of Pyrazine Derivatives Used as Flavor Ingredients. *Food Chem Toxicol* 40:429-451.

Munro, I.C., Hlywka, J.J., and Kennepohl, E.M. 2002. Risk Assessment of Packaging Materials. *Food Addit Contam.* 19(Suppl. 3-12):3-12.

Munro, I.C., Haighton, L.A., Hlywka, J.J., Lynch, B.S., Doull, J., and Kroes, R. 2002. Letter to the Editor – Carcinogenicity Bioassay of Bisphenol A. *Toxicol Sci* 66(2) p. 356.

Stephen, A.M., Liston, A.J., Anthony, S.P., Munro, I.C., and Anderson, G.H. 2002. Regulation of Foods with Health Claims: A Proposal. *Can J Pubic Health* 93(5):328-331.

Haighton, L.A., Hlywka, J.J., Doull, J., Kroes, R., Lynch, B.S., and Munro, I.C. 2002. An Evaluation of the Possible Carcinogenicity of Bisphenol A to Humans. *Reg Toxicol Pharmacol* 35(2, Part 1) pp. 238-254.

Kennepohl, E., and Munro, I.C. 2001. Phenoxy Herbicides (2,4-D). Volume 2. *Handbook of Pesticide Toxicology.* Academic Press, pp. 1623-1638.

Chassy, B.M., Abramson, S.H., Bridges, A., Dyer, W.E., Faust, M.A., Harlander, S.K., Hefle, S.L., Munro, I.C., Rice, M.E. 2001. Evaluation of the U.S. Regulatory Process for Crops Developed Through Biotechnology. *CAST* 19:September.

Chassy, B., and Munro, I.C. 2001. Evolution d'un Principe Fondateur. *La Recherche* (February) 339:70-72.

Munro, I.C., and Kennepohl, E. 2001. Comparison of Estimated Daily *Per Capita* Intakes of Flavouring Substances with No-Observed-Effect Levels from Animal Studies. *Food Chem Toxicol* 39(4):47-70.

Hoover, D., Chassy, B.M., Hall, R.L., Klee, H.J., Luchansky, J.B., Miller, H. I., Munro, I.C., Weiss, R., Hefle, S.L., and Qualset, C.O. 2000. Human Food Safety Evaluation of rDNA Biotechnology-Derived Foods. Institute of Food Technologists Expert Report on Biotechnology and Foods. Reprinted from *Food Technol* 54(9), September.

Kroes, R., Galli, C., Munro, I., Schilter, B., Tran, L.-A., Walker, R., and Würtzen. 2000. Threshold of Toxicological Concern for Chemical Substances Present in the Diet: A Practical Tool for Assessing the Need for Toxicity Testing. Reprinted from *Food Technol* 38(2-3):255-312.

Munro, I.C., et al. 2000. Safety Aspects of Genetically Modified Foods of Plant Origin. Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology. WHO Headquarters, Geneva, Switzerland, May 29-June 2, 2000.

Wilson, R.M., Sigal, E.A., Bacigalupo, C.M., Willes, R.F., and Munro, I.C. 2000. Derivation of Risk Management Criteria for Chemicals of Unknown Toxic Potency at Contaminated Sites. *Hum Ecol Risk Assessment* 6(1):131-139.

Newberne, P., Smith, R.L., Doull, J., Feron, V.J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Waddell, W.J., Wagner, B.M., Weil, C.S., Adams, T.B., and Hallagan, J.B. 2000. GRAS Flavoring Substances 19. *Food Technol* 54(6):66-84.

Williams, G.M., Kroes, R., and Munro, I.C. 2000. Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient, Glyphosate, for Humans. *Regul Toxicol Pharmacol* 31:117-165.

Davies, T.S., Lynch, B.S., Monro, A.M., Munro, I.C., and Nestmann, E.R. 2000. Rodent Carcinogenicity Tests Need to Be No Longer Than 18 Months: An Analysis Based on 210 Chemicals in the IARC Monographs. *Food Chem Toxicol* 38(2-3):219-235.

Newberne, P., Smith, R.L., Doull, J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Wagner, B.M., Weil, C.S., Woods, L.A., Adams, T.B., Lucas, C.D., and Ford, R.A. 1999. The FEMA GRAS Assessment of *trans*-Anethole Used as a Flavouring Substance. *Food Chem Toxicol* 37:789-811.

Munro, I.C., Delzell, E.S., Nestmann, E.R., and Lynch, B.S. 1999. Viadent Usage and Oral Leukoplakia: A Spurious Association. *Regul Toxicol Pharmacol* 30:182-196.

Institute of Medicine*. 1999. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press, Washington, D.C. *(Dr. Ian Munro, Chair, Subcommittee on Upper Reference Levels of Nutrients).

Bechtel, D.H. (Introduction by Munro, I.C.) 1999. Carcinogenicity Assessment of Allylthiocyanate with Regard to IARC Classification Criteria. (Abstract) *Intl J Toxicol* 18(1):84.

Munro, I.C., Kennepohl, E., and Kroes, R. 1999. A Procedure for the Safety Evaluation of Flavouring Substances. *Food Chem Toxicol* 37(2/3):207-232.

Munro, I.C., Bernt, W.O., Borzelleca, J.F., Flamm, G., Lynch, B.S., Kennepohl, E., Bär, E.A., and Modderman, J. 1998. Erythritol: An Interpretive Summary of Biochemical, Metabolic, Toxicological and Clinical Data. *Food Chem Toxicol* 36:1139-1174.

Newberne, P., Smith, R.L., Doull, J., Goodman, J.I., Munro, I.C., Portoghese, P.S., Wagner, B.M., Weil, C.S., Woods, L.A., Adams, T.B., Hallagan, J.B., and Ford, R.A. 1998. GRAS Flavoring Substances 18. *Food Technol* 52(9):65-92.

Munro, I.C., Shubik, P., and Hall, R. 1998. Principles for the Safety Evaluation of Flavoring Substances. *Food Chem Toxicol* 36(1998):529-540.

Adams, T.B., Greer, D.B., Doull, J., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1998. The FEMA GRAS Assessment of Lactones Used as Flavour Ingredients. *Food Chem Toxicol* 36(4):249-278.

Lynch, B.L., Bryant, D.W., Hook, H.J., Nestmann, E.R., and Munro, I.C. 1998. Carcinogenicity of Monochloro-1,2-Propanediol (α -Chlorohydrin, 3, MCPD). *Int J Toxicol* 17(1):47-76.

Munro, I.C. and Kennepohl, E. 1997. A Procedure for the Safety Evaluation of Flavoring Substances. In: Colombo, E. (Ed.), Proceedings from the International Symposium on Flavours and Sensory Related Aspects - March 6 & 7, 1997, Cernobbio (Como), Italy. *Rivista Italiana EPPOS*, pp 81-85.

Adams, T.B., Doull, J., Goodman, J.I., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1997. The FEMA GRAS Assessment of Furfural Used as a Flavour Ingredient. *Food Chem Toxicol* 35(8):739-751.

Miller, S.A., and Munro, I.C. 1997. Upper Safe Reference Levels for Nutrients. Proceedings of the 16th International Congress of Nutrition, Montreal, Quebec, July 28-August 31, 1997.

Munro, I.C. and Kroes, R. 1997. Application of a Threshold Of Regulation Concept in the Safety Evaluation of Certain Flavoring Substances. Prepared for the 49th Joint FAO/WHO Expert Committee on Food Additives.

Adams, T.B., Hallagan, J.B., Putman, J.M., Gierke, T.L., Doull, J., Munro, I.C., Newberne, P., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., and Ford, R.A. 1996. The

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FEMA GRAS Assessment of Alicyclic Substances Used as Flavour Ingredients. *Food Chem Toxicol* 34(9):763-828.

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Lynch, B.S., Tischler, A.S., Capen, C., Munro, I.C., McGirr, L.G., McClain, R.M. 1996. Low Digestible Carbohydrates (Polyols and Lactose): Significance of Adrenal Medullary Proliferative Lesions in the Rat. *Regul Toxicol Pharmacol* 23:256-297.

Munro, I.C., Ford, R.A., Kennepohl, E., and Sprenger, J.G. 1996. Correlation of Structural Class With No-Observed Effect Levels: A Proposal for Establishing a Threshold of Concern. *Food Chem Toxicol* 34(9):829-867.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1996. Alternative Approaches to the Safety Assessment of Macronutrient Substitutes. *Regul Toxicol Pharmacol* 23(1)Part 2:S6-S14.

Munro, I.C. 1996. A Procedure For the Safety Evaluation of Flavoring Substances. Toxicological Evaluation of Certain Food Additives and Contaminants. Prepared for the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series #35, Annex 5.

Munro, I.C., Ford, R.A., Kennepohl, E., and Sprenger, J.G. 1996. Thresholds of Toxicological Concern Based on Structure-Activity Relationships. *Drug Metab Rev* 28(1&2):209-217.

Kraus, A.L., Munro, I.C., Orr, J.C., Binder, R.L., LeBeouf, R.A., and Williams, G.M. 1995. Benzoyl Peroxide: An Integrated Human Safety Assessment for Carcinogenicity. *Regul Toxicol Pharmacol* 21:87-107.

Munro, I.C., Lynch, B.S., Kittur, A., and Nestmann, E.R. 1995. Modulators of Carcinogenesis. *Regul Toxicol Pharmacol* 21:60-70.

Kroes, R., Munro, I., and Poulsen, E. 1993. Workshop on the Scientific Evaluation of the Safety Factor for the Acceptable Daily Intake (ADI): Editorial Summary. *Food Addit Contam* 10(3):269-273.

Willes, R.F., Nestmann, E.R., Miller, P.A., Orr, J.C., and Munro, I.C. 1993. Scientific Principles for Evaluating the Potential for Adverse Effects from Chlorinated Organic Chemicals in the Environment. *Regul Toxicol Pharmacol* 18:313-356.

Munro, I.C., Kennepohl, E., Erickson, R.E., Portoghese, P.S., Wagner, B.M., Easterday, O.D., and Manley, C.H. 1993. Safety Assessment of Ingested Heterocyclic Amines: Initial Report. *Regul Toxicol Pharmacol* 17(2):S1-S109.

Munro, I.C., Carlo, G.L., Orr, J.C., Sund, K.G., Wilson, R.M., Kennepohl, E., Lynch, B.S., Jablinske, M., and Lee, N.L. 1992. A Comprehensive, Integrated Review and Evaluation of the Scientific Evidence Relating to the Safety of the Herbicide 2,4-D. *J Am Coll Toxicol* 11(5).

Munro, I.C. 1992. Ecological Risk Estimation. In: Bartell, S., Gardner, R., and O'Neill, R. (Eds.) *Toxicology and Environmental Health Series*. Editorial Board. Lewis Publishers, Chelsea, Maine.

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Nestmann, E.R., Munro, I.C., Willes, R.F., and Orr, J. 1992. Risk Assessment: An Overview. In: *Canadian Environmental Directory*. Second Edition. Canadian Almanac and Directory Publishing Company Ltd. pp. 13-16.

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Munro, I.C. 1990. Safety Assessment Procedures for Indirect Food Additives: An Overview. Regul Toxicol Pharmacol 12(1):2-13.

Munro, I.C., et al. 1990. Biotechnologies and food: Assuring the safety of foods produced by genetic modification. International Food Biotechnology Council. Washington, D.C. Regul Toxicol Pharmacol (In Press).

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Clayson, D.B., Munro, I.C., Shubik, P., and Swenberg, J.A. (Eds.) 1990. Progress in Predictive Toxicology. Elsevier Science Publishers.

Zimmerman, R. Borzelleca, J., Crump, K., Doull, J., Gardner, D., Gardner, H., Hughes, D., Munro, I.C., Parke, D.M., Rodericks, J., Tardiff, R.G., and Travis, C. (Eds.) 1990. Governmental Management of Chemical Risk. Lewis Publishers, Inc.

Munro, I.C. 1990. Sweeteners: Health Effects-Neoplasm Promotion. In: Williams, G.M. (Ed.) Sweeteners: Health Effects.

PRESENTATIONS

Munro, I.C. 2006. Thresholds for Food Flavorings Used by JECFA. Presented at FDA Grand Rounds on Thresholds: Crossing the Thresholds of Tomorrow, College Park, Maryland, June 8.

Munro, I.C. 2006. New Developments in Flavor Science. Flavor and Extract Manufacturers Association, 97th Annual Convention, Sunny Isles Beach, Florida, May 9.

Munro, I.C. 2006. The Canadian Food Regulatory System – It's Strengths and Limitations. Presented at Smarter Regulations of Foods in Canada Conference, Ottawa, Ontario, March 21-22.

Munro, I.C. 2006. Talk 1 - Can the Concept of Thresholds Help? Promises and Problems. Talk 2 - Regulatory Differences in Risk Assessment Requirements For Food Products From Biotech And Conventionally Bred Crops. The ILSI/ILSI North America Annual Meeting, San Juan, Puerto Rico, January 16-18.

Munro, I.C. 2005. Assessing the Safety of Biotechnology-Derived Foods. Korean Food and Drug Administration, Seoul, Korea, December 2.

Munro, I.C. 2005. Assessing the Safety of Biotechnology-Derived Foods. Food Industry Research and Development Institute Hsinchu, Taiwan, November 29.

Munro, I.C. 2005. Talk 1 - Thresholds of Toxicological Concern and Safety Evaluation of Food Ingredients. Talk 2 - The Threshold of Toxicological Concern Concept. ECB Workshop on Chemical Similarity and TTC Approaches, Ispra, November 7-8.

Munro, I.C. 2005. Safety Evaluation of Ferric Sodium Ethylenediaminetetraacetate (NaFeEDTA) For Use as a Source of Iron in Foods. Symposium on the Role of NaFeEDTA in Iron Deficiency Control, Beijing, China, November 3.

Munro, I.C. 2005. Talk 1 - Nutritional Assessment of GM Foods. Talk 2: Assessing the Safety of Nutritionally Enhanced GM Foods. Presented at Foods Derived from GM Crops: Issues for Consumers, Regulators and Scientists, New Delhi, India, September 26-27.

Munro, I.C. 2005. The Feasibility of Postmarket Monitoring of Foods Derived Through Biotechnology to Identify Effects on Human Health. Presented at EUROTOX 2005, Cracow, Poland, September 12-13.

Munro, I.C. 2005 The Threshold of Toxicological Concern Concept. Presented at the National Food Safety & Toxicology Centre, Michigan State University, East Lansing, Michigan, April 18.

Munro, I.C. 2004. An Overview of the Safety Evaluation of Essential Oils by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Presented at the FEMA Expert Panel Meeting, Lisbon, Portugal, October 27-29.

Munro, I.C. 2004. Safety Assessment of Nutritionally Improved Foods and Feeds Developed Through the Application of Modern Biotechnology. **Hlywka, J., and Munro, I.C.** The Feasibility of Postmarket Monitoring of Foods Derived Through Biotechnology to Identify Effects on Human Health. Presented at the ILSI Workshop on Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved through Biotechnology, Buenos Aires, Argentina, October 7-8.

Munro, I.C. 2004. Threshold of Toxicological Concern and Safety Evaluation of Food Ingredients. Presented at the 31st Annual Meeting of the Japanese Society of Toxicology, Osaka, Japan, July 6-8, 2004.

Munro, I.C. 2004. Biomarkers and Standards of Evidence: Requirements for a Health Claim on Foods. Presented at the Canadian Society for Clinical Nutrition (CSCN) 3rd Annual Scientific Meeting, "Nutrition and Cardiovascular Disease in Cancer", Toronto, Ontario, April 23, 2004.

Munro, I.C. 2003. Safety Assessment of Nutritionally Improved Foods and Feeds Developed through the Application of Modern Biotechnology. **Hlywka, J., and Munro, I.C.** The Feasibility of Postmarket Monitoring of Foods Derived Through Biotechnology to Identify Effects on Human Health. Presented at the Workshop on Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved Through Biotechnology. Organized by the ILSI International Food Biotechnology Committee (IFBiC), Paris France, December 18.

Munro, I.C. 2003. The JECFA Procedure for the Safety Evaluation of Flavoring Substances. Presented at the 3rd ASEAN Food Safety Standards Harmonization Workshop, Jakarta, Indonesia, December 10-11.

Munro, I.C. 2003. 1. The JECFA Procedure for the Safety Evaluation of Flavoring Substances. 2. The FEMA GRAS Program for Flavors. Presented at the Safety Assessment of Flavors – Indonesia Roundtable, Jakarta, Indonesia, December 9.

Munro, I.C. 2003. Setting Tolerable Upper Intake Levels for Nutrients. Presented at The Annual European Meeting of The Toxicology Forum, Brussels, Belgium, October 28-30.

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Munro, I.C. and Roberts, A.S. 2003. The Regulatory Evaluation of Functional Foods and Nutraceuticals – CANTOX Seminar co-sponsored by the Canadian Embassy, September 4, Tokyo, Japan.

Munro, I.C. 2003. Key Elements in Developing a Global Regulatory Strategy. Presented at the International Food Technologists' Pre-Annual Meeting Program "International Regulatory Approval of Food Ingredients and Dietary Supplements", July 11-12, Chicago, IL.

Munro, I.C. 2003. Managing and Interpreting Vitamin and Mineral Science. Presented at the EANS one-day workshop on "Risk Assessment and Beyond: Vitamins and Minerals", April 30, Brussels, Belgium.

Munro, I.C. 2003. Setting Tolerable Upper Intake Levels for Nutrients. Presented at the National Institute of Nutrition (NIN) – Annual Meeting, April 28, Toronto, ON.

Munro, I.C. 2003. Setting Tolerable Upper Intake Levels for Nutrients. Presented at ILSI North America – Understanding Tolerable Upper Levels Workshop, April 23-24, Washington, DC.

Munro, I.C. 2003. Managing and Interpreting Vitamin and Mineral Science. Presented at the European Academy of Nutritional Sciences (EANS) one-day workshop - Risk Assessment and Beyond: Vitamins and Minerals, April 20, Brussels, Belgium.

Munro, I.C. 2003. The Threshold of Toxicological Concern Concept. Presented at the ILSI Europe Workshop on Structure-based Thresholds of Toxicological Concern: Guidance for Application to Substances Present at Low Levels in the Diet, March 20-21, Vienna, Austria.

Munro, I.C. 2003. Current Dietary Supplement Safety Issues. Presented at the Food and Drug Law Institute's Conference: Dietary Supplements...At a Crossroads, January 16-17, Washington, D.C.

Munro, I.C., Hlywka, J., and Reid, J. 2003. Determining Unintended Health Effects of Biotechnology Derived Foods. Presented at the Workshop of the Committee on Identifying and Assessing the Unintended Effects of Genetically Engineered Foods on Human Health, The National Academies, January 7, Wash., D.C.

Munro, I.C. and Roberts, A.S. 2002. Functional Foods and Nutraceuticals - How to Launch Nutraceuticals on the U.S. Market. A workshop conducted by Dr. Ian Munro and Dr. Ashley Roberts in association with Archimex, November 26, Paris, France.

Munro, I.C. 2002. Setting Tolerable Upper Intake Levels for Nutrients. Presented at the workshop on "Dietary Reference Intakes and Discretionary Fortification". Sponsored by the Committee on Use of Dietary Reference Intakes in Nutrition Labelling of the Food and Nutrition Board, Institute of Medicine, November 21, Washington, DC.

Munro, I.C. 2002. Setting Tolerable Upper Intake Levels for Nutrients. Presented at the American Dietetic Association, Food & Nutrition Conference & Exhibition 2002, October 21, Philadelphia, PA.

Munro, I.C. 2002. Regulatory and Safety Requirements for Obtaining GRAS Status. Presented at the American College of Nutrition's 43rd Annual Meeting, October 3, San Antonio, TX.

Munro, I.C. 2002. The JECFA Procedure for the Safety Evaluation of Flavoring Substances. Presented at the JECFA Symposium organized by the Japanese Flavor & Fragrance Material's Association (JFFMA), September 26, Tokyo, Japan.

Munro, I.C. 2002. Risks From Acrylamide in Food. Presented at the Ceres Roundtable: Acrylamide: Lessons Learned, Plans Ahead, September 9, VirginiaTech, Alexandria, VA.

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Munro, I.C. 2002. The Precautionary Principle and the Scientific Risk Assessment Process. Presented at the International Society of Regulatory Toxicology and Pharmacology Meeting, June 21-22, Arlington, VA.

Munro, I.C. 2002. OECD/FAO Substantial Equivalence Framework for Whole Food Safety Assessment. Presented at the 41st Annual Meeting & ToxExpo, March 17-21, Nashville, TN.

Munro, I.C. 2001. Dietary Exposure from Migration of Packaging Materials. Presentation at the Joint JRC/ILSI Europe Workshop on Exposure from Food Contact Materials, October 15-16, Ispra, Italy.

Munro, I.C. 2001. Safety Evaluation of Foods Derived from Genetically Modified Crops. Presented at the 222nd American Chemical Society Meeting, August 29, Chicago, IL.

Munro, I.C. 2001. Appropriate Use of Preclinical Data in Drug Development. Presented at the joint meeting of the Michigan Chapter of the Society of Toxicology (MISOT) and the Michigan Society for Medical Research (MISMR), May 18, Ann Arbor, Michigan.

Munro, I.C. 2001. Risk Analysis of Food Derived from Genetically Modified Plants. Presented at the Food and Agriculture Organization of the United Nations' (FAO) "Seminar on Risk Analysis for Food Control: A Practical Approach Through Case Studies" organized jointly with ILSI and the University of Brasilia, May 9-11, Brasilia, Brazil.

Munro, I.C. 2000. Safety Evaluation of Foods Derived from Genetically Modified Crops. Presented at the Brazilian Association of Food Industries' "Safety Assessment of Biotechnology Derived Foods" seminar, December 5, 6 & 7, São Paulo, Brazil.

Munro, I.C. 2000. Risk Assessment of Packaging Materials. Presented at the 2nd International Symposium on Food Packaging. Ensuring Safety and Quality of Foods, November 8-10, Vienna, Austria.

Munro, I.C. 2000. EUROTOX/SOT Debate. An evaluation demonstrating that foods derived from GM crops are as safe as their traditional counterparts is an appropriate paradigm for assessing the safety of genetically modified foods. For the motion: Ian C. Munro (SOT). EUROTOX 2000, XXXVIII European Congress of Toxicology, September 17-20, London, England.

Munro, I.C. 2000. Safety of Foods Produced by rDNA Technology. Presented at the Institute of Medicine/Food and Nutrition Board Meeting, July 20, Woods Hole, MA.

Munro, I.C. 2000. Society of Toxicology/EUROTOX Debate Presentation. 2000 Society of Toxicology Annual Meeting, March 21, Philadelphia, PA.

Munro, I.C. 2000. Developing Integrated Scientific & Regulatory Strategies, Resolving Complex Scientific Issues, and Facilitating Timely Regulatory Approvals. TNO Nutrition and Food Research Institute, February 29, Zeist, The Netherlands.

Munro, I.C. 2000. Applying a Threshold of Regulation Concept to the Safety Evaluation of Packaging Materials. Nutripack Food & Beverage Packaging Congress, January 26-27, Paris, France.

Munro, I.C. 1999. Key Safety Issues in Bringing a Functional Food or Nutraceutical to Market. Nutraceutical Opportunities Summit, December 8-9, Toronto, Ontario.

Munro, I.C. 1999. The Concept of Thresholds in Safety Assessment. ILSI Europe Workshop on Threshold of Toxicological Concern for Chemical Substances Present in the Diet, October 5-6, Paris France.

Munro, I.C., Bechtel, D., Schinkel, H., and McCoil, D. 1999. Functional Foods: International Comparisons of the Scientific and Regulatory Attributes Affecting Product Development and Market Access.

Munro, I.C., McColl, D., Bailey, R., Coutrelis, N., and Schinkel, H. 1999. Special Forum: International Regulatory Issues in Marketing Functional Foods: Barriers and Opportunities. Institute of Food Technologist's Annual Meeting, July 24-28, Chicago, IL.

Munro, I.C. 1999. 1) Safety Assessment of Process Flavors. 2) Perspective of the Food and Nutrition Board's Subcommittee on Upper Reference Levels of Nutrients. 1999 Annual Summer Meeting of The Toxicology Forum, July 12 - 16, Aspen, Colorado.

Munro, I.C. 1999. The Crucial Role of Safety and Efficacy Principles for Nutraceuticals, Functional and Medical Foods - Nutraceutical, Functional & Medical Foods Conference, May 6-7, Toronto, Ontario.

Munro, I.C. 1999. Assessing the Safety of Flavoring Substances. Flavor and Extract Manufacturers' Association of the United States - 90th Annual Convention, May 2-5, Palm Beach, Florida.

Munro, I.C. 1999. Concepts in Safety Evaluation of HPV Food Substances. Vision 20/20 Workshop: TestSmart - A Humane and Efficient Approach to SIDS Data, April 26-27, Fairfax, Virginia.

Munro, I.C. 1999. Effect of Intake Level on the Safety Evaluation of Flavoring Substances. Scientific Committee on Food - DGIII - DGXXIV Joint Workshop on Chemically Defined Flavouring Substances, March 25, Brussels, Belgium.

Munro, I.C., Berndt, W., Borzelleca, J., Flamm, G., Lynch, B., Kennepohl, E., Bär, A., and Modderman, J. 1999. Erythritol: An Interpretive Summary of the Biochemical, Metabolic, Toxicological and Clinical Data. Poster presentation at the Society of Toxicology Annual Meeting, March 14-18, New Orleans, Louisiana.

Munro, I.C. 1998. FNB Model for Development of Tolerable Upper Intake Levels. Presented at the European Toxicology Forum Meeting, May 13, Brussels, Belgium.

Munro, I.C. 1998. International Perspectives for Ensuring Safe Food. Presented at the Institute of Medicine, April 29, Washington, D.C.

Munro, I.C. 1997. The Development of Tolerable Upper Intake Levels for Nutrients. Presented at the Insight Information Inc. Conference - New Nutrition Recommendations - Capitalizing on New Opportunities, December 11, Toronto, Ontario.

Munro, I.C. 1997. A Model for the Development of Upper Levels. Presented at the Dietary Reference Intakes Conference - New Vision, New Challenges, Ontario Institute for Studies in Education, November 24, Toronto, Ontario.

Munro, I.C. 1997. A Model for the Development of Tolerable Upper Intake Levels for Nutrients. Presented at the Calcium Workshop, Program in Food Safety, University of Toronto, October 30, Toronto, Ontario.

Munro, I.C. 1997. A Model for the Development of Tolerable Upper Intake Levels for Nutrients. Presented at Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride Workshop, Institute of Medicine, September 23, Washington, D.C.

Munro, I.C., Daniels, J.M., and Lynch, B.S. 1997. A Review of the Safety of Vitamin B6 (Pyridoxine): Implications for Determining the Safe Upper Intake from Dietary Supplements. Presented at Vitamin B6: New Data, New Perspectives, Council for Responsible Nutrition, September 8, London, England.

Munro, I.C., and Kroes, R. 1997. Application of a Threshold of Regulation Concept in the Safety Evaluation of Certain Flavoring Substances. Presented at the Forty-ninth Meeting of the Joint FAO/WHO Expert Committee on Food Additives, June 17-26, Rome, Italy.

Bechtel, D., Locke, L., and Munro, I.C. 1997. Need for Scientific Substantiation for Functionality of Food Components for Health Promotion. Presented at the ILSI N.A. Workshop - The Future of Functional Foods for Health Promotion: A Public Health Opportunity, June 4-5, Washington, D.C.

Munro, I.C. 1997. Need for Scientific Substantiation for Functionality of Food Components for Health Promotion. Presented at the ILSI N.A. Workshop - The Future of Functional Foods for Health Promotion: A Public Health Opportunity, June 4-5, Washington, D.C.

Munro, I.C. 1997. 2,4-D - Safety and Exposure. Presented to Poisons Centre staff, academic pharmacology staff and postgraduate students at the University of Dunedin, March 13, Dunedin, New Zealand.

Munro, I.C. 1997. 2,4-D - Safety and Exposure. Presented to toxicologists and occupational health specialists from the New Zealand Ministry of Agriculture and Ministry of Environment, March 12, Wellington, New Zealand.

Munro, I.C. 1997. Development of a Procedure for the Safety Evaluation of Flavouring Substances. Presented at the International Symposium on Flavours and Sensory related Aspects, March 6-7, Cernobbio (Como), Italy.

Munro, I.C. 1996. 1) Current Issues in the Evaluation of the Safety of Food and Food Ingredients. 2) Issues in the Safety Assessment of Carbohydrate/Fat Substitutes. Presented at the ASCEPT Toxicology Workshop, June 17-18, Canberra, Australia.

Munro, I.C. 1995. Interpretive Review of the Potential Adverse Effects of Chlorinated Organic Chemicals on Human Health and the Environment. Report of an Expert Panel. Presented at Dioxin 95, 15th International Symposium on Chlorinated Dioxins and Related Compounds, August 21-25, Edmonton, AB.

Munro, I.C. 1995. The Safety Evaluation of Flavoring Substances: The GRAS Process. Presented at the Second Workshop - Harmonization and Food Safety, April 20-21, Hong Kong.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1994. Macronutrient Substitutes: Safety Factor Alternatives and Human Mimetic Models. Thirty-third Annual Meeting of Society of Toxicology, Dallas, TX.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1994. Macronutrient Substitutes: Alternatives to Traditional Safety Testing. Annual Meeting of Institute of Food Technologists, Atlanta, Georgia.

Munro, I.C. 1993. Harmonization of Conventional Toxicology Studies - A Commentary. Presented at ILSI Conference on RedBook II, December 16, Washington, DC.

Munro, I.C. 1993. The Exposure and Toxicity of 2,4-D. Presented at The Toxicology Forum, Aspen, CO. (July).

Munro, I.C. 1992. Novel Foods, Workshop on Novel Foods and Novel Food Processes. Presented at the Program in Food Safety, Nutrition and Regulatory Affairs, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto. Toronto, ON. (November).

Munro, I.C. 1992. Toxicology and Drug Development: Managing the Issues. Presented to Ciba-Geigy Canada Ltd., Mississauga, ON. (October).

Munro, I.C. 1992. Adverse Effects and Indoor Air Pollution. Presented at the Thirteenth Annual Meeting of the American College of Toxicology, San Francisco, CA. (October).

Munro, I.C. 1992. Toxicology of Benzoyl Peroxide. Presented at The Toxicology Forum, Aspen, CO. (July).

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Munro, I.C., Borzelleca, J.F., and Squire, R.A. 1991. The Safety of Xylitol for Use in Food. Report of an Expert Panel.

Munro, I.C. 1991. Food Safety. Presented at a Food Safety Seminar Embassy of the United States, Ottawa, Ontario, Canada.

Munro, I.C., and Orr, J. 1991. Dioxins in Paper Products. Canadian Paediatric Society Workshop on Infant Diapers.

Munro, I.C., and Orr, J. 1991. The Saccharin Lesson. Presented at the Symposium on Chemical Carcinogenesis: The Relevance of Mechanistic Understanding in Toxicological Evaluation. Berlin, Germany.

Munro, I.C. 1991. Impact of Agricultural Activities on Health Risks From Drinking Water. Presented at the Interdisciplinary Symposium on Agriculture and Water Quality Centre for Soil and Water Conservation. University of Guelph, ON.

Munro, I.C. 1990. Scientific Aspects of the IFBC Report. Presented to the Toxicology Forum. Washington, DC.

Munro, I.C., and Hall, R.L. 1990. Food Safety and Quality - Impact of Biotechnology. Presented at the Agricultural Biotechnology, Food, Safety and Nutritional Quality for the Consumer Second Annual Meeting. Ithaca, NY.

Munro, I.C. 1990. Food Safety and Environmental Issues in the year 2010. Presented to the Western Canadian Wheat Growers' Association, Regina, Saskatchewan, Canada.

Munro, I.C. 1990 & 1989. Issues in Food Safety, "Later in Life Learning Series", Toronto Ontario and The Environmental Forum, Belleville, Ontario.

A MORE DETAILED LIST OF PUBLICATIONS AND PRESENTATIONS IS AVAILABLE UPON REQUEST

Aug-06

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SUBMISSION END

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APR 27 2007BY: **(b)(6)**

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

15th March 2007

Dear Sir/Madam

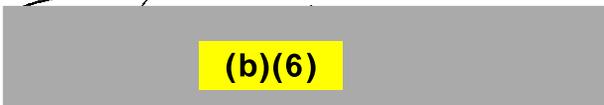
Re GRN 000210

We recently received documentation from yourselves regarding the above Grass Notice Number to our old address, namely,

10 William House
Manchester Science Park
Lloyd Street North
Manchester
M15 6SE
UK

I would be grateful if you would change your records to show our new address as given below and if you would also address all correspondence to Mr Stephen Moon, our current CEO. If you require any further clarification on this matter please contact me either by email or telephone

Yours


(b)(6)

Jane Harris
Financial Controller

Direct Line 0208 392 6639

Email jane.harris@provexis.com

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SW14 8JN

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