

3R



ORIGINAL SUBMISSION

000006

**Kyowa Hakko U.S.A., Inc.**

767 Third Avenue, 19th Fl  
New York, NY 10017

Telephone 212 319-5353

Facsimile 212 421-1283



03-07-07PC2 56 KCV6

June 26, 2003

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

**Re: GRAS Notification**

Dear Sir or Madam:

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, Kyowa Hakko U.S.A. Inc, 767 Third Avenue 19th Floor, New York, NY 10017, a GRAS notification of c-fraction soy protein hydrolyzate with bound phospholipids (CSPHP) 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

The notification replaces the incomplete notification sent earlier.

Sincerely,

Kohei Yamamoto  
Director of Marketing

000007

03-07-07P02:56 RCVD

**C-FRACTION SOY PROTEIN HYDROLYZATE WITH BOUND  
PHOSPHOLIPIDS (CSPHP) GRAS NOTIFICATION**

**GENERALLY RECOGNIZED AS SAFE (GRAS)  
EXEMPTION CLAIM**

***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:***

Kyowa Hakko USA, Inc  
767 Third Avenue, 19<sup>th</sup> Floor  
New York, NY  
10017

June 26, 2003

**000008**

CSPHP 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)]

C-Fraction Soy Protein Hydrolyzate with Bound Phospholipids (CSPHP) 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 CSPHP in food as described below is exempt from the requirement of premarket approval.

Signed,

Kohei Yamamoto  
Kyowa Hakko U S A, Inc  
767 Third Avenue, 19<sup>th</sup> Floor  
New York, NY  
10017

June 26, 2003  
Date

B. Name and Address of Notifier

Kohei Yamamoto  
Kyowa Hakko USA, Inc  
767 Third Avenue, 19<sup>th</sup> Floor  
New York, NY  
10017

C. Common Name of the Notified Substance

C-fraction soy protein hydrolyzate with bound phospholipids (CSPHP). The C stands for "crude" since the material is not further purified or fractionated following mixing of ingredients.

000009

**D. Conditions of Intended Use in Food**

The individual proposed food uses and use-levels of CSPHP are summarized in Table 1. The proposed levels in food are based on the addition of 3g/serving or per RACC. Clinical trials have demonstrated that 3 g/day is efficacious in normalizing serum cholesterol

<b>Table 1 Summary of the Individual Proposed Food Uses and Use-Levels for CSPHP in the U.S.</b>			
<b>Food Category</b>	<b>Proposed Food Use</b>	<b>Use-Levels for CSPHP (%)</b>	<b>Use-Levels for CSPHP (g/RACC<sup>1</sup>)</b>
Baked Goods and Baking Mixes	Breads	6	3
	Rolls	6	3
	Bagels	5.5	3
	English Muffins	5.5	3
Breakfast Cereals	Ready-to-Eat Cereals	5.5 - 20	3
Dairy Product Analogs	Soy/Imitation Milks	1.3	3
Fats and Oils	Margarines	21.4	3
	Salad dressings	10	3
Grain Products and Pastas	Health Bars	7.5	3
Health Beverages	Meal Replacements	1.3	3
Meat Products	Meat Patty with Soy Protein	5.5	3
Milk Products	Flavored Milk Drinks	1.3	3
	Milk Based Meal Replacements	1.3	3
	Yogurt (Regular and Frozen)	1.3-2.7	3
Plant Protein Products	Meat Alternatives	2.1 - 42.9	3
Processed Fruits and Fruit Juices	Fruit Juice	1.3	3
	Nectars	1.3	3
	Fruit-Flavored Drinks	1.3	3
Processed Vegetables and Vegetable Juices	Vegetable/Tomato Juice	1.3	3
Soups and Soup Mixes	Prepared Soups, Dry Soup Mixes, and Condensed Soups	1.2	3

<sup>1</sup>RACC – Reference amounts customarily consumed per eating occasion

**000010**

CSPHP is also sold as a dietary supplement in tablet form. Recommended consumption is also 3 g/day divided into several tablets per day.

## CSPHP NOTIFICATION

The consumption of CSPHP from all proposed food uses was estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). The mean and 90<sup>th</sup> percentile consumption of CSPHP by the total population from all proposed food uses and use as a dietary supplement was estimated to be 13.6 and 18.6 g/person/day, respectively. Based on the estimated consumption of CSPHP and the ratio of soy protein/enzymatically modified lecithin of 80/20, the mean consumption of hydrolyzed soy protein would be approximately 10.9 g/day. This is significantly lower than the recommended intake of 25 g soy protein/day required for health claims.

On a total population basis, the mean consumption of enzymatically-modified lecithin (lysolecithin) from proposed food and dietary supplement use of CSPHP could reach 2.7 g/day. The estimated daily intake (EDI) of enzymatically-modified lecithin from its approved use as an emulsifier in foods is 326 mg/day. This, taken together with the consumption of enzymatically-modified lecithin from the proposed uses of CSPHP, could potentially result in a mean intake of approximately 3.0 g/day.

The estimated consumption of lysolecithin from its natural occurrence in foods is 1.7 g/day, while the *per capita* intake of processed lecithin, most likely lecithin modified with hydrogen peroxide, is 0.19 mg/day. Although the consumption of enzymatically-modified lecithin (lysolecithin) from proposed uses of CSPHP and approved uses in food as an emulsifier exceeds the intake of lysolecithin from its natural occurrence in food, the consumption is significantly less than the consumption of lecithin from its natural occurrence in food, which is estimated to be 6.8 g/day.

### E. Basis for the GRAS Determination

000011

Pursuant to 21 CFR § 170.30, CSPHP 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 CSPHP as a component of food. The safety of CSPHP is supported by a number of published studies on CSPHP, enzymatically-modified lecithin, and soy protein, including metabolic studies, acute, and subchronic toxicity studies in experimental animals and clinical studies investigating the effects of CSPHP on serum cholesterol. This determination is further supported by an expert panel evaluation of the health aspects of CSPHP (See Appendix I – EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE STATUS OF CSPHP FOR USE IN FOODS).

In addition, the constituents of CSPHP, enzyme modified lecithin and hydrolyzed soy protein are both permitted for food use. Enzyme-modified lecithin is affirmed as GRAS under 21 CFR §184.1063 for use in food as an emulsifier with no limitation other than current good manufacturing practice. Hydrolyzed soy protein is affirmed GRAS under 21 CFR §184.1553 (peptones) as a nutrient supplement, processing aid and surface active agent at levels

CSPHP NOTIFICATION

consistent with current good manufacturing practice The protease from *Aspergillus niger* was the subject of a recent GRAS Notification (GRN 000089) based on its use in food prior to 1958

**F. Availability of Information**

The data and information that serve as the basis for this GRAS determination are generally available and are accessible from the offices of

Kohei Yamamoto  
Kyowa Hakko USA, Inc  
767 Third Avenue, 19<sup>th</sup> Floor  
New York, NY  
10017

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

**II. Detailed Information About the Identity of the Substance**

**A. Identity**

CSPHP is a light yellowish powder with a slight soy odor CSPHP is the crude form or fraction of soy protein hydrolyzate with bound phospholipids A more purified form of soy protein hydrolyzate with bound phospholipids (SPHP), which undergoes additional centrifugation and precipitation, has been used in developmental/research studies.

<b>Common or Usual Name:</b>	C-fraction soy protein hydrolyzate with bound phospholipids (CSPHP)
<b>Chemical Name:</b>	Not applicable
<b>Chemical Abstracts Service (CAS) Number:</b>	CSPHP has not been assigned a CAS number
<b>Empirical Formula and Formula Weight:</b>	Not defined
<b>Molecular weight:</b>	Not defined
<b>Structural Formula</b>	Not defined

**B. Method of Manufacture**

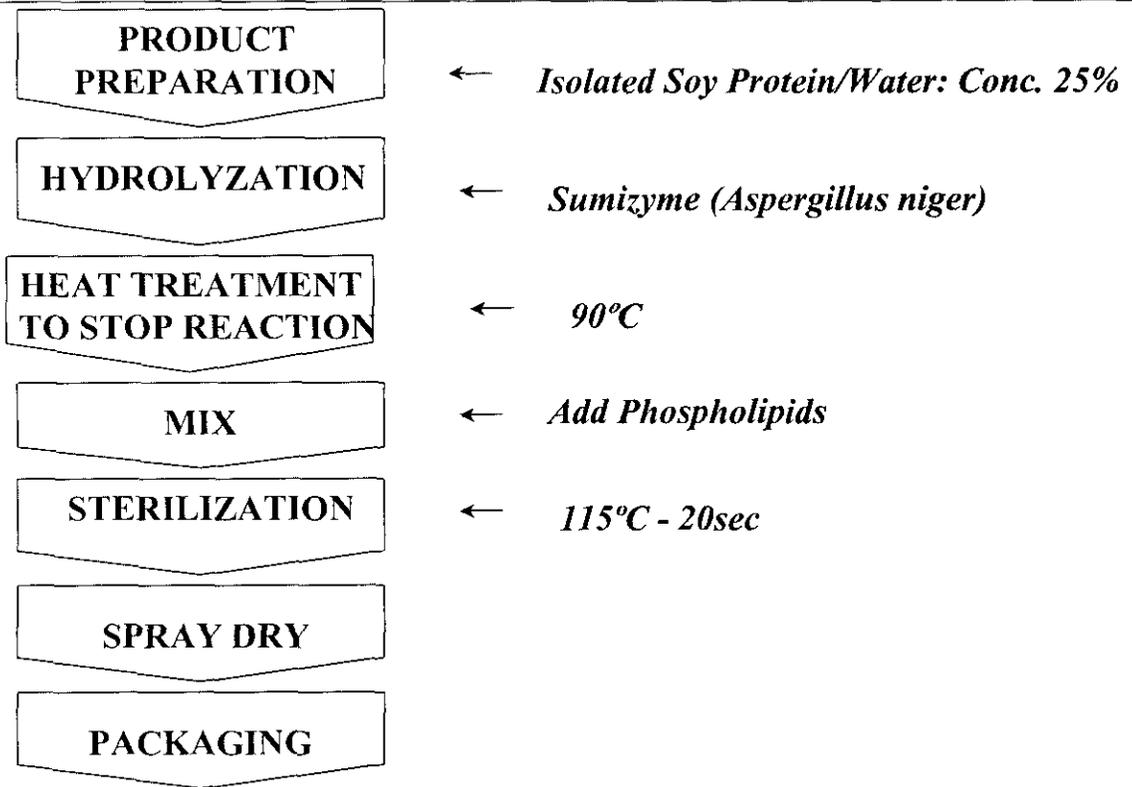
CSPHP is manufactured using isolated soy protein, a purified (deoiled) preparation of enzyme-modified lecithin, and a protease from *Aspergillus niger* (Sumizyme FP). The materials involved

000012

are appropriate for food use and meet food grade specifications. The method of manufacture of CSPHP is illustrated in Figure 1.

In general, a microbial protease (Sumizyme FP) is added to a water solution of isolated soy protein at a level of 1% (w/w) and incubated for 5 hours. The protease treatment hydrolyzes the soy protein to smaller peptides and amino acids. The mixture is then heated to 90°C for 30 minutes to inactivate the protease and stop the reaction. Enzymatically-modified lecithin is then added to the solution to achieve a final soy protein phospholipid ratio of 4:1. The resulting mixture is sterilized and freeze-dried.

**Figure 1 Schematic Overview of the Manufacturing Process for CSPHP**



**C. Specifications for Food Grade Material**

**000013**

<b>Table 2 Chemical and Microbiological Specifications for CSPHP</b>	
<b>Specification Parameter</b>	<b>Specification</b>
Appearance	Light yellowish powder having slight soy odor
Protein	>60%

CSPHP NOTIFICATION

Specification Parameter	Specification
Total Phospholipids	>18%
Free Phospholipids	<0.2%
Arsenic	<2 ppm
Heavy Metals (as Pb)	<30 ppm
Lead	<10 ppm
Loss on Drying	<7%
Microbiological Specifications	
Total Plate Count	Less than $3 \times 10^3$ /g
Escherichia coli	Negative
Thermophilic Bacteria	Less than 300/g

Component	Content (g/100 g)
lysophosphatidylcholine	25.8
glycerophosphorylethanolamine	15.4
phosphatidylinositol	13.2
lysophosphatidic acid	8.4
phosphatidylcholine	8.1
phytic acid	7.0
phosphatidylethanolamine	5.4
phosphatidic acid	4.9
glycerophosphoinositol	3.5
triglyceride	3.0
lysophosphatidylethanolamine	0.1
lysophosphatidylinositol	0.1

**000014**

As with all soy protein containing products, CSPHP contains moderate amounts of isoflavones. Specific analysis indicated that CSPHP contained genistin, daidzin and glycitein at levels quantified as the aglycones, genistein (96 mg/100g CSPHP), daidzein (49 mg/100 g CSPHP) and glycitein (9.5 mg/100 g CSPHP). Thus a heavy consumer of foods and dietary supplements

## CSPHP NOTIFICATION

containing CSPHP may consume up to 38 mg total isoflavones equivalents as the aglycone, considerably less than the heavy consumer of soy protein containing products.

In addition, soy protein-containing products have been reported to contain trypsin inhibitors. Typical trypsin inhibitor levels present in soy protein isolates are reported to range from 1.11 to 4.49 mg/g protein (Peace *et al.*, 1992). However, heat treatment and processing of soy products are known to significantly reduce trypsin inhibitor levels (Rackis *et al.*, 1979, Peace *et al.*, 1992). Thus, as a result of the drying process and treatment with protease during the manufacturing process, the level of trypsin inhibitor present in CSPHP is anticipated to be greatly reduced.

### III. Self-Limiting Levels of Use

Although soy protein isolates and hydrolyzates have more favorable organoleptic properties than other soy ingredients such as soy flour, soy protein isolates and hydrolyzates have "beany" and bitter flavoring characteristics that limit the amounts of CSPHP that can be formulated into food products.

### IV. Basis for GRAS Determination

The determination that CSPHP is GRAS is on the basis of scientific procedures. (See Appendix I – EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF C-FRACTION SOY PROTEIN HYDROLYZATE WITH BOUND PHOSPHOLIPIDS (CSPHP) FOR USE IN FOODS).

The safety of soy protein concentrates and isolates have been well established in animal feeding trials, clinical trials and from widespread historical consumption (Anastasia *et al.*, 1990; Wang *et al.*, 1995, Gooderham *et al.*, 1996, Nestel *et al.*, 1997; Baum *et al.*, 1998, Nagata *et al.*, 1998; Potter *et al.*, 1998, Crouse *et al.*, 1999; Hodgson *et al.*, 1999; Samman *et al.*, 1999; Jenkins *et al.*, 2000, Teede *et al.*, 2001, Badger *et al.*, 2002, Dewell *et al.*, 2002, Munro *et al.*, 2003). Regardless, there are a number of minor components in soybeans and soybean products that have historically raised safety concerns, for example, trypsin inhibitors and isoflavones. The significance of these compounds in CSPHP in relation to the safety of CSPHP is discussed below.

The estimated consumption of soy protein hydrolyzate for the heavy consumer from proposed uses of CSPHP is 14.9 g/day (90<sup>th</sup> percentile consumer).

000015

## Effects Related to Soy Isoflavones

### Estrogenic Effects

The structural similarity of the soy isoflavones to estrogen has prompted studies into the estrogenic effects of the isoflavones, particularly genistein and daidzein. Numerous clinical studies have been conducted to assess the effects of isoflavones on the proliferation of estrogen-sensitive tissues, circulating hormone levels, fertility, and sexual development.

Studies in premenopausal women consuming soy-based diets in which the soy isoflavone content ranged from <5 to 128 mg/person/day for 1 menstrual cycle have demonstrated a number of estrogenic effects, including increased breast lobular epithelium proliferation, increased follicular phase length, prolonged menstruation, increased or decreased estrogen levels, increased luteinizing hormone and follicle-stimulating hormone levels, decreased progesterone levels, delayed peak progesterone concentrations, and decreased mean luteal cycle length (Cassidy *et al.*, 1994, 1995, Lu *et al.*, 1996; 2000; 2001; McMichael-Phillips *et al.*, 1998, Watanabe *et al.*, 2000, Wu *et al.*, 2000) However, longer-term studies in which premenopausal women consumed diets containing soy isoflavones ranging from 10 to 128 mg/person/day for up to 3 menstrual cycles showed no significant effects on breast tissue proliferation, menstrual cycle length, or hormone levels (Nagata *et al.*, 1998; Duncan *et al.*, 1999, Hargreaves *et al.*, 1999; Martini *et al.*, 1999) In addition, studies in postmenopausal women reported no significant effects following consumption of 37.4 or 103 mg soy isoflavones/person/day for up to 6 months (Baird *et al.*, 1995, Petrakis *et al.*, 1996)

Petrakis *et al.* (1996) reported stimulation of breast epithelium and increased nipple aspirate fluid in premenopausal women who consumed approximately 38 g of soy protein/day (37.4 mg genistein/day) for a period of 6 months. However, no effects were observed in postmenopausal women and a control group was not used in the study. The authors concluded that results were "suggestive of an estrogenic stimulus", but noted that the sample size (14 subjects) was very small and that further studies with a large sample size be conducted.

Studies on the effect of soy diets on endocrine function in men have revealed some conflicting results. Habito *et al.* (2000) reported an increase in sex hormone-binding globulin but no change in serum estradiol concentrations in Caucasian men who consumed tofu (containing approximately 119 mg/person/day of isoflavones) for a period of 4 weeks, while Mitchell *et al.* (2001) reported no significant effects following consumption of 40 mg isoflavones/person/day for a period of 8 weeks. A decrease in estrogen levels was reported in Japanese men who consumed soy foods (containing approximately 22 mg soy isoflavones/person/day) for a 1-year period (Nagata *et al.*, 2000)

000016

## CSPHP NOTIFICATION

Although studies of the estrogenic effects of soy isoflavones have produced some conflicting results, high levels of soy consumption in Asian populations have produced no adverse effects on endocrine function, reproduction, or sexual development (Badger *et al.*, 2002; Munro *et al.*, 2003). In addition, the incidence of breast cancer in these populations has been reported to be lower than that of North American populations (Cassidy, 1996; Wiseman, 1997; Messina and Bannink, 1998). Furthermore, dietary intervention studies provide evidence for the safety of chronic intake of soy isoflavones at levels of up to 131 mg/day for periods of up to 6 months (Gooderham *et al.*, 1996; Nestel *et al.*, 1997; Baum *et al.*, 1998; Potter *et al.*, 1998; Crouse *et al.*, 1999; Hodgson *et al.*, 1999; Samman *et al.*, 1999; Jenkins *et al.*, 2000; Teede *et al.*, 2001; Dewell *et al.*, 2002). Soy isoflavones were well-tolerated and no adverse effects were reported.

### Infant Exposure

There has been concern expressed over early exposure to soy, in particular, infant exposure to soy protein-based formulas. Human exposure to high levels of estrogens occurs only after puberty, however, high circulating concentrations of estrogenic isoflavones have been reported in infants fed soy formula, prompting concerns over the possible adverse effects of soy isoflavones on the development of the reproductive system. Infants fed soy formula have been reported to have plasma concentrations of isoflavones that are approximately 50 to 100 times higher than  $17\beta$ -estradiol (E2) concentrations in pregnant women, and 3,000 times higher than the E2 concentrations that occur during the estrogen surge of the menstrual cycle (Badger *et al.*, 2002). However, the isoflavone genistein is frequently assumed to be approximately 1,000 times less potent than E2 (Badger *et al.*, 2002). Multigenerational studies have shown no significant differences in the number of offspring, gender ratios, birth weights, birth lengths, health, and general appearance of rats fed soy-based diets when compared to casein controls (Badger *et al.*, 2001). Vaginal opening was reported to occur 1 day earlier in soy-fed rats; however, the significance of this finding was determined to be unclear due to the fact that early puberty is "not a recognized issue in Asia" (Badger *et al.*, 2002). Soy-based foods have been historically consumed in high amounts in Asian populations with no deleterious effects. No significant adverse effects on fetal development or subsequent reproductive development have been reported in children born to Asian women who consumed soy-based diets throughout pregnancy (Badger *et al.*, 2002). Furthermore, only the sulfate and glucuronide conjugates of isoflavones were detected in the plasma of infants exclusively fed soy formula, both of which would be rapidly excreted (Huggett *et al.*, 1997).

Thus, even in infants consuming significantly more isoflavones than individuals consuming CSPHP, there were no adverse effects. Considering that CSPHP is not directed towards infants or young children, these groups will not be exposed to significant levels of isoflavones from consumption of CSPHP.

000017

## Thyroid

The soy isoflavones genistein and daidzein also have been reported to be irreversible inhibitors of thyroid peroxidase (TPO), the enzyme that produces the thyroid hormones triiodothyronine (T3) and thyroxine (T4) (Divi *et al.*, 1997; Fitzpatrick, 2000; Doerge and Sheehan, 2002), prompting concerns about the development of goiter. The goitrogenic activity of soy isoflavones has been demonstrated in rats and humans, however, this activity was reported to be inhibited by dietary iodide supplementation (Kimura *et al.*, 1976; Doerge and Sheehan, 2002; Munro *et al.*, 2003). In a review of numerous animal studies on the effects of soy isoflavones on the thyroid, Doerge and Chang (2002) concluded, "the absence of observed hypothyroid indicators in rats following genistein consumption, despite extensive inactivation of TPO, and from mixed isoflavone consumption, makes it clear that additional risk factors for thyroid dysfunction, particularly iodine deficiency, are necessary before soy consumption can induce anti-thyroid effects in rats." In the 1960's, supplementation of infant soy formulas with iodine was initiated to mitigate the effects of soy on the thyroid (Fitzpatrick, 2000, Doerge and Sheehan, 2002; Munro *et al.*, 2003). Ishizuki *et al.* (1991) reported goiter and increased thyroid-stimulating hormone (TSH) levels in healthy adults within 1 month of consuming diets that included 30 g soybeans per day, however, the dietary iodide content was not measured, and no changes in serum thyroid hormone levels occurred (Doerge and Sheehan, 2002). No adverse effects on thyroid function have been reported in other controlled clinical and non-clinical studies with dietary soy isoflavones (Chang and Doerge, 2000, Son *et al.*, 2001, Persky *et al.*, 2002). Furthermore, the incidence of goiter has not been reported to be increased in populations that traditionally consume high amounts of soy in the diet (Munro *et al.*, 2003). Exposure to soy isoflavones from CSPHP is therefore not expected to induce adverse effects on the thyroid.

## Effects Related to Soy Proteins

### Allergenicity of Soy Protein

Soy protein has been reported to be less sensitizing than cow-milk proteins when tested in animal models (Businco *et al.*, 1998). In addition, soy protein has been reported to induce more complete tolerance in rabbits than cow-milk proteins (Eastham *et al.*, 1982). In a review of the literature on the allergenicity of soy protein, Businco *et al.* (1998) concluded that numerous reports of soy protein sensitization or allergy in humans fail to use any scientific diagnostic criteria or oral challenge to soy to demonstrate true allergenicity. Other studies that employed placebo-controlled challenge tests to soy reported a 4 to 7% incidence of soy sensitivity in patients with atopic dermatitis or cow's milk allergy (Giampietro *et al.*, 1992; Businco *et al.*, 1998). In addition, Giampietro *et al.* (1992) reported a lower incidence of sensitization and immunoglobulin E (IgE) formation in response to soy when compared to cow-milk protein.

000018

## Trypsin Inhibitors

Soy proteins have long been reported to contain trypsin inhibitors, which has prompted investigations of the effects of soy proteins on the pancreas. Gumbmann *et al.* (1985) reported nodular hyperplasia and acinar adenoma of the pancreas in male Wistar rats fed diets containing soy flour or soy protein isolate at protein levels of 10 to 30% and trypsin inhibitor levels of 93 to 1,271 mg/100 g diet for a period of 2 years. Conversely, diets containing raw or toasted soy flour, soy protein isolate or soy concentrate at protein levels of 24 or 30% and comparable trypsin inhibitor levels for periods of up to 18 months were reported not to induce the formation of pancreatic lesions in rats (Rackis *et al.*, 1979; Richter and Schneeman, 1987). Pancreatic hypertrophy and increased pancreatic enzyme and protein levels were reported, however, these changes were demonstrated to be reversible (Rackis *et al.*, 1979, Richter and Schneeman, 1987). Sensitivity to trypsin inhibitors from soy also has been reported to have interspecies variability (Flavin, 1982, Richter and Schneeman, 1987, Liener, 1995; Friedman and Brandon, 2001). Ausman *et al.* (1985) reported no significant changes in pancreatic protein, RNA and trypsin concentrations or any evidence of pancreatic hypertrophy or hyperplasia in monkeys fed diets containing soy protein isolate and 65.5 mg trypsin inhibitor/100 g diet. Diffuse interstitial fibrosis of the pancreas, mild to moderate atrophy of the acinar tissue and decreased pancreatic protein, DNA, RNA, trypsin, and chymotrypsin levels were reported in 1 of 2 monkeys fed diets containing soy concentrate with 2,419 mg trypsin inhibitor/100 g diet, however, no adverse effects were observed in the second monkey, and due to the small population size, no conclusions on the effect of soy concentrate could be reached (Ausman *et al.*, 1985). The trypsin inhibitor levels present in soy protein isolates is reported to range from 1.11 to 4.49 mg/g protein, which is comparable to the levels present in commercial infant soy formulas and several-fold lower than the levels present in raw soybeans (34.30 to 56.14 mg/g protein) (Peace *et al.*, 1992). The expected level of trypsin inhibitors in CSPHP is many times lower than levels found to have effects in animal studies.

## Conclusions

Clinical studies in which subjects consumed isolated soy protein or soy isoflavones have provided no definitive data that indicate that the effects of these compounds would pose serious health effects to consumers. Furthermore, epidemiological studies of populations that traditionally consume high amounts of soy in the diet have not demonstrated any adverse effects on reproduction, endocrine function, sexual development, or digestive function. The consumption of isolated soy protein and soy isoflavones from CSPHP is therefore not anticipated to have any deleterious health effects.

000019

References

- Anastasia, J V , Braun, B L , Smith, K T. 1990. General and histopathological results of a two-year study of rats fed semi-purified diets containing casein and soya protein. *Food Chem Toxicol* 28(3).147-156
- Ausman, L M , Harwood, J.P., King, N W ; Sehgal, P.K ; Nicolosi, R.J ; Hegsted, D.M.; Liener, I.E , Donatucci, D , Tarcza, J 1985. The effects of long-term soy protein and milk protein feeding on the pancreas of *Cebus albifrons* monkeys *J Nutr* 115(12).1691-1701
- Badger, T M , Ronis, M J , Hakkak, R 2001 Developmental effects and health aspects of soy protein isolate, casein, and whey in male and female rats. *Int J Toxicol* 20(3):165-174
- Badger, T M , Ronis, M J., Hakkak, R ; Rowlands, J C., Korourian, S. 2002 The health consequences of early soy consumption. *J Nutr* 132(3).559S-565S
- Baird, D D , Umbach, D M., Lansdell, L , Hughes, C L., Setchell, K D.R., Weinberg, C R., Haney, A F , Wilcox, A J., and McLachlan, J A 1995. Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. *J Clin Endocrinol Metab* 80(5) 1685-1690
- Baum, J A , Teng, H ; Erdman, J W (Jr), Weigel, R.M ; Klein, B P.; Persky, V.W.; Freels, S., Surya, P , Bakhit, R.M , Ramos, E., Shay, N F., Potter, S M. 1998. Long-term intake of soy protein improves blood lipid profiles and increases mononuclear cell low-density-lipoprotein receptor messenger RNA in hypercholesterolemic, postmenopausal women *Am J Clin Nutr* 68.545-51.
- Businco, L , Bruno, G , Giampietro, P.G 1998 Soy protein for the prevention and treatment of children with cow-milk allergy *Am J Clin Nutr* 68(Suppl).1447S-1452S
- Cassidy, A 1996 *Physiological effects of phyto-estrogens in relation to cancer and other human health risks* *Proc Nutr Soc* 55(1B).399-417
- Cassidy, A , Bingham, S , Setchell, K D R 1994 Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women *Am J Clin Nutr* 60:333-40
- Cassidy, A , Bingham, S ; Setchell, K 1995 Biological effects of isoflavones in young women. Importance of the chemical composition of soybean products. *Br J Nutr* 74(4):587-601.
- Chang, H C , Doerge, D R 2000 *Dietary genistein inactivates rat thyroid peroxidase in vivo without an apparent hypothyroid effect* *Toxicol Appl Pharmacol* 168(3).244-252.

000020

## CSPHP NOTIFICATION

- Crouse, J R (III); Morgan, T., Terry, J G , Ellis, J , Vitolins, M , Burke, G.L 1999. A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. *Arch Intern Med* 159 2070-6
- Dewell, A , Hollenbeck, C B , Bruce, B. 2002 The effects of soy-derived phytoestrogens on serum lipids and lipoproteins in moderately hypercholesterolemic postmenopausal women *J Clin Endocrinol Metab* 87 118-21
- Divi, R I , Chang, C , Doerge, D R 1997 Anti-thyroid isoflavones from soybean. Isolation, characterization, and mechanisms of action *Biochem Pharmacol* 54(10).1087-1096.
- Doerge, D R , Chang, H C 2002. Inactivation of thyroid peroxidase by soy isoflavones, in vitro and in vivo *J Chromatogr B Analyt Technol Biomed Life Sci* 777(1&2) 269-279.
- Doerge, D R , Sheehan, D.M 2002 Goitrogenic and estrogenic activity of soy isoflavones. *Environ Health Perspect* 110(Suppl 3):349-353
- Duncan, A M 1999 Hormonal effects of soy isoflavone in pre and post menopausal women PhD Thesis University of Minnesota, Minneapolis, Minnesota.
- Eastham, E J , Lichauco, T , Pang, K ; Walker, W A 1982. Antigenicity of infant formulas and the induction of systemic immunological tolerance by oral feeding: cow's milk versus soy milk *J Pediatr Gastroenterol Nutr* 1(1) 23-28 Cited In: Businco *et al.*, 1998.
- Fitzpatrick, M 2000 Soy formulas and the effects of isoflavones on the thyroid. *N Z Med J* 113(1103) 24-26
- Flavin, D F 1982 The effects of soybean trypsin inhibitors on the pancreas of animals and man. A review *Vet Hum Toxicol* 24(1):25-28.
- Friedman, M , Brandon, D L 2001 Nutritional and health benefits of soy proteins. *J Agric Food Chem* 49(3) 1069-1086
- Giampietro, P G , Ragno, V , Daniele, S.; Cantani, A., Ferrara, M ; Businco, L 1992. Soy hypersensitivity in children with food allergy. *Ann Allergy* 69(2).143-146
- Gooderham, M H , Adlercreutz, H , Ojala, S T., Wahalä, K ; Holub, B.J 1996. A soy protein isolate rich in genistein and daidzein and its effects on plasma isoflavone concentrations, platelet aggregation, blood lipids and fatty acid composition of plasma phospholipid in normal men *J Nutr* 126(8) 2000-2006.

000021

CSPHP NOTIFICATION

- Gumbmann, M R , Spangler, W.L , Dugan, G M., Rackis, J.J.; Liener, I E. 1985. The USDA trypsin inhibitor study. IV The chronic effects of soyflour and soy protein isolate in rats after two years Qual Plant Plant Foods Hum Nutr 35:275-314
- Habito, R C , Montalto, J , Leslie, E , Ball, M J 2000. Effects of replacing meat with soyabean in the diet on sex hormone concentrations in healthy adult males. Br J Nutr 84:557-63.
- Hargreaves, D F , Potten, C S , Harding, C , Shaw, L E , Morton, M S., Roberts, S A.; Howell, A.; Bundred, N J 1999 Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast J Clin Endocrinol Metab 84(11).4017-4024
- Hodgson, J M , Puddey, I B , Croft, K D., Mori, T A ; Rivera, J , Beilin, L.J 1999. Isoflavonoids do not inhibit *in vivo* lipid peroxidation in subjects with high-normal blood pressure. Atherosclerosis 145 167-72
- Huggett, A C , Pridmore, S., Malnoe, A , Haschke, F.; Offord, E A. 1997. Phyto-estrogens in soy-based infant formula Lancet 350 815-816
- Ishizuki, Y , Hirooka, Y , Murata, Y , Togasho, K 1991 The effects on the thyroid gland of soybeans administered experimentally to healthy subjects Folia Endocrinologica Japonica (Nihon Naibunri Gakkai Zasshi) 67(5).622-629 Cited In. Doerge and Sheenan, 2002
- Jenkins, D J , Kendall, C W ; Garsetti, M., Rosenberg-Zand, R S.; Jackson, C.J , Agarwal, S., Rao, A V , Diamandis, E P , Parker, T , Faulkner, D , Vuksan, V ; Vidgen, E. 2000. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial Metabolism 49:537-43
- Kimura, S , Suwa, J , Ito, B ; Sato, H 1976 Development of malignant goiter by defatted soybean with iodine-free diet in rats. GANN 67(5).763-765.
- Liener, I E 1995 Possible adverse effects of soybean anticarcinogens. J Nutr 125(3, Suppl ) 744S-750S
- Lu, L -J W , Anderson, K E., Grady, J J , Nagamani, M 1996. Effects of soya consumption for one month on steroid hormones in premenopausal women. Implications for breast cancer risk reduction Cancer Epidemiol Biomarkers Prev 5 63-70.
- Lu, L -J W , Anderson, K E , Grady, J J ; Kohen, F., Nagamani, M 2000 Decreased ovarian hormones during a soya diet Implication for breast cancer prevention Cancer Res 60 4112-21

000022

CSPHP NOTIFICATION

- Lu, L -J W , Anderson, K E , Grady, J J., Nagamani, M 2001. Effects of an isoflavone-free soy diet on ovarian hormones in premenopausal women *J Clin Endocrinol Metab* 86:3045-52
- Martini, M C , Dancisak, B B , Haggans, C.J., Thomas, W , Slavin, J.L. 1999 Effects of soy intake on sex hormone metabolism in premenopausal women *Nutr Cancer* 34(2):133-139
- McMichael-Phillips, D F , Harding, C , Morton, M , Roberts, S.A ; Howell, A.; Potten, C S.; Bundred, N J 1998 Effects of soy-protein supplementation on epithelial proliferation in histologically normal human breast *Am J Clin Nutr* 68(Suppl ) 1431S-1436S
- Messina, M , Bennink, M. 1998 Soyfoods, isoflavones and risk of colonic cancer. A review of the in vitro and in vivo data *Baillieres Clin Endocrinol Metab* 12(4):707-728
- Mitchell, J H , Cawood, E , Kinniburgh, D ; Provan, A ; Collins, A.R., Irvine, D.S. 2001 Effect of a phytoestrogen food supplement on reproductive health in normal males. *Clin Sci* 100 613-8
- Munro, I C , Harwood, M , Hlywka, J J , Stephen, A M , Doull, J., Flamm, W.G.; Adlercreutz, H 2003 Soy isoflavones: A safety review. *Nutrition Reviews* 61(1):1-33.
- Nagata, C , Takatsuka, N , Inaba, S , Kawakami, N., Shimizu, H. 1998. Effect of soymilk consumption on serum estrogen concentrations in premenopausal Japanese women *J Natl Cancer Inst* 90(23) 1830-1835.
- Nagata, C , Inaba, S , Kawakami, N , Kakizoe, T , Shimizu, H. 2000 Inverse association of soy product intake with serum androgen and estrogen concentrations in Japanese men. *Nutr Cancer* 36 14-18
- Nestel, P J , Yamashita, T , Sasahara, T , Pomeroy, S ; Dart, A ; Komesaroff, P.; Owen, A.; Abbey, M 1997 Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol* 17.3392-8
- Peace, R W , Sarwar, G., Touchburn, S P. 1992 Trypsin inhibitor levels in soy-based infant formulas and commercial soy protein isolates and concentrates. *Food Res Int* 25(2) 137-141
- Persky, V W , Turyk, M E , Wang, L ; Freels, S., Chatterton, R. (Jr ), Barnes, S.; Erdman, J. (Jr.), Sepkovic, D W , Bradlow, H L , Potter, S 2002 Effect of soy protein on endogenous hormones in postmenopausal women *Am J Clin Nutr* 75(1):145-153.

000023

CSPHP NOTIFICATION

- Petrakis, N L , Barnes, S , King, E B , Lowenstein, J.; Wiencke, J.; Lee, M.M.; Mirke, R.; Kirk, M ; Coward, L 1996 Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women *Cancer Epidemiol Biomarkers Prevent* 5(10):785-794.
- Potter, S M , Baum, J A , Teng, H , Stillman, R.J.; Shay, N.F.; Erdman, J W (Jr). 1998. Soy protein and isoflavones Their effects on blood lipids and bone density in postmenopausal women *Am J Clin Nutr* 68(Suppl ):1375-9.
- Rackis, J J , McGee, J E , Gumbmann, M R , Booth, A N 1979. Effect of soy protein containing trypsin inhibitors in long term feeding studies in rats. *J Am Oil Chem Soc* 56:162-168.
- Richter, B D , Schneeman, B O 1987 Pancreatic response to long-term feeding of soy protein isolate, casein or egg white in rats *J Nutr* 117(2).247-252
- Samman, S , Wall, P M L , Chan, G S M ; Smith, S J ; Petocz, P. 1999. The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women *Atherosclerosis* 147:277-83.
- Son, H Y , Nishikawa, A , Ikeda, T , Imazawa, T., Kimura, S., Hirose, M. 2001 Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine-deficient diet *Jpn J Cancer Res* 92(2) 103-108.
- Teede, H J , Dalais, F S , Kotsopoulos, D ; Liang, Y -L ; Davis, S.; McGrath, B.P. 2001. Dietary soy has both beneficial and potentially adverse cardiovascular effects. A placebo-controlled study in men and postmenopausal women *J Clin Endocrinol Metab* 86:3053-60
- USDA 2002 Food Consumption (Data) *Per Capita* System. U S. Department of Agriculture. Commodity Economics Division, Economic Research Service [[http //www ers.usda gov/data/foodconsumption/spreadsheets asp](http://www.ers.usda.gov/data/foodconsumption/spreadsheets.asp)]
- Wang, M -F , Yamamoto, S., Chung, H -M., Chung, S.Y., Miyatani, S ; Mori, M ; Okita, T ; Sugano, M 1995 Antihypercholesterolemic effect of undigested fraction of soybean protein in young female volunteers. *J Nutr Sci Vitaminol* 41(2):187-195.
- Watanabe, S , Terashima, K , Sato, Y , Arai, S.; Eboshida, A. 2000. Effects of isoflavone supplement on healthy women *Biofactors* 12 233-41.
- Wiseman, H 1997. Dietary phytoestrogens. *Disease prevention versus potential hazards. Nutr Food Sci* (1):32-38
- Wu, A H , Stanczyk, F L Z , Hendrich, S ; Murphy, P.A., Zhang, C , Wan, P.; Pike, M.C. 2000. Effects of soy foods on ovarian function in premenopausal women. *Br J Cancer* 82:1879-86

000024

Appendix 1

2

**APPENDIX 1**

**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE  
(GRAS) STATUS OF C-FRACTION SOY PROTEIN HYDROLYZATE WITH BOUND  
PHOSPHOLIPIDS (CSPHP) FOR USE IN FOODS**

**000026**

**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS  
SAFE (GRAS) STATUS OF C-FRACTION SOY PROTEIN HYDROLYZATE  
WITH BOUND PHOSPHOLIPIDS (CSPHP) FOR USE IN FOODS**

**December 12, 2002**

**INTRODUCTION**

As independent experts qualified by relevant national and international experience and scientific training to evaluate the safety of food ingredients, we, the undersigned, Joseph F. Borzelleca, Ph D (Medical College of Virginia), W Gary Flamm, Ph D (Flamm Associates), and Walter H Glinsmann, M D (Glinsmann, Inc ), were requested by the manufacturer, Kyowa Hakko USA, Inc , as an Expert Panel (hereinafter referred to as the Panel) to evaluate the safety and to determine the Generally Recognized As Safe (GRAS) status of C-Fraction Soy Protein Hydrolyzate with Bound Phospholipids (CSPHP) for use in foods. *Curricula vitae* evidencing the qualifications of the Panel for evaluating the safety of food ingredients are provided in Attachment 1

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature and other published sources. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by Kyowa Hakko USA, Inc. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, the intended use of CSPHP in foods, exposure data, and comprehensive literature on the safety of CSPHP and its individual components.

Following independent and collective critical evaluation of available data and information summarized herein, the Panel was asked to render an opinion on whether CSPHP, meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices, is Generally Recognized As Safe (GRAS) based on scientific procedures.

**COMPOSITION, MANUFACTURING AND SPECIFICATIONS**

CSPHP is composed of 80% soy protein isolate and 20% enzymatically-modified lecithin, which are homogenized and subjected to proteolysis by a protease from *Aspergillus niger*. The protease treatment hydrolyses the soy protein to smaller peptides and amino acids. The protease activity is heat inactivated during the manufacturing process and the final product is spray dried. All starting materials and processing chemicals involved in the manufacturing

**000027**

process meet food grade specifications of the Food Chemicals Codex. Product specifications are presented in Table 1.

## REGULATORY STATUS

The constituents of CSPHP, enzyme modified lecithin and hydrolyzed soy protein are both permitted for food use. Enzyme-modified lecithin is affirmed as GRAS under 21 CFR §184.1063 for use in food as an emulsifier with no limitation other than current good manufacturing practice. Hydrolyzed soy protein is affirmed GRAS under 21 CFR 184.1553 (peptones) as a nutrient supplement, processing aid and surface active agent at levels consistent with current good manufacturing practice. The protease from *Aspergillus niger* was the subject of a recent GRAS Notification (GRN 000089) based on its use in food prior to 1958.

## INTENDED USE

The individual proposed food uses and use-levels of CSPHP are summarized in Table 2. The proposed levels in food are based on the addition of 3g/serving or per Reference Amount Customarily Consumed (RACC). Clinical trials have demonstrated that 3 g/day is efficacious in maintaining normal serum cholesterol levels.

CSPHP is also sold as a dietary supplement in tablet form. Recommended consumption is also 3 g/day divided into several tablets per day.

## EXPOSURE ESTIMATES

The consumption of CSPHP from all proposed food uses was estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996) and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). The mean and 90<sup>th</sup> percentile consumption of CSPHP by the total population from all proposed food uses and use as a dietary supplement cumulatively was estimated to be 13.6 and 18.6 g/person/day, respectively. Based on the estimated consumption of CSPHP and the ratio of soy protein/enzymatically modified lecithin of 80/20, the mean consumption of hydrolyzed soy protein would be approximately 10.9 g/day. This is significantly lower than the recommended intake of 25 g soy protein/day required for health claims.

On a total population basis, the mean consumption of enzymatically-modified lecithin (lysolecithin) from proposed food and dietary supplement use of CSPHP could reach 2.7 g/day. The estimated daily intake (EDI) of enzymatically-modified lecithin from its approved use as an emulsifier in foods is 326 mg/day. This, taken together with the consumption of enzymatically-modified lecithin from the proposed uses of CSPHP, could potentially result in a mean intake of approximately 3.0 g/day (0.06 g/kg bw/day).

000028

The estimated consumption of lysolecithin from its natural occurrence in foods is 1.7 g/day, while the *per capita* intake of processed lecithin, most likely lecithin modified with hydrogen peroxide, is 0.19 mg/day. Although the consumption of enzymatically-modified lecithin (lysolecithin) from proposed uses of CSPHP and approved uses in food as an emulsifier exceeds the intake of lysolecithin from its natural occurrence in food, the consumption is significantly less than the consumption of lecithin from its natural occurrence in food, which is estimated to be 6.8 g/day.

## **DATA PERTAINING TO SAFETY**

The safety of CSPHP is based on (a) metabolic, toxicological, and clinical studies on the components of CSPHP, and (b) mutagenicity, toxicological and clinical studies of CSPHP.

## **ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)**

CSPHP is expected to be metabolized in the gastrointestinal tract to its components, enzymatically modified lecithin (lysolecithin) and soy protein peptides/amino acids. Soy protein peptides are expected to undergo normal further degradation to amino acids by proteases in the gastrointestinal tract and will not be discussed further. The absorption, distribution, metabolism, and elimination of lysolecithin are discussed below.

Lysolecithin has been reported to be the predominant phospholipid in the human small intestine, accounting for 62 to 100% of the total lipid phosphorus content (Borgström, 1957; Saunders *et al.*, 1968). It has been postulated that in humans, lecithin produced in the bile and provided by the diet must first be converted to lysolecithin prior to absorption by the enterocyte and transfer from the blood to other tissues (Scow, *et al.*, 1967; Tso and Scobey, 1986). Lysolecithin has been reported to be completely and rapidly absorbed from the small intestine following oral and intraduodenal administration in laboratory animals and distributed to a number of tissues, including liver, lung, brain, kidney, and skeletal muscle (Stein and Stein, 1966; Saunders *et al.*, 1968; Sato, 1970; Akino *et al.*, 1972; Portman and Illingworth, 1974).

Lysolecithin has been reported to be metabolized by most tissues, with the predominant sites of metabolism being the liver and small intestine (Tso and Scobey, 1986). Three possible pathways have been identified for the metabolism of lysolecithin: direct acylation to lecithin (Stein and Stein, 1966; Nilsson, 1968; Sato, 1970; Subbaiah *et al.*, 1970; Akino *et al.*, 1972; Portman and Illingworth, 1974; Tso and Scobey, 1986); hydrolysis to form glycerophosphocholine (GPC) and water-soluble products (Portman and Illingworth, 1974; Tso and Scobey, 1986), and transesterification of 2 lysolecithin molecules to yield lecithin and GPC (Subbaiah and Ganguly, 1971; Subbaiah and Bagdade, 1978; Tso and Scobey, 1986). Small amounts of lysolecithin have been reported to be excreted in the feces (Saunders *et al.*, 1968).

**000029**

## MECHANISM OF SERUM CHOLESTEROL-MAINTENANCE EFFECTS OF CSPHP

CSPHP has been demonstrated to help maintain normal serum cholesterol levels in humans by inhibiting the absorption of dietary cholesterol. *In vitro* studies have shown that soy protein peptic hydrolysate with bound phospholipids (SPHP), a purified form of CSPHP, alters the micellar stability of cholesterol, thereby affecting the solubility of cholesterol (Nagaoka *et al.*, 1999). In addition, SPHP has been demonstrated to have a high bile acid-binding capacity and has been shown to increase fecal bile acid excretion in rats, indicating that SPHP may also inhibit the reabsorption of bile acids and thus control the plasma level of cholesterol by this mechanism (Nagaoka *et al.*, 1999).

Clinical studies of CSPHP at doses of 3 to 9 g/day in normocholesterolemic and hypercholesterolemic subjects have demonstrated the efficacy of CSPHP in maintaining normal serum cholesterol and LDL cholesterol levels, and in suppressing the expected increase in serum cholesterol levels in subjects that consumed cholesterol-enriched diets (Hori *et al.*, 2000, 2001, 2002).

## TOXICOLOGICAL STUDIES

### Acute Studies

#### *Studies Related to Enzymatically Modified Lecithin (Lysolecithin) (Studies on the Mucosal Barrier and Red Blood Cell Membranes)*

Numerous investigators have studied the effect of lysolecithin on the mucosal barrier in isolated gastric preparations and in whole animals (Davenport, 1970; Kivilaakso *et al.*, 1976, 1978; Ammon *et al.*, 1979; Cl  men  on *et al.*, 1980; Bolin *et al.*, 1981; Slomiany *et al.*, 1982, 1986; Maksem *et al.*, 1984; Duane *et al.*, 1986; Salo *et al.*, 1987; Armstrong *et al.*, 1994) reporting changes in barrier properties and release of macromolecules indicative of cellular damage which were reduced or comparable to that observed with bile acids (Kivilaakso *et al.*, 1978; Bolin *et al.*, 1981; Maksem *et al.*, 1984; Slomiany *et al.*, 1986; Armstrong *et al.*, 1994). Although the effect of lysolecithin on the integrity of the gastric mucosa has been suggested to be important in the development of gastric and duodenal ulcers (Johnson and McDermott, 1974) from higher basal duodenogastric reflux rates (Johnson and McDermott, 1974; Schumpelick *et al.*, 1984), Schumpelick *et al.*, (1984) concluded that there is "no evidence for a major role of reflux in the pathogenesis of gastroduodenal ulcer" based on comparisons of levels in postoperative reflux gastritis patients.

Considering that the effects on the gastric mucosa have not been found in toxicological studies with lysolecithin or from high exposure to lysolecithin from normal digestive processes, these effects were not considered to be relevant.

000030

*In vitro* studies have indicated that lysolecithin can cause lysis of red blood cells at high concentrations (Larsson and Johansson, 1978). Decreased hemoglobin levels and packed cell volumes indicative of red blood cell lysis have been reported in rats fed diets containing enzymatically-modified lecithin at a concentration of 200 g/kg diet for a period of 3 weeks (Dutilh and Groger, 1981). Decreased packed cell volumes also were observed in female rats fed similar diets for a period of 13 weeks, however, these changes were observed at the end of an 8-week observation period and were not observed at the end of the feeding period (Dutilh and Groger, 1981). In addition, the diet produced no changes in hemoglobin levels at the end of the 13-week feeding period. Moreover, no significant differences in spleen weights were observed in either study. These results were therefore not considered to be relevant.

### **Subchronic and Chronic Studies**

#### *Studies Related to CSPHP*

No significant toxicological effects were reported in short-term studies in which rats were fed CSPHP or SPHP in the diet at concentrations of 0.5 to 20% (approximately 0.75 to 29.15 g CSPHP/kg body weight/day and 0.86 to 38 g SPHP/kg body weight/day) for up to 10 days (Hori *et al.*, 1999, Morishita *et al.*, 1999, Nagaoka *et al.*, 1999). Both CSPHP and SPHP were reported to significantly lower serum total cholesterol and liver cholesterol and increase HDL total cholesterol ratio following consumption of cholesterol-enriched and cholesterol-free diets.

In a 90-day oral toxicity study of CSPHP, groups of 10 Crj CD (SD) IGS rats per sex were administered CSPHP at doses of 0, 2,250 or 4,500 mg/kg body weight/day (Kyowa Hakko Kyogo, 1998). A lower food intake was reported in males in the high dose group (4,500 mg/kg body weight/day) on Days 13 to 27; however, there was no effect on body weight gain. No compound-related toxic effects were reported in urinalysis, hematological and blood biochemistry parameters, and following macroscopic and histopathological examination. The no-observed-effect level (NOEL) was 4.5 g/kg body weight/day, the highest dose tested.

#### *Studies Related to Enzymatically-Modified Lecithin*

The toxicity of enzymatically-modified lecithin was evaluated in a 3-week feeding study in which groups of 10 male and 10 female Colworth-Wistar rats were fed purified diets containing 0, 50, 100, 200, 300, or 400 g lecithin or enzymatically-modified lecithin/kg diet/day (Dutilh and Groger, 1981). On a body weight basis, the experimental diets provided approximately 0, 4.6, 9.2, 18.4, 27.7, and 37 g enzymatically-modified lecithin/kg body weight/day in males and 0, 5.1, 10.3, 20.5, 30.8, and 41 g enzymatically-modified lecithin in females. Compared to the lecithin diet, changes produced by the enzymatically-modified lecithin diet at the highest dose level (400 g/kg diet) included nephrocalcinosis, and decreased absolute kidney weight in males at 3 weeks and

**000031**

granular kidneys at the end of a 2-week observation period in females. A dose-related increase in kidney weights accompanied by intratubular deposition of calcium and phosphate salts and secondary degenerative, inflammatory, and reparative lesions were reported in the lecithin- and enzymatically-modified lecithin-fed groups. No other significant compound-related effects were reported

The same authors conducted a 13-week study in which Colworth-Wistar rats were fed purified diets providing 0, 10, 25, 50, 100, or 200 g lecithin or enzymatically-modified lecithin/kg diet/day for a period of 13 weeks (Dutilh and Groger, 1981). On a body weight basis, the experimental diets provided approximately 0, 0.9, 2.3, 4.6, 9.2, and 18.4 g enzymatically-modified lecithin/kg body weight/day in males and 0, 1.0, 2.6, 5.1, 10.3, and 20.5 g enzymatically-modified lecithin/kg body weight/day in females. Changes in the kidneys in both the lecithin and enzymatically-modified lecithin groups were similar to those detailed in the 3-week study described above, however, the renal effects were more pronounced in a positive control group fed choline chloride and sodium dihydrogen phosphate when compared to rats fed lecithin or enzymatically-modified lecithin. Nephrocalcinosis has been reported to be a common spontaneous occurrence in Colworth-Wistar rats fed purified diets. The authors reported no other significant compound-related effects at any dose level. The no-observed-adverse-effect level (NOAEL) was 20.5 g/kg body weight/day, the highest dose tested, based on the lack of significant adverse effects. This value is 342 times (20.5/0.06) the expected mean human consumption of enzymatically-modified lecithin from all proposed and permitted food uses.

In a 90-day toxicity study, groups of 30 Wistar rats (15 rats/sex) were administered 0 or 2 g enzymatically-modified lecithin/kg body weight by gavage daily for 30 days, followed by a 60-day period in which the compound was administered 6 days per week (Kyowa Hakko Kogyo, 1982). No mortality, adverse symptoms or any significant differences in body weight, food or water consumption were observed between groups. Specific examination of the gastrointestinal tract for ulcerous changes revealed no such effect in the treatment group. No other significant compound-related effects were observed. The NOAEL was 2 g/kg body weight/day, the only dose tested, based on the absence of serious adverse effects.

#### *Studies Related to Soy Protein*

Anastasia *et al.* (1990) conducted a 22-month study to evaluate the ability of a semi-purified diet containing soy protein to support normal growth and health in rats. Groups of 43 or 50 rats per sex were fed diets containing 0 or 21.82% soy protein. On a body weight basis, this would be equivalent to approximately 0 and 7.7 g/kg body weight/day of soy protein in males and 0 and 10.3 g/kg body weight/day of soy protein in females. Evaluations of body weight, organ weight, feed consumption, feed efficiency, protein efficiency, organ-to-body weight ratios, selected organ mineral levels, gross pathology and histopathology did not indicate toxic effects attributable to the soy protein present in the diet.

000032

## Genotoxicity Study

The mutagenic potential of CSPHP was evaluated in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* WP2 *uvrA* (Bacterial Reversion Test, 1997) CSPHP was reported not to be mutagenic in the presence or absence of metabolic activation at concentrations ranging from 313 to 5,000 µg/plate.

## Clinical Studies

### *Clinical Studies Relating to CSPHP*

The effects of CSPHP on serum cholesterol were investigated in normocholesterolemic Japanese male subjects given a cholesterol-enriched diet for a period of 3 weeks (Hori *et al.*, 2000) CSPHP was administered in the form of a powdered drink at doses of 0, 3, 6, or 9 g/day (approximately 0, 43, 86, and 129 mg/kg body weight/day) Suppression of the increase in total serum cholesterol was reported in all CSPHP dose groups. No adverse effects or clinical abnormalities were reported in any subjects throughout the study Similar results were reported in a 3-month study in which hypercholesterolemic male subjects were given 0, 3, or 6 g CSPHP per day (approximately 0, 44, and 85 mg/kg body weight/day) in powdered drink form for a period of 3 months (Hori *et al.*, 2001) Serum total cholesterol, LDL-cholesterol and LDL/HDL ratio were significantly reduced in the CSPHP groups in a dose-dependent manner compared with the placebo group Cholesterol levels returned to baseline when subjects resumed their normal diet during a 2-week post-feeding phase of the study The authors reported no adverse effects in any subjects throughout the study

Another clinical study was conducted in which groups of 11 hypocholesterolemic men were given a test diet of miso soup with 3 g CSPHP or casein hydrolyzate daily for a period of 3 months (Hori *et al.*, 2002) Compared to the control group and baseline values, serum total cholesterol and LDL cholesterol were significantly decreased in subjects that consumed the soup containing CSPHP; however, there was no significant difference between groups in HDL cholesterol levels In addition, there were no significant differences between groups in the serum concentration of β-carotene, 1,25-dihydroxy vitamin D, and vitamin E indicating no impact on the nutritional availability of these vitamins

### *Clinical Studies Related to Lecithinated Soy Protein*

Sirtori *et al.* (1985) conducted a 16-week study to evaluate the effects of textured vegetable (soy) proteins containing 6% lecithinated textured vegetable protein (L-TVP) on plasma cholesterol in hypocholesterolemic and hyperlipoproteinemic patients The study consisted of 4 phases, each 4 weeks in duration, in which subjects consumed varying amounts of animal protein (10 to 60% of total protein content) and L-TVP (70 to 90% of total protein content). Plasma total and LDL-cholesterol were reported to significantly decrease in the phases in which

L-TVP was substituted for animal protein, and were more pronounced in patients with higher initial cholesterol levels. Minor adverse effects associated with consumption of L-TVP included occasional diarrhea, abdominal cramps, and bloating. These effects were resolved within 2 weeks. No other significant adverse effects were reported.

#### *Clinical Studies Related to Isolated Soy Protein*

The antihypercholesterol effects of the undigested high molecular weight (HMF) fraction of soybean protein were studied among female university students with relatively high serum cholesterol for their age (Wang *et al* , 1995). Subjects consumed HMF as 8% of their total daily energy intake for a period of 14 days or as 4% of their total daily energy intake for a period of one menstrual cycle (approximately 30 days) with a cholesterol-enriched diet. No significant changes in serum total cholesterol were observed, however, HDL-cholesterol was significantly increased. LDL-cholesterol was significantly reduced in subjects that consumed HMF as 4% of total daily calories for one menstrual period. No adverse effects were reported in any of the subjects.

#### **SUMMARY**

CSPHP, an 80/20 mixture of hydrolyzed soy protein and enzymatically-modified lecithin, is considered to have a low toxicity potential. This statement is largely supported by toxicological studies on the individual components. Soy protein has been considered to be safe at levels greater than 25 g/day. Two 90-day rat-feeding studies conducted with enzymatically-modified lecithin indicated that it had no significant adverse effects up to 2 g/kg body weight and 20.5 g/kg body weight/day, respectively.

These studies are also supported by toxicological studies on CSPHP itself. It is non-mutagenic in the Ames assay and did not have any significant adverse effects in a 90-day rat feeding study at levels of 4.5 g/kg body weight/day. No adverse effects were noted at levels up to 9 g/day in a short-term 3-week tolerance trial or up to 6g/day in longer-term 3-month tolerance type clinical trials where CSPHP maintained serum cholesterol and LDL cholesterol levels in the lower normal range.

Based on CSPHP's low potential for toxicity and proposed uses in food and in dietary supplements, no adverse health effects would be expected in individuals consuming CSPHP.

**CONCLUSION**

We, the Expert Panel, have independently and collectively critically evaluated the data and information summarized above and conclude that C-Fraction Soy Protein Hydrolyzate with Bound Phospholipids (CSPHP), meeting food grade specifications and produced in compliance with cGMP, is Generally Recognized As Safe (GRAS) by scientific procedures for use in foods under the conditions of intended use described herein.

\_\_\_\_\_  
Joseph F. Borzelleca, Ph.D.  
Professor, Pharmacology and  
Toxicology  
Medical College of Virginia  
Virginia Commonwealth University

24 December 2002  
Date

\_\_\_\_\_  
W. Gary Flamm, Ph.D.  
Flamm Associates

January 2, 2003  
Date

\_\_\_\_\_  
Walter H. Glinzmann, M.D.  
Glinzmann, Inc

DEC 20 2002  
Date

**000035**

<b>Table 1 Chemical and Microbiological Specifications for CSPHP</b>	
<b>Specification Parameter</b>	<b>Specification</b>
Appearance	Light yellowish powder having slight soy odor
Protein	>60%
Total Phospholipids	>18%
Free Phospholipids	<0.2%
Arsenic	<2 ppm
Heavy Metals (as Pb)	<30 ppm
Lead	<1.0 ppm
Loss on Drying	<7%
Total Plate Count	Less than $3 \times 10^3$ /g
<i>Escherichia coli</i>	Negative
Thermophilic Bacteria	Less than 300/g

000036

Food Category	Proposed Food Use	Use-Levels for CSPHP (%)	Use-Levels for CSPHP (g/RACC <sup>1</sup> )
Baked Goods and Baking Mixes	Breads	6	3
	Rolls	6	3
	Bagels	5.5	3
	English Muffins	5.5	3
Breakfast Cereals	Ready-to-Eat Cereals	5.5 - 20	3
Dairy Product Analogs	Soy/Imitation Milks	1.3	3
Fats and Oils	Margarines	21.4	3
	Salad dressings	10	3
Grain Products and Pastas	Health Bars	7.5	3
Health Beverages	Meal Replacements	1.3	3
Meat Products	Meat Patty with Soy Protein	5.5	3
Milk Products	Flavored Milk Drinks	1.3	3
	Milk Based Meal Replacements	1.3	3
	Yogurt (Regular and Frozen)	1.3-2.7	3
Plant Protein Products	Meat Alternatives	2.1 - 42.9	3
Processed Fruits and Fruit Juices	Fruit Juice	1.3	3
	Nectars	1.3	3
	Fruit-Flavored Drinks	1.3	3
Processed Vegetables and Vegetable Juices	Vegetable/Tomato Juice	1.3	3
Soups and Soup Mixes	Prepared Soups, Dry Soup Mixes, and Condensed Soups	1.2	3

<sup>1</sup> RACC – Reference amounts customarily consumed per eating occasion

000037

## REFERENCES

- Akino, T , Yamazaki, I., Abe, M 1972 Metabolic fate of lysolecithin injected into rats. *Tohoku J Exp Med* 108(2) 133-139.
- Ammon, H V , Luedtke, L A ; Andrade, M A 1979 Effect of lysolecithin on water and solute transport in the rat jejunum *Gastroenterology* 76(5, Part 2):1091 [Abstract]
- Anastasia, J V , Braun, B L , Smith, K.T. 1990 General and histopathological results of a two-year study of rats fed semi-purified diets containing casein and soya protein. *Food Chem Toxicol* 28(3):147-156.
- Armstrong, D , Rytina, E R C., Murphy, G M , Dowling, R.H 1994 Gastric-mucosal toxicity of duodenal juice constituents in the rat Acute studies using *ex vivo* rat gastric chamber model *Dig Dis Sci* 39(2) 327-339
- Bacterial Reversion Test 1997 Bacterial Reversion Test of KR-1552 (CSPHP). [Unpublished data].
- Bolin, T , Sjobahl, R , Sundqvist, T , Tagesson, C. 1981. Passage of molecules through the wall of the gastrointestinal tract Increased passive permeability in rat ileum after exposure to lysolecithin *Scand J Gastroenterol* 16(7):897-901
- Borgstrom, B 1957 Studies of the phospholipids of human bile and small intestinal content. *Acta Chem Scand* 11(4) 749.
- Clémençon, G , Fehr, H , Aebi, M 1980 Lysolecithin und Stressulkuks bei der Ratte = [Lysolecithin and stress ulcers in rats] *Schweiz Med Wochenschr* 110(22) 863-864.
- Davenport, H W 1970 Effect of lysolecithin, digitonin, and phospholipase A upon the dog's gastric mucosal barrier *Gastroenterology* 59(4):505-509
- Duane, W C , McHale, A P , Sievert, C E 1986 Lysolecithin-lipid interactions in disruption of the canine gastric mucosal barrier *Am J Physiol* 250(3, Part 1):G275-G279.
- Dutilh, C E , Groger, W 1981 Improvement of product attributes of mayonnaise by enzymic hydrolysis of egg yolk with phospholipase A<sub>2</sub> *J Sci Food Agric* 32:451-458.
- Hori, G , Yamamoto, K , Morishita, K., Mukawa, S , Kamiya, T., Nagaoka, S. 1999. Cholesterol-lowering effects of isolated soybean protein hydrolyzate with bound phospholipids in rats *Nihon Eiyō Shokuryō Gakkaishi* 52(3):135-145.
- Hori, G , Kamiya, T , Hara, T , Yamamoto, K.; Nagaoka, S ; Motoya, N.; Yamamoto, S. 2000. The effect of soybean protein hydrolyzate with bound phospholipids on serum cholesterol levels in adult male subjects receiving high cholesterol diet. *Nippon Rinsyo Eiyō Gakkaishi* 22:21-27

000038

- Hori, G , Wang, M -F , Chang, Y -C , Komatsu, T , Wong, Y , Chen, T.-H.; Yamamoto, K.; Nagaoka, S., Yamamoto, S. 2001 Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem* 65(1) 72-78.
- Hori, G , Kakinuma, S , Nagaoka, S , Yamamoto, K 2002 The effects of the miso soup containing soy protein hydrolyzate with bound phospholipids on serum cholesterol levels. Unpublished
- Johnson, A G , McDermott, S J. 1974 Lysolecithin: A factor in the pathogenesis of gastric ulceration? *Gut* 15 710-713.
- Kivilaakso, E , Ehnholm, C , Kalima, T V , Lempinen, M 1976 Duodenogastric reflux of lysolecithin in the pathogenesis of experimental porcine stress ulceration. *Surgery* 79(1) 65-69
- Kivilaakso, E , Fromm, D , Silen, W 1978 Effects of lysolecithin on isolated gastric mucosa. *Surgery* 84(5) 616-621
- Kyowa Hakko Kogyo. 1982 Toxicological Studies of MML - Subacute Oral Toxicity Tests in Rats Kyowa Hakko Kogyo Co , Ltd Safety Research Lab ; Japan. [Unpublished data]
- Kyowa Hakko Kogyo Co 1998 Toxicological Studies of CSPHP. Subacute Oral Toxicity Tests in Rats Kyowa Hakko Kogyo Co., Ltd [Unpublished data].
- Larsson, K and Johansson, L -A 1978 Hemolytic effect of some polar lipids used as food additives. *LWT* 11.206-208
- Maksem, J , Jacobson, N , Neiderhiser, D.H 1984 Lysophosphatidylcholine-induced gastric injury and ulceration in the guinea pig. *Am J Pathol* 115(2).288-295.
- Morishita, K , Yamamoto, K , Hori, G ; Tanaka, M.; Kamiya, T Nagaoka, S. 1999. Cholesterol-lowering effects of soy protein peptic hydrolyzate with bound phospholipids in rats-- Cross-over test, dose-response test, and comparison with materials possessing cholesterol-lowering effects *Nihon Eiyo Shokuryo Gakkaishi* 52(4) 183-191.
- Nagaoka, S , Miwa, K , Eto, M ; Kuzuya, Y., Hori, G ; Yamamoto, K 1999 Soy protein peptic hydrolyzate with bound phospholipids decreases micellar solubility and cholesterol absorption in rats and *caco-2* cells. *J Nutr* 129(9) 1725-1730.
- Nilsson, Å 1968 Intestinal absorption of lecithin and lysolecithin by lymph fistula rats *Biochim Biophys Acta* 152(2) 379-390
- Portman, O W , Illingworth, D R. 1974 Factors determining the concentrations of lysolecithin in plasma and tissues *Scand J Clin Lab Invest Suppl* 33(Suppl 137):49-55.
- Salo, J A , Myllarniemi, H , Kivilaakso, E. 1987 Morphology of lysolecithin-induced damage on esophageal mucosa An experimental light and scanning electron microscopical study. *J Surg Res* 42(3) 290-297

000039

- Sato, Y 1970 The metabolic fate of lysolecithin administered into rat duodenal lumen. *Tohoku J Exp Med* 100(3) 277-287
- Saunders, D R , Parmentier, C M., Ways, P O. 1968. Metabolism of lysolecithin by rat small intestine *Gastroenterology* 54(3).382-391.
- Schumpelick, V , Stemme, D , Hofmann, G , Begemann, F 1984. Intragastric bile acid and lysolecithin in gastroduodenal ulcer and gastric cancer *Scand J Gastroenterol Suppl* 92 172-177
- Scow, R O , Stein, Y , Stein, O 1967 Incorporation of dietary lecithin and lysolecithin into lymph chylomicrons in the rat *J Biol Chem* 242(21).4919-4924.
- Sirtori, C R , Zucchi-Dentone, C ; Sirtori, M., Gatti, E., Descovich, G C., Gaddi, A., Cattin, L., Da Col, P G , Senin, U , Mannarino, E ; Avellone, G.; Colombo, L., Fragiaco, C.; Nosedà, G , Lenzi, S 1985 Cholesterol-lowering and HDL-raising properties of lecithinated soy proteins in type II hyperlipidemic patients *Ann Nutr Metab* 29(6) 348-357.
- Slomiany, B L ; Jerzy Glass, G B , Kojima, K.; Banas-Gruszka, Z ; Slomiany, A. 1982 Effect of lysolecithin on the constituents of gastric mucus. *In* Chantler, E.N., Elder, J B.; Elstein, M (Eds ) *Mucus in Health and Disease--II*. Plenum Press; New York. *Advances in Experimental Medicine and Biology*, Vol. 144, pp. 163-174
- Slomiany, B L , Sarosiek, J , Liau, Y.H , Laszewicz, W., Slomiany, A 1986. Lysolecithin affects the viscosity, permeability, and peptic susceptibility of gastric mucin. *Scand J Gastroenterol* 21(9).1073-1079
- Stein, Y , Stein, O 1966. Metabolism of labeled lysolecithin, lysophosphatidyl ethanolamine and lecithin in the rat *Biochim Biophys Acta* 116(1).95-107
- Subbaiah, P V , Bagdade, J D. 1978 Demonstration of enzymatic conversion of lysolecithin to lecithin in normal human plasma. *Life Sci* 22(22).1971-1977.
- Subbaiah, P V , Ganguly, J. 1971 Transesterification of lysolecithin in the intestinal mucosa of rats *Indian J Biochem Biophys* 8(4) 197-203
- Subbaiah, P V ; Sastry, P S ; Ganguly, J. 1970 Acylation of lysolecithin in the intestinal mucosa of rats *Biochem J* 118(2) 241-246
- Tso, P , Scobey, M 1986 The role of phosphatidylcholine in the absorption and transport of dietary fat *In* Kuksis, A (Ed ) *Fat Absorption* CRC Press; Boca Raton, Florida, Vol. 1, pp 177-195
- USDA 2002 Food Consumption (Data) *Per Capita* System U S Department of Agriculture. Commodity Economics Division, Economic Research Service.  
[<http://www.ers.usda.gov/data/foodconsumption/spreadsheets.asp>]
- Wang, M -F , Yamamoto, S , Chung, H -M., Chung, S Y., Miyatani, S.; Mori, M.; Okita, T.; Sugano, M 1995 Antihypercholesterolemic effect of undigested fraction of soybean protein in young female volunteers *J Nutr Sci Vitaminol* 41(2) 187-195.

000040

Attachment 1

000041

**ATTACHMENT 1**

***CURRICULA VITAE OF EXPERT PANEL MEMBERS***

**000042**

Joseph Francis Borzelleca

Educational Background.

B S St Joseph's University, Philadelphia, PA, Major: Biology, Chemistry

M S School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, Major: Pharmacology, Physiology.

Ph D School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA Major: Pharmacology, Biochemistry

**Academic Appointments**

Instructor-Associate Department of Pharmacology, Medical College of Pennsylvania, 1956-1959

Assistant Professor Department of Pharmacology, Toxicology, Medical College of Virginia, 1959-62 and 1962-1967.

Professor Department of Pharmacology, Toxicology, Medical College of Virginia, 1967-

Head Division of Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, 1972-1986

Professor Emeritus Pharmacology & Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, July 1996 –

**Professional Certification**

Fellow, Academy of Toxicological Sciences

**Professional Affiliations**

**Societies**

Academy of Toxicological Sciences\* \*\*

American Association for the Advancement of Science

American Chemical Society

American College of Toxicology\*

000043

American Society of Pharmacology and Experimental Therapeutics\*\*

(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)

International Society of Regulatory Toxicology and Pharmacology\*

(Member of Council)

Sigma Xi

Society of Experimental Biology and Medicine\*

(Councilor, Program Chairman of Southeastern Section)

Society for Risk Analysis

Society of Toxicology\* \*\*

(Member and/or Chairman. Awards, Education, Legislative Affairs, Membership, Nominating Committees, Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)

Virginia Academy of Science\*

(Chairman, Medical Sciences Division)

\* Held elected office

\*\* Held appointed office or position

### **Board of Directors**

ILSI

### **Board of Scientific and Policy Advisors**

American Council on Science and Health

Journals

Editor, Food Chemical Toxicology, 1992-

### **Editorial Board**

Environmental Carcinogenesis Reviews, 1981-

Journal of Environmental Pathology, Toxicology and Oncology 1977-

Journal of Environmental Science and Health, 1979-

Journal of the American College of Toxicology, 1982-

Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992

Journal of Applied Toxicology, 1989-

000044

Pharmacology, 1978-

Pharmacology and Drug Development, 1980-

Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

Food and Drug Administration

National Institute of Mental Health

National Cancer Institute

Environmental Protection Agency

Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)

U S Army - Research and Development Command

Non-Governmental

National Academy of Sciences - NRC

Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental  
Health Hazards

Safe Drinking Water Committee

Evaluation of Household Substances Committee (1138 Committee)

Food Protection Committee

Food Additives Survey Committee

Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes

Committee on Risk Assessment of Flame-Retardant Chemicals

Federation of American Societies of Experimental Biology

Select Committee on GRAS Substances

Flavors and Extracts

Biotechnology Product Safety

Caprenin GRAS Committee

000045

World Health Organization

Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

### **Industrial**

Chemical Companies; Trade Associations

### **University Activities**

#### **Related to Instruction**

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)  
Introduced the use of closed circuit TV and TV tapes in pharmacology (11960)  
Introduced clinical pharmacological experiments into the medical and dental programs (1960)

Planning and participation in continuing education program  
(Schools of Dentistry, Medicine and Pharmacy)

Planning and administering each of the three major efforts in pharmacology  
(dental, medical, pharmacy) since 1960

Graduate Program - assisted in developing graduate training program in toxicology

#### **Current Teaching Activities**

Presents lectures on Toxicological Issues, Food Intake and Control

#### **Not Directly Related to Instruction**

Elected senator from the graduate school, then vice-president of the University Senate  
Served on various committees (e g Curriculum, Search, Animal Care) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

### **Research**

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S., N.I.H., E.P.A., N.I.D.A.) and non-governmental (industrial). A list of publications is attached)

### **Awards**

DOD - US Army - Chemical Research Development and Engineering Center

Distinguished Service Award, 1986

National Italian - American Foundation Award

Excellence in Medicine and Community Service, 1987

**000046**

Thomas Jefferson University

Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences

Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of  
Pharmacology and Toxicology

Professor of the Year- 1992

American College of Toxicology

Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

2001 Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists

## **PUBLICATIONS**

Borzelleca, J F and Manthei, R W · Factors influencing pentobarbital sleeping time in mice  
Arch Int Pharmacodyn 111 296, 1957

Borzelleca, J F Studies of the contribution of bladder absorption to the physiological changes  
induced by pentobarbital J Pharm Exp Ther 129 305, 1960.

Borzelleca, J F The absorption of nicotine from the urinary bladder of the dog. Arch Int.  
Pharmacodyn 133 444, 1961.

Borzelleca, J F , Bowman, E R and McKennis, H , Jr.: The cardiovascular and respiratory  
effects of (-)-cotinine J. Pharmacol Exp Ther. 137 313, 1962.

Borzelleca, J F · Drug absorption from the urinary tract of the rat. Nicotine. Arch. Int.  
Pharmacodyn 143 595, 1963

Borzelleca, J F Influence of saline and glucose infusions on the course of barbiturate  
intoxication Arch Int Pharmacodyn 146 163, 1963.

Larson, P S , Borzelleca, J F., Bowman, E R., Crawford, E.M., Smith, R B., Jr. and Henningar,  
G R Toxicologic studies on a preparation of p-tertiary octylphenoxy-polyethoxy ethanols (Triton  
X-405) Toxicol Appl Pharmacol 5 782, 1963.

Borzelleca, J F , Larson, P.S., Henningar, G R , Hug, E.G., Crawford, E M. and Smith, R.B., Jr.:  
Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate.  
Toxicol Appl Pharmacol 6:29, 1964

Borzelleca, J.F and Cherrick, H · The excretion of drugs in saliva. Antibiotics. J. Oral Therap  
Pharmacol 2 180, 1965

000047

Borzelleca, J F. and Lester, D Acute toxicity of some perhalogenated acetones. *Toxicol. Appl. Pharmacol* 7 592, 1965

Borzelleca, J.F Drug movement from the isolated urinary bladder of the rabbit. *Arch Int. Pharmacodyn* 154 40, 1965

Borzelleca, J F Rabbit urinary bladder potentials. *Invest. Urol.* 3 77, 1965.

Borzelleca, J F Studies on the mechanisms of drug movement from the isolated urinary bladder *J Pharmacol Exp Ther* 148:111, 1965

Lowenthal, W and Borzelleca, J F Drug absorption from the rectum I *J. Pharm. Sci.* 541790, 1965

Ambrose, A M , Borzelleca, J.F , Larson, P S , Smith, R.B., Jr and Hennigar, G.R : Toxicologic studies on monochloroacetaldehyde 2,4-dinitrophenylhydrazone, a foliar fungicide. *Toxicol. Appl Pharmacol* 8 472, 1966

Borzelleca, J F and Doyle, C H Excretion of drugs in saliva Salicylate, barbiturate, sulfanilamide *J Oral. Therap Pharmacol* 3104, 1966.

Borzelleca, J F and Lowenthal, W.. Drug absorption from the rectum. II. *J Pharm. Sci.* 55151, 1966

Wooles, W R and Borzelleca, J.F . Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system. *J. Reticuloendo Soc.* 341, 1966.

Wooles, W R , Borzelleca, J F and Branham, G W The effects of acute and prolonged salicylate administration on liver and plasma triglyceride levels and dietary-induced hypercholesterolemia *Toxicol Appl Pharmacol.* 10:1 1967

Borzelleca, J F , Harris, T and Bernstein, S. The effect of DIVISO on drug movement through the wall of the urinary bladder of the rabbit. *J. Invest. Urol.* 643, 1968.

Borzelleca, J F The excretion of glucose in saliva. *Dog J Oral Therap. Pharmacol.* 4338, 1968

Kim, K S , Borzelleca, J F , McKennis, H and Bowman, E R. Pharmacological effects of some nicotine metabolites and related compounds *J. Pharmacol. Exp. Ther* 16159, 1968

Marcus, S and Borzelleca, J F Observations of reserpine-induced bradycardia. *Arch Int. Pharmacodyn* 174 12, 1968

Schwartz, S L and Borzelleca, J F Adrenergic blood pressure response in the shark. *Science* 163 395, 1969

Ambrose, A M , Borzelleca, J F , Larson, P S and Hennigar, G R. The toxicology of a foliar fungicide, GC4072 *Toxicol Appl Pharmacol.* 17:323, 1970.

Borzelleca, J F and Putney, J W , Jr A model for the movement of salicylate across the parotid epithelium *J Pharmacol Exp Ther.* 174:527, 1970.

000048

Borzelleca, J F and Putney, J W., Jr Studies on the biotransformation of salicylic acid by the salivary gland Arch. Int Pharmacodyn 188127, 1970

Lowenthal, W , Borzelleca, J F and Corder, C D., Jr · Drug absorption from the rectum. 111. Aspirin and some aspirin derivatives. J Pharm Sci. 59 1353, 1970.

Putney, J W , Jr and Borzelleca, J F : A method for the determination of small quantities of salicylate metabolites in the presence of a great excess of salicylic acid. Arch. Int. Pharmacodyn. 188119, 1970.

Wynn, J E , van't Riet, B. and Borzelleca, J.F : Excretion and toxicity of EGTA and EDTA after oral administration to rats Toxicol Appl. Pharmacol 16807, 1970.

Ambrose, A M , Larson, P.S , Borzelleca, JR, Smith, R B , Jr. and Hennigar, G.R.: Toxicologic studies on 2,4-dichloropheny-p-nitrophenyl ether Toxicol. Appl Pharmacol. 19263, 1971

Borzelleca, J F , Larson, P S., Crawford, E M., Hennigar, G R , Jr., Kuchar, E.J. and Klein, H.H.. Toxicologic and metabolism studies on pentachloronitrobenzene. Toxicol. Appl Pharmacol. 18 522, 1971

Putney, J W , Jr and Borzelleca, J F On the mechanisms of <sup>14</sup>C- salicylic acid distribution in rat submaxillary gland *in vitro*. J Pharmacol Exp Ther. 117263, 1971.

Putney, J W , Jr and Borzelleca, J F On the mechanisms of <sup>14</sup>C-nicotine distribution in rat submaxillary gland *in vitro* J Pharmacol Exp. Ther. 178180, 1971

Ambrose, A M., Larson, P S , Borzelleca, J F. and Hennigar, G.R.. Toxicologic studies on 3',4'-dichloropropionanilide Toxicol Appl Pharmacol 23650, 1972.

Egle, J L , Jr , Putney, J W., Jr and Borzelleca, J F.. Cardiac rate and rhythm in mice affected by haloalkane propellants J.A.M.A. 222786, 1972.

Putney, J W , Jr and Borzelleca, J.F. On the mechanisms of <sup>14</sup>C-salicylic acid excretion by the rat submaxillary gland J Phamacol Exp. Ther 182515, 1972.

Putney, J W , Jr and Borzelleca, J F · Active accumulation of <sup>14</sup>C-salicylic acid by rat kidney cortex *in vitro*. J Pharmacol Exp. Ther 186600, 1973.

Borzelleca, JR Safety evaluation and toxicological tests and procedures. J A.O.A.C. 58692, 1975

Adams, M D , Wedig, J H., Jordan, R L., Smith, L W , Henderson, R and Borzelleca, J.F.. Urinary excretion and metabolism of salts of 2-pyridinethiol-I -oxide following intravenous administration to female Yorkshire pigs Toxicol. Appl Pharmacol 36523,1976

Allen, M A , Wrenn, J M , Putney, J W., Jr and Borzelleca, J.F.: A study of the mechanism of transport of diphenylhydantoin in the rat submaxillary gland *in vitro*. J. Pharmacol Exp. Ther 197 408, 1976

Ambrose, A M , Larson, P S , Borzelleca, J F. and Hennigar, G.R.: Long-term toxicologic assessment of nickel in rats and dogs J Food Science and Technology 13181, 1976.

000049

Egle, J L , Jr , Long, J.E , Simon, G S and Borzelleca, J.F : An evaluation of the cardiac sensitizing potential of a fabric protector in aerosol form, containing 1,1,1-trichloroethane. *Toxicol Appl Pharmacol.* 38:369,1976.

EGLE, J L , Jr , Fernandez, S B , Guzelian, P S. and Borzelleca, J.F.. Distribution and excretion of chlordecone (Kepone) in the rat *Drug Metab Dispos* 691, 1976

Munson, A E , Barrett, B A. and Borzelleca, J F.: *In vitro* experimental approaches to detection of sensitive agents In *Cutaneous Toxicity*, (V. Drill, ed.), Academic Press, Inc., San Francisco, p. 175, 1977

Weinberg, A D , Dimen, E M , Borzelleca, J F. and Harris, L S · Weight and activity in male mice after daily inhalation of cannabis smoke in an automated smoke exposure chamber. *J Pharm & Pharmac* 29:477, 1977.

Weinberg, A D , Dimen, E.M , Simon, G S., Harris, L.S and Borzelleca, J.F.: Measurements of weight and activity in male mice following inhalation of cannabis smoke in a controlled smoke exposure chamber *Toxicol Appl Pharmacol* 42:301, 1977.

Allen, M A , Wrenn, J M , Putney, J W , Jr and Borzelleca, J.F : A study of the mechanisms of transport of benzy1penicillin in the rat submaxillary gland. *Arch. Int. Pharmacodyn.* 233:180, 1978

Bowman, F J , Borzelleca, J F and Munson, A E. The toxicity of some halomethanes in mice *Toxicol Appl Pharmacol.* 44:213,1978

Egle, J L , Jr , Fernandez, S.B , Guzelian, P S and Borzelleca, J.F Distribution and excretion of chlordecone (Kepone) in the rat *Drug Metab Dispos* 691, 1978.

McConnell, W R and Borzelleca, J F A study of the mechanism of transport of A9-tetrahydrocannabinol in the rat submaxillary gland *in vivo*. *Arch Int. Pharmacodyn* 235:180, 1978

McConnell, W R , Dewey, W L , Harris, L S. and Borzelleca, J.F.: A study of the effect of delta-9-tetrahydrocannabinol (delta-9-THC) on mammalian salivary flow *J Pharmacol. Exp Ther.* 206:567, 1978

Schumann, A M and Borzelleca, J F . An assessment of the methemoglobin and Heinz body inducing capacity of pentachloronitrobenzene in the cat *Toxicol. Appl. Pharmacol.* 44:523, 1978.

Simon, G S , Tardiff, R G. and Borzelleca, J.F · Potential mutagenic and adverse male reproductive effects of 1,2,3,4-tetrabromobutane A dominant lethal study in the rat. *Toxicol. Appl Pharmacol* 44:661, 1978

Carmines, E L , Carchman, R A. and Borzelleca, J F.. Kepone: Cellular sites of action *Toxicol. Appl Pharmacol* 49:543, 1979.

Egle, J L , Jr , Guzelian, P S and Borzelleca, J F · Time course of the acute toxic effects of sublethal doses of chlordecone (Kepone). *Toxicol Appl Pharmacol* 48:533, 1979

Larson, P S , Egle, J.L , Jr., Hennigar, G R and Borzelleca, J.F.. Acute and subchronic toxicity of mirex in the rat, dog, and rabbit *Toxicol Appl Pharmacol.* 49:271, 1979.

000050

Larson, P S , Egle, J L , Jr , Hennigar, G.R , Lane, R.W and Borzelleca, J F.. Acute, subchronic and chronic toxicity of chlordecone Toxicol Appl. Pharmacol 4829, 1979.

Simon, G S , Kuchar, E J , Klein, H H and Borzelleca, J F. Distribution and clearance of pentachloronitrobenzene in chickens Toxicol. Appl Pharmacol. 50401,1979

Simon, G S , Tardiff, R G and Borzelleca, J F Failure of hexachlorobenzene to induce dominant lethal mutations in the rat Toxicol. Appl. Pharmacol. 47415, 1979.

Borzelleca, J F and Skalsky, H L.. The excretion of pesticides in saliva and its value in assessing exposure J Environ Sci Health, B15(6), 843, 1980

Borzelleca, J F , Egle, J L , Jr , Hennigar, G.R , Klein, H.H , Kuchar, E.J , Lane, R.W. and Larson, P S A toxicologic evaluation of 5-ethoxy-3- trichloromethyl-1,2,4-triazole (ETMT). Toxicol Appl Pharmacol 56.164,1980

Carmines, E L , Carchman, R A and Borzelleca, J.F. A method for the evaluation of dose-effect data utilizing a programmable calculator J Environ. Path. and Tox. 423, 1980

Kessler, F K , Laskin, D L , Borzelleca, J F. and Carchman, R.A. Assessment of somatogenotoxicity of povidone-iodine using two *in vitro* assays J. Environ. Path. and Tox. 3 327, 1980

Skalsky, H L , Wrenn, J M and Borzelleca, J F *In vitro* and *in vivo* evaluation of the movement of Kepone in the rat submaxillary gland J. Environ. Path and Tox. 3529, 1980.

Smith, L W and Borzelleca, J F Excretion of cadmium and mercury in rat saliva. Toxicol. Appl Pharmacol 54 134, 1980

Smith, L W and Borzelleca, J F *In vitro* stimulation of oxygen consumption in rat submaxillary gland by pilocarpine J Dent Res (59)91539, 1980

Smith, L W and Borzelleca, J F. Movement of cadmium in rat submaxillary slices. Toxicol Appl. Pharmacol 55 403, 1980

Smith, L W and Borzelleca, J F Movement of mercury in rat submaxillary slices. Toxicology 18 169, 1980

Borzelleca, J F Report of the NATO/CCMS drinking water pilot study on health aspects of drinking water contaminants Sci of the Total Environ. 18205, 1981.

Carmines, E L , Carchman, R A and Borzelleca, J F. Investigations into the mechanism of paraquat toxicity utilizing a cell culture system. Toxicol Appl Pharmacol. 58353, 1981.

Simon, G S , Borzelleca, J F and Dewey, W L . Narcotics and diabetes 11. Streptozotocin-induced diabetes selectively alters the potency of certain narcotic analgesics Mechanism of diabetes morphine interaction J Pharmacol. Exp. Ther 218324, 1981.

Balster, R L and Borzelleca, J F The behavioral toxicity of trihalomethane contaminants of drinking water in mice Environ. Health Perspec 46127, 1982.

Kauffmann, B M , White, K.L , Jr., Sanders, V.M , Douglas, K A , Sain, L E., Borzelleca, J.F and Munson A E.: Humoral and cell-mediated immune status in mice exposed to chloral hydrate. *Environ Health Perspec.* 44 147, 1982.

Lane, R W , Riddle, B L and Borzelleca, J F · Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. *Toxicol. Appl Pharmacol* 63 409, 1982

Munson, A E , Sain, L E., Sanders, V.M , Kauffmann, B.M , White, K.L., Jr , Page, D.G , Barnes, D W , and Borzelleca, J.F Toxicology of organic drinking water contaminants. trichloromethane, bromodichloromethane, dibromochloromethane and tribromomethane *Environ. Health Perspec.* 46 117, 1982

Sanders, V M , Kauffmann, B M , White, K L., Douglas, K A , Barnes, D.W., Sain, L.E., Bradshaw, T J , Borzelleca, J F and Munson, A.E Toxicology of chloral hydrate in the mouse *Environ Health Perspec* 44 137, 1982

Sanders, V M , Tucker, A N , White, K L , Jr., Kauffmann, B.M., Hallett, P., Carchman, R.A., Borzelleca, J F and Munson, A E Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water *Toxicol Appl. Pharmacol* 62 358, 1982

Borzelleca, J.F A review of volatile organic contaminant data. *Proc AWWA Water Quality Tech Conf* 225, 1983

Charles, J L , Kram, D , Borzelleca, J F and Carchman, R A · The kinetics of *in vivo* sister chromatid exchange induction in mouse bone marrow cells by alkylating agents. I Cyclophosphamide *Environ Mut.* 5: 825, 1983

Borzelleca, J F , Condie, L W and Hayes, J R Toxicological evaluation of selected chlorinated phenols *Proceedings of the 5th International Water Disinfection Conference, Williamsburg, VA,* 1984

Borzelleca, J F Food safety regulations, research, and results *Va. Med.* 111:390, 1984.

Seyler, D.E , East, J M , Condie, L.W and Borzelleca, J F.: The use of *in vitro* methods for assessing reproductive toxicity of dichlorophenols. *Tox. Letters* 20:309, 1984.

Shopp, G M , White, K L , Jr , Holsapple, M P., Barnes, D.W , Duke, S.S., Anderson, A C., Condie, L W , Jr , Hayes, J R and Borzelleca, J F : Naphthalene toxicity in CDA mice: general toxicology and immunotoxicology *Fund Appl. Toxicol.* 4:406, 1984

Borzelleca, J F and Hogan, G K Chronic toxicity/carcinogenicity study of FD&C Blue No. 2 in mice *Food Chem Tox* 23 719, 1985

Borzelleca, J F , Hayes, J R , Condie, L W and Egle, J L , Jr.: Acute toxicity of monochlorophenols, dichlorophenols and pentachlorophenol in the mouse. *Toxicol. Letters* 29 39, 1985

Borzelleca, J F , Hayes, J R., Condie, L W and Egle, J.L · Acute and subchronic toxicity of 2,4-dichlorophenol in CD-1 mice. *Fund Appl Toxicol* 5:478, 1985

Borzelleca, J.F., Hogan, G.K and Koestner A.. Chronic toxicity/carcinogenicity study of FD&C Blue No 2 in rats. *Food Chem. Tox* 23:551, 1985

000052

Hayes, J R and Borzelleca, J.F Nutrient interaction with drugs and other xenobiotics, J. Am. Dietetic Assoc 85 3 335, 1985

Lane, R W , Simon, Glen, S S , Dougherty, R W , Egle, J.L. and Borzelleca, J.F.. Reproductive toxicity and lack of dominant lethal effects of 2,4-dinitrotoluene in the male rat. Drug and Chem. Tox 4 265,1985

Borzelleca, J F , Goldenthal, E.I and Wazeter, FX: A multigeneration study of FD&C Blue No 2 in rats Food Chem Tox 24:159, 1986.

Charles, J L , Jacobson-Kram, D , Condie, L W., Jr , Borzelleca, J.F and Carchman, R A : The kinetics of *in vitro* sister chromatid exchange induction in mouse bone marrow cells by ethylnitrosourea and methylnitrosourea Toxicol Appl. Pharmacol 8456, 1986.

Hayes, J R , Condie, L.W , Jr. and Borzelleca J F.: The subchronic toxicity of tetrachorethylene (perchloroethylene) administered in the drinking water of rats. Fund. Appl Toxicol 7:119, 1986.

Hayes, J R , Condie, L W., Jr and Borzelleca, J F. Acute, 14-day repeated dosing and 90-day subchronic toxicity studies of carbon tetrachloride in CD-1 mice. Fund. Appl. Toxicol 7:454, 1986

Hayes, J R , Condie, L W , Jr. and Borzelleca, J F.: Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of potassium picloram Fund. Appl. Toxicol. 7:464, 1986.

Hayes, J R , Condie, L.W., Jr and Borzelleca, J F. Toxicology of haloacetonitriles Environ. Health Perspec. 69 183, 1986

Lane, R W , Sturm, R J , Borzelleca, J F and Carchman, R.A.. Effect of *in vitro* differentiation on phorbol diester receptor number in human promyelocytic leukemia (HL-60) cells Cancer Res 46 3782,1986

Simon, G S , Egle, J L , Jr , Dougherty, R W and Borzelleca, J F.. Dominant lethal assay of chlordecone and its distribution in the male reproductive tissues of the rat. Tox. Letters 30:237, 1986

Tarka, S M., Jr , Applebaum, R S and Borzelleca, J.F : Evaluation of the perinatal, postnatal and teratogenic effects of coca powder and theobromine in Sprague-Dawley/CD rats. Food Chem Tox 24 375, 1986

Tarka, S M , Jr , Applebaum, R S. and Borzelleca, J.F.. Evaluation of the teratogenic potential of cocoa powder and theobromine in New Zealand white rabbits Food Chem. Tox. 24:363, 1986.

Borzelleca, J.F., Capen, C C and Hallagan, J B.: Lifetime toxicity/carcinogenicity study of FD&C Red no 3 (erythrosine) in rats Fd Chem Toxic 25:723, 1987

Borzelleca, J F , Capen, C C , and Hallagan, J.B. Lifetime toxicity/carcinogenicity study of FD&C Red No 3 (erythrosine) in mice Fd Chem Toxic. 25:735, 1987

**000053**

Hayes, J R , Condie, L W , Jr , Egle, J L , Jr. and Borzelleca, J F.. The acute and subchronic toxicity in rats of *trans*-1,2 dichloroethylene in drinking water J. Am. Coll. Toxicol. 6:471, 1987.

Borzelleca, J F and Hallagan, J B. Chronic toxicity/carcinogenicity studies of FD&C Yellow No. 5 (tartrazine) in rats Fd Chem. Toxic 26:179, 1988

Borzelleca, J F , Condie, L W., Jr. and Egle, J L : Short-term toxicity (one- and ten-day gavage) of barium chloride in male and female rats. *J Am. Coll Toxicol.* 7675-685, 1988.

Condie, L W , Jr , Hill, J R and Borzelleca, J F.: Oral toxicology studies with xylene isomers and mixed xylenes *Drug and Chem Toxic.* 11:329, 1988.

Borzelleca, J F and Hallagan, J B A chronic toxicity/carcinogenicity study of FD&C yellow no. 5 (tartrazine) in mice *Fd Chem Toxic.* 26:189, 1988

Borzelleca, J F , Clark, E C and Condie, L W , Jr : Short-term toxicity (1 and 10 days) of cadmium chloride in male and female rats: gavage and drinking water. *J Am. Coll. Toxicol.* 8 377, 1989

Borzelleca, J F , Condie, L W , Jr , Clarke, E C and Egle, J.L : Short-term toxicity (one and ten day gavage) of potassium dichromate in male and female rats. *J Am. Coll Toxicol.* 8,1197, 1989

Borzelleca, J F , Olson, J W.A and Reno, F A Lifetime toxicity/carcinogenicity study of FD&C red No 40 (allura red) in Sprague-Dawley rats. *Fd. Chem. Toxic.* 27:701, 1989.

Borzelleca, J F Status of colors and flavors used in the confectionery industry. *Proc 106<sup>th</sup> Annual Convention of the National Confectioners Association of the United States.* 33, 1989.

Lamb, R G , Borzelleca, J F , Condie, L W and Gennings, C.: Toxic interactions between carbon tetrachloride and chloroform in cultured rat hepatocytes. *Toxicol. Appl. Pharmacol* 10:1106, 1989

O'Hara, T M , Borzelleca, J.F , Clark, E C , Sheppard, M.A. and Condie, L.W., Jr : A CCl<sub>4</sub>/CHCl<sub>3</sub> interaction study in isolated hepatocytes selection of a vehicle. *Fund Appl. Toxicol.* 13:605, 1989

Borzelleca, J F and Hallagan, J.B Multigeneration study of FD&C red no 3 (erythrosine) in Sprague-Dawley rats *Fd Chem Toxic* 28:813, 1990

Borzelleca, J F , Depukat, K and Hallagan, J B Lifetime toxicity/carcinogenicity studies of FD&C blue no 1 (brilliant blue FCF) in rats and mice. *Fd Chem. Toxic* 28:221, 1990.

Borzelleca, J F , O'Hara, T M , Gennings, C , Granger, R.H., Sheppard, M.A. and Condie, L W. Jr Interactions of water contaminants I Plasma enzyme activity and response surface methodology following gavage administration of CCl<sub>4</sub> and CHCl<sub>3</sub> or TCE singly and in combination in the rat *Fund Appl. Toxicol.* 14:477, 1990

Borzelleca, J F., Olson, J W A and Reno, F A.. Lifetime toxicity/carcinogenicity study of FD&C red no 40 (allura red) in mice *Fd. Chem Toxic.* 29:313, 1991.

O'Hara, T M , Sheppard, M A , Clarke, E.C., Borzelleca J F., Gennings, C. and Condie, L.W., Jr.. A CCl<sub>4</sub>/CHCl<sub>3</sub> interaction study in isolated hepatocytes: non-induced, and phenobarbital pretreated cells. *J Appl Toxicol.* 11 147, 1991

Borzelleca, J.F Assessment of Safety/Risk of Chemicals- Inception and Evolution of the ADI and Dose-Response Modeling Procedures- *Commentary Tox Letters* 59:1, 1991

**000054**

Borzelleca, J F The safety evaluation of macronutrient substitutes. *CRC Critical Reviews in Food Science and Nutrition.* 32 127, 1992

Borzelleca, J F Macronutrient Substitutes. *Safety Evaluation. Reg Tox. Pharm.* 16253, 1992

Waddell, W J , Borzelleca, J.F , Doull, J , Grasso, P , LeBourhis, B., Levy, P.S. and Tamburro, C H *Alcohol and Cancer Br. J. Cancer* 661200, 1992.

Borzelleca, J F Evaluation of the safety of tara gum as a food ingredient: a review of the literature *J Am Coll. Tox* 12(1) 81,1993

Borzelleca, J F. and Egle, J L Jr An evaluation of the reproductive and developmental effects of tara gum in rats *J Am Coll. Tox.* 12(1) 91, 1993

Borzelleca, J F Interactions of environmental chemicals and toxins in *Proceedings of the Second Princess Chulabhorn Science Congress: " Environment, Science and Technology. the Challenges of the 21st Century "* 1993

Borzelleca, J F , Egle, J L., Jr., Harris, L.S , Johnson, D.N , Terrill, J.B. and Belleville, J.A.N.: Toxicological Evaluation of u-Agonists, Part 1 Assessment of Toxicity Following 30 Days of Repeated Oral Dosing of Male and Female Rats with Levo-Alpha-Acetylmethadol HCl (LAAM). *J Appl Tox* 14 (6) 435,1994

Conn, R E , Kolstad, J J , Borzelleca, J F , Dixler, D.S , Filer, L J , Jr, LaDu, B.N., Jr., and Pariza, M W Safety Assessment of Polylactide (PLA) for Use as a Food-contact Polymer. *Fd. Chem Tox* 33 273-283, 1995

Hallagan, J B , Allen, D C , and Borzelleca, J F The safety and regulatory status of food, drug and cosmetics color additives exempt from certification *Fd. Chem. Toxic.* 33:515, 1995

Borzelleca, J F Post-Marketing Surveillance of Macronutrient Substitutes *Fd. Tech* 49 107-113, 1995

Borzelleca, J F , Egle, J.L Jr , Harris, L S and Belleville, J A.N : Toxicological Evaluation of u-Agonists Part II. Assessment of Toxicity Following 30 Days of Repeated Oral Dosing of Male and Female Rats with Levo-alpha-noracetylmethadol HCl (NorLAAM). *J Appl. Tox.* 15(5):339-355, 1995

Moore, K A , Lichtman, A H , Poklis, A., and Borzelleca, J F *alpha-Benzyl-N-methylphenethylamine (BNMPA), an impurity of illicit methamphetamine synthesis pharmacological evaluation and interaction with methamphetamine.* *Drug and Alcohol Dependence* 39 83-89, 1995

Borzelleca, J F , Filer, L J , Jr., Kinoshita, F K , Gerrish, T C , Kuo, P K., and LaDu, B.N.. Evaluation of the safety of sodium pectate as a food ingredient. *Fd Chem Toxic.* 34.21-25, 1996

Borzelleca, J F A proposed model for safety assessment of macronutrient substitutes. *Reg. Tox Pharm* 23:S15-S18, 1996.

Steinberg, M , Borzelleca, J.F , et al A new approach to the safety assessment of pharmaceutical excipients. *Reg Tox. Pharm.* 24 149-154, 1996

000055

Berndt, W O , Borzelleca, J F , Flamm, W G , and Munro, I.C.: Erythritol: A Review of Biological and Toxicological Studies Reg Tox. Pharm. 24 S191-198, 1996.

Hallagan, J B , LaDu, B N , Pariza, M W , Putnam, J M , and Borzelleca, J.F.: Assessment of Cassia Gum Fd Chem Toxic 35 625-632,1997

Graham, D M , Pariza, M.W , Glaze, W.H., Newell, G W , Erdman, JW, and Borzelleca, J.F.: Use of Ozone in Food Processing Fd. Tech. June 1997

Pariza, M W , Borzelleca, J F et al Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods. CAST Issue Paper Number 8, November 1997.

Borzelleca, JF Paracelsus Herald of Modern Toxicology. Toxicological Sciences 53: 2-4 1999

### ABSTRACTS

Borzelleca, J F and Manthei, R W Influence of dehydration on pentobarbital sleeping time in mice Fed Proc 15 403, 1956

Borzelleca, J F The effect of blood pH on barbiturate sleeping time in mice. Fed. Proc 16 284,1957

Borzelleca, J F Drug absorption from the urinary bladder Fed Proc. 18370, 1959.

Borzelleca, J F Nicotine absorption from the urinary bladder of the dog. Fed. Proc 19.391,1960

Borzelleca, J F , Bowman, E R. and McKennis, H , Jr.: Depressor effects arising from (-)-cotinine Pharmacologist 2 72, 1960

Borzelleca, J F . Influence of saline infusions on the course of barbiturate intoxication. Pharmacologist 3 63,1961

Borzelleca, J F · Drug absorption from the urinary tract of the rat Nicotine Fed. Proc. 21451, 1962

Borzelleca, J F Drug movement from the isolated urinary bladder of the rabbit Fed. Proc. 22 661, 1963

Borzelleca, J F Studies on the mechanisms of drug movement from the isolated urinary bladder Pharmacologist 6:178, 1964.

Kim, K S , Borzelleca, J F , McKennis, H., Jr. and Bowman, E.R.. Effects of cotinine and other nicotine metabolites *in vitro* on duodenum and ileum segments. Fed. Proc. 23330, 1964.

Borzelleca, J F and Doyle, H : Salivary excretion of drugs Fed. Proc. 24546, 1965

Cherrick, H and Borzelleca, J F . Salivary excretion of drugs Antibiotics. Toxicol. Appl Pharmacol 7 481 1965

**000056**

Wooles, W R and BorzelleGa, J.F Prolongation of barbiturate sleeping time in mice by stimulation of the RES J R.E.S, 1 574,1965.

Borzelleca, J F : Salivary excretion of glucose, salicylate, penicillin. Fed. Proc. 24564, 1966.

Lowenthal, W and Borzelleca, J F Rectal absorption of salicylates Toxicol. Appl Pharmacol. 8 347, 1966

Bernstein, S and Borzelleca, J F The effect of dimethylsulfoxide on drug transfer from the urinary bladder Va. J Sci 18:195, 1967

Kim, K S and Borzelleca, J F . Pharmacological effects of some nicotine metabolites and related compounds Fed Proc. 26:683, 1967

Mullen, K and Borzelleca, J.F : Predictive model for blood glucose concentration in the dog. Va J Sci 18 200,1967

Schwartz, S L and Borzelleca, J F.. Adrenergic blood pressure responses in the shark. Proc Shark Res Panel of Am Inst. Biol Sci , 26 April 1968

Schwartz, S L and Borzelleca, J.F Adrenergic responses in the shark Toxicol. Appl. Pharmacol 12:307,1968

Wynn, J E , van't Riet, B and Borzelleca, J.F.: Excretion and toxicity of EGTA and EDTA after oral administration to rats Fed. Proc 27:465, 1968.

van't Riet, B , O'Rear, C E , Wynn, J E and Borzelleca, J.F : Effect of EGTA and EDTA on bladder stone formation in rats Toxicol. Appl Pharmacol. 14:638, 1969.

Borzelleca, J.F and van't Riet, B Hydrolysis and excretion of esters of EDTA and EGTA after oral administration to rats Va. J. Sci 29:143, 1970.

Borzelleca, J F , Larson, P S , Hennigar, G.R. and Kuchar, E J : A toxicological evaluation of pentachloronitrobenzene (PCNB) Pharmacologist 12:208, 1970.

Borzelleca, J F The role of pharmacology in the training of toxicologists Pharmacologist 12:217, 1970

Putney, JW, Jr and Borzelleca, J F. A model for drug movement across the salivary epithelium. Va J Sci 21:147, 1970

Putney, JW, Jr and Borzelleca, J F. Factors modifying excretion of salicylate by the dog, comparison of urinary and salivary routes J. Toxicol. Appl Pharmacol. 16:23,1970.

Putney, J W , Jr and Borzelleca, JR Studies on salicylate biotransformation by the salivary gland Pharmacologist 12 272, 1970.

Borzelleca, J F , Larson, P S , Hennigar, G.R and Kuchar, E J. A toxicologic evaluation of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole (terrazole) Toxicol Appl Pharmacol. 19:79, 1971.

Putney, J W , Jr and Borzelleca, J F : Mechanisms of <sup>14</sup>C-salicylate uptake by submaxillary gland slices Fed Proc 30 448, 1971.

**000057**

Putney, J W , Jr and Borzelleca, F. Active uptake of <sup>14</sup>C-salicylic acid by rat kidney cortex slices. Fed Proc 31 518, 1972.

Putney, J W., Jr and Borzelleca, J.F.: Participation of extracellular hydrogen ion in the efflux of nicotine-<sup>14</sup>C from submaxillary gland cells. Pharmacologist 13:518,1972.

Allen, M A and Borzelleca, J F · On the method of benzyl penicillin-<sup>14</sup>C potassium distribution in rat submaxillary gland. Fed. Proc 32733, 1973

Allen, M A and Borzelleca, J F.. On the method of diphenyl hydantoin distribution in rat submaxillary gland Pharmacologist 15 229, 1973.

Jordan, R L and Borzelleca, J F Teratogenic studies with pentachloronitrobenzene in rats. Toxicol Appl Pharmacol. 25 454, 1973.

Allen, M A and Borzelleca, J F Diphenylhydantoin distribution in rat submaxillary gland: influence of age Fed. Proc 33 525, 1974

Burnett, C M , Agersborg, H P.H , Jr , Borzelleca, J.F., Egle, Jr., E., Ebert, A.G , Pierce, E.C., Kirschman, J C and Scala, R A.. Teratogenic studies with certified colors in rats and rabbits. Toxicol Appl Pharmacol. 29 121, 1974

Pierce, E G , Agersborg, H P K , Jr , Borzelleca, J F., Burnett, C M., Egle, E , Ebert, A.G , Kirschman, J C and Scala, R A Multigeneration reproduction studies with certified colors in rats Toxicol Appl Pharmacol 29:121, 1974.

Adams, M , Wedig, J H , Jordan, R , Smith, L , Henderson, R. and Borzelleca, J.F..Excretion and metabolism of three 2-6-<sup>14</sup>C Omadines following intravenous injection in female Yorkshire pigs. Toxicol Appl Pharmacol. 33 180, 1975

Egle, J L , Jr , Borzelleca, J F and Long, J E An evaluation of the cardiac sensitizing potential of Scotchgard brand fabric protector. Toxicol Appl. Pharmacol 33:154,1975.

Jordan, R L and Borzelleca, J F. Teratogenic studies with zinc Omadine in swine. Anat. Rec 18.388,1975

McConnell, W R , Borzelleca, J F and Chambers, JW The effects of delta-9-tetrahydrocannabinol (THC) on electrically stimulated saliva from cat submaxillary gland Fed. Proc 34 782,1975

Smith, L W , Borzelleca, J F and Bowman, E.R.. Application of isolated cell suspensions to the study of membrane phenomena in mammalian salivary cells Fed. Proc 34752, 1975

Wrenn, J M and Borzelleca, J.F Effect of phenobarbital and pentobarbital on the transport of diphenylhydantoin in salivary tissues and saliva Fed. Proc. 34573, 1975

Egle, J L , Jr , Gochberg, B J and Borzelleca, J F. The distribution of <sup>14</sup>C-Kepone in the rat. Pharmacologist 18 195, 1976

McConnell, W R and Borzelleca, J F On the method of 3H-delta-9 tetrahydrocannabinol (3H-delta-9-THC) distribution in the submaxillary gland of the rat. Pharmacologist 18149, 1976.

McConnell, W R , Borzelleca, J F and Dewey, W.L. The mechanism by which delta-9-tetrahydrocannabinol (THC) produces a decrease in salivary flow following electrical stimulation Fed Proc 35 644,1976.

**000058**

McCoy, W D , Kuchar, E J , Klein, H H. and Borzelleca, J F Biotransformation and distribution of pentachloronitrobenzene in chickens Toxicol Appl Pharmacol. 37175, 1976

Schumann, A M and Borzelleca, J F The potential methemoglobin and Heinz body inducing capacity of pentachloronitrobenzene (PCNB) in the cat. *Toxicol. Appl Pharmacol.* 37:171, 1976.

Schumann, A M , Bloom, A S., Dewey, W L , Harris, L S and Borzelleca, JR: Development of central catecholamine systems in the postnatal rat brain *The Pharmacologist* 18:243, 1976.

Smith, L W and Borzelleca, J F Uptake of cadmium in rat submaxillary slices. *The Pharmacologist* 18 196,1976

Bagshaw, B , Schumann, A , Borzelleca, J and Dewey, W : The effects of chloroform and bromoform on the noradrenergic and dopaminergic systems of the mouse brain. *Pharmacologist* 9 200, 1977

Barrett, B A , Sanders, V M , Borzelleca, J F , Munson, E Growth rates and tumor takes in mice with transplanted tumors exposed to halomethanes. *Va. J Sci.* 28:100, 1977.

Brady, K T., Sanders, V M, Borzelleca, J.F and Munson, A.E.: The acute toxicity of the halomethanes drinking water contaminants. *Va J Sci* 28:100, 1977.

Martin, B R , Dewey, W L , Beckner, J S. and Borzelleca, J.F.: Synthesis and metabolism of brain serotonin in mice following acute exposure to several haloalkanes. *Toxicol. Appl Pharmacol* 19 200, 1977

Munson, A , Sanders, V , Borzelleca, J and Barnes, D : Toxicologic studies on adult and neonatal mice exposed to the trichloromethanes drinking water contaminants *Pharmacologist* 19 200, 1977

Munson, A E , Sanders, V M , Barrett, B A and Borzelleca, JR: Functional activity of the reticuloendothelial system in mice exposed to haloalkanes for ninety days. *J. Reticuloendo. Soc* 22 17a, 1977

Sanders, V M , Barrett, B.A , Borzelleca, J F and Munson, A.E. Reticuloendothelial system activity and cell mediated immune responsiveness in mice exposed to polychlorinated biphenyls. *J Reticuloendo Soc.*22:16a,1977

Schumann, A M , Dewey, W L. and Borzelleca, J.F : The effects of triethyllead on central catecholamine function in the adult rat *Toxicol. Appl Pharmacol.* 41:208, 1977.

Schumann, A M , Dewey, W L., Borzelleca, J F. and Alphin, R S.. The effects of lead acetate on central catecholamine function in the postnatal mouse *Fed. Proc.* 36 405, 1977.

Smith, L W and Borzelleca, J F The excretion of cadmium and mercury in saliva. *Toxicol. Appl. Pharmacol* 41 153, 1977

Smith, L W , Ismay, J A and Borzelleca, JR Movement of mercury in rat submaxillary slices. *Fed. Proc* 36 355,1977

Carmines, E L , Burkhalter, J A., Carchman, R.A and Borzelleca, J.F Inhibitory effects of chloroform on P388D macrophage cell. *Fed Proc.* 37:320, 1978.

**000059**

Dougherty, R W , Simon, G.S., Campbell, K.I and Borzelleca, J F. Failure of 2,4-dinitrotoluene to induce dominant lethal mutations in the rat *Pharmacologist* 20:155, 1978.

Larson, P S , Hennigar, G R , Lane, R.W and Borzelleca, J F.. Acute, subchronic and chronic toxicological studies with kepone Toxicol. Appl Pharmacol. 95331, 1978.

Munson, A E , Sanders, V M , Borzelleca, J F , Tardiff, R.G and Barrett, B A.: Reticuloendothelial system function in mice exposed to four haloalkane drinking water contaminants Toxicol Appl Pharmacol. 45 329,1978.

Schuller, G B , Kauffmann, B.M., Borzelleca, J.F., Sanders, V.M. and Munson, A.E.: Effect of four haloalkanes on humoral and cell mediated immunity in mice. Toxicol. Appl. Pharmacol. 45 329, 1978

Simon, G S , Carchman, R A and Borzelleca, J F.: Diabetes responses to selected pharmacologic agents Pharmacologist 20 151, 1978.

Simon, G S., Kipps, B R , Tardiff, R G and Borzelleca, J F. Failure of Kepone and hexachloroberizene to induce dominant lethal mutations in the rat Toxicol. Appl. Pharmacol. 45 330 1978

Smith, S H , Sanders, V M , Barrett, B A , Borzelleca, J.F. and Munson, A.E.: Immunotoxicological evaluation on mice exposed to polychlorinated biphenyls Toxicol. Appl. Pharmacol 45 330, 1978

Zimmerman, M L , Lane, R W., Skalsky, H L and Borzelleca, J.F.: Excretion of carbaryl into saliva and its effect on cholinesterase 10<sup>th</sup> Inter-American Conf. on Toxicol. and Occupational Med , p 47,1978

Zimmerman, M L , May, R G and Borzelleca, J.F.: Excretion of carbaryl into the saliva of the rat. Toxicol Appl Pharmacol. 45 35,1978.

Balster, R L , Burkhalter, J. and Borzelleca, J F : Behavioral toxicity evaluation of four halomethane contaminants of drinking water in adult mice. Fed Proc. 38846, 1979.

Carmines, E L , Carchman, R.A and Borzelleca, J F . *In vitro* effects of Kepone Va. J Sci 30 89, 1979

Borzelleca, J F , Skalsky, H L and Riddle, B.L Effects of dibromochloromethane in drinking water on reproduction and development in mice. Fed Proc 39999, 1980.

Carmines, E.L., Carchman, R A and Borzelleca, J F : Analysis of the interactions between paraquat and DNA Fed Proc. 39545,1980

Balster, R L , Kallman, M J and BorzelleGa, J.F. Behavioral toxicity evaluation of trihalomethane contaminants of drinking water. Health Effects of Drinking Water Symposium, 1981

Carchman, R A , Cardlin, E L , Skalsky, H L and Borzelleca, J.F : The effects of selected water disinfectant products on testicular DNA metabolism Health Effects of Drinking Water Symposium, 1981

**000060**

Kallman, M J , Balster, R.L , Kaempf, G L. and Borzelleca, J F.: Behavioral toxicity evaluation of chloral in adult mice Fed Proc 40698, 1981.

Tarka, S M , Jr , Keeney, P G , and Borzelleca, J F . The effect of pretreatment with dietary cocoa on growth and reproductive performance in young and adult rats Fed. Proc. 40668, 1981

Lane, R W , Carchman, R A and Borzelleca, J.F. Characterization of DNA metabolism in mouse primary spermatocytes Toxicologist 1:39(#143), 1981.

Riddle, B L , Carchman, R A and Borzelleca, J F . Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicologist 1 26 (#95), 1981

Tarka, S M , Jr , Keeney, P G and Borzelleca, J.F : A comparison of the effects of methylxanthine-containing food stuffs on reproductive capacity in rats. Toxicologist 1147 (#533), 1981

Borzelleca, J F , Hallagan, J , Reese, C , Goldenthal, E. and Hogan, G : Chronic oral toxicity/carcinogenicity studies of food, drug and cosmetic colors in CD-1 mice J Am. Coll. Tox. 2 240 (#108), 1982

Charles, J L , Carchman, R A , Kram, D and BorzelleGa, J F . Time course of *in vivo* induction of sister chromatid exchange by ethylnitrosoarea and methylnitrosoarea. Toxicologist 2175 (613), 1982

Hayes, J R , Condie, L W , Jr , and Borzelleca, J F.. Kinetics of naphthalene (NTL) covalent binding to hepatic DNA, RNA and protein in CD-1 mice. J. Am. Coll. Tox 3144, 1982.

Lane, R W , Coles, R B , Carchman, R A. and BorzelleGa, J F . Phorbol diester receptors on HL-60 human promyelocytic leukemia cells Toxicologist 2105 (#373), 1982.

Seyler, D , East, J and Borzelleca, J F Cadmium depression of mouse *in vitro* fertilization. Toxicologist 2.238 (#764), 1982

Borzelleca, J.F , Hallagan, J , Reese, C , Goldenthal, E. and Hogan, G : Chronic oral toxicity/carcinogenicity studies of food, drug and cosmetic colors in CD rats. Toxicologist 3129 (#514), 1983.

Condie, L W , Hayes, J R and Borzelleca, J.F . Acute and subchronic oral toxicity of 2,4-dichlorophenol (2,4-DCP) in male and female CD-1 mice Pharmacologist 25228, 1983.

Hayes, J R and Borzelleca, J F Implications of nutrient-drug interactions. Proc. Ann Meeting Inst Fd Technol ,1983

Hayes, J R and Borzelleca, J F Diet-nutrient interactions Proc. Ann. Mtg of the Am. Diet. Assoc , 1983

Hayes, J R , Condie, L W., Jr , and Borzelleca, J.F. : Pharmacokinetics of oral naphthalene (NTQ) in CD-1 mice Toxicologist 3 161 (#644), 1983

Kalliman, M J , Borzelleca, J F and Condie, L , Jr.. Behavioral toxicity of naphthalene in adult mice J Am Coll Tox 2247 (#136), 1983

**000061**

Kessler, F K , Charles, J L., Borzelleca, J F. and Carchman, R.A : Effects of chlorinated phenols on mouse bone marrow sister chromatid exchange J. Am Coll Tox 2249 (#142), 1983.

Lane, R W , Carchman, R A and Borzelleca, J F.. Phorbol diester (PDE) binding and oxygen metabolism of differentiated HL-60 cells Toxicologist 3144 (#575), 1983.

Shopp, G M , White, K L , Jr , Holsapple, M P , Barnes, D.W , Condie, L.W., Jr. and Borzelleca, J.F General toxicology and immunotoxicology of mice exposed to naphthalene (NAP). Toxicologist, 3 57 (#226), 1983

Smith, B , Lane, R W , Carchman, R A and Borzelleca, J.F.: A comparison of the reversibility of phorbol diester induced changes in macrophage morphology Toxicologist 3144 (#574), 1983

Borzelleca, J F , Hayes, J,R and Condie, L.. Toxicological evaluation of selected chlorinated phenols and haloacetonitriles Proc of 5th International Conf. on Water Chlorination: Environmental Impact and Health Effects 1.100, 1984.

Hayes, J R , Condie, L and Borzelleca, J.F Subchronic toxicity of carbon tetrachloride administered by oral gavage to CD-1 mice Toxicologist 4183 (#730), 1984

Hayes, J R , Condie, L W and Borzelleca, J F Acute and 14-day continuous dosing toxicity of dichloroacetonitrile (DCA) and dibromoacetonitrile (DBA). Pharmacologist 28233, 1984.

Condie, L W Hayes, J R and Borzelleca, J F . Acute, 14-day and subchronic toxicity of potassium picloram (PIC) administered to rats via the drinking water Toxicologist 5222, 1985

Capen, C C , Nishikawa, S , Ingbar, S H., Braverman, L E., and Borzelleca, J F.. Mechanisms of thyroid oncogenesis by chronic erythrosine (red. no. 3) feeding: ultrastructural and morphometric evaluation of thyroid glands and changes in circulating levels of thyroid hormones and thyrotropin (TSH) Abstract No 48, 75<sup>th</sup> Annual Meeting of the International Academy of Pathology, New Orleans, 10-14 March, and published in Laboratory Investigations 54: 54 a, 1986

Lamb, R G , Bush, S R , Condie, L.W , and Borzelleca, J F.. Influence of chlorinated hydrocarbon mixtures on cultured hepatocyte function Pharmacologist 28180, 1986.

Lamb, R G , Coleman, J B., Condie, L W., and Borzelleca, J.F : Influence of chlorinated hydrocarbons on cultured hepatocyte function Toxicologist 6116 (#470), 1986.

Granger, R H , Coleman, J B , Condie, L.W., Lamb, R.G and Borzelleca, J.F.: Effect of vehicle on the relative uptake of haloalkanes administered by gavage. Toxicologist 7. 265 (#1060), 1987

Lamb, R G., Coleman, J B., Granger, H , Condie, L W and Borzelleca, J.F.: The influence of chlorinated hydrocarbons on hepatocyte function *in vivo* and *in vitro*. Toxicologist 7.267 (#1068), 1987

Coleman, J B , Condie, L W., Borzelleca, J F. and Lamb, R G.. The influence of structural analogues of carbon tetrachloride (CC14) on hepatocyte functions *in vitro* Toxicologist 8:96 (#381), 1988.

Granger, R H , O'Hara, T M., Condie, L W , and Borzelleca, J.F.. A study of the joint action of carbon tetrachloride (CC14) and trichloroethylene (C2HCl3) following simultaneous gavage administration in the rat. Toxicologist 895 (#378), 1988.

000062

O'Hara, T M , Granger, R H., Condie, L W. and Borzelleca, J F.. A study of the joint hepatotoxic action of carbon tetrachloride (CC14) and chloroform (CHC13) following simultaneous gavage administration in the rat *Toxicologist* 96 (#380), 1988

Borzelleca, J F , O'Hara, T M , Gennings, C. and Condie, L.W., A CC14-CHC13 interaction study in isolated hepatocytes-the role of P-450 metabolism. *Toxicologist* 958 (#229), 1989.

Lamb, R G , Gennings, C , Borzelleca, J F , and Condie, L W.. Toxic Interactions between carbon tetrachloride (CC14) and chloroform (CHC13) *Toxicologist* 959 (#233), 1989.

O'Hara, T M., Borzelleca, J F and Condie, L W. A CC14/CHC13 interaction study in isolated hepatocytes-selection of a vehicle. *Toxicologist* 959 (#235), 1989.

Borzelleca, J F , Gennings, C , Bercz,P and Lamb, R G.. Toxic interactions between carbon tetrachloride (CC14) and perchloroethylene (PCE) in cultured rat hepatocytes. *Toxicologist* 10 54 (#213), 1990

Lamb, R G , Gennings, C , Borzelleca, J.F and Bercz,P Toxic interactions between carbon tetrachloride (CC14) and trichloroethylene (TCE) in cultured rat hepatocytes. *Toxicologist* 1053 (#212), 1990

Wolfe, G , Myers, B , Lemen, J , Lauer, W., Johns, F., Condie, L. and Borzelleca, J : Preliminary report of the findings of the health effects for Denver's potable reuse demonstration project. *Toxicologist* 10 176 (#704), 1990

Egle, J L , Jr , Borzelleca, J F and Harris, L.S. Acute and subchronic toxicity of Levo-alpha-acetyl-methadol (LAAM) and Levo-alpha-acetyl-normethadol (NORLAAM) in male and female rats *Toxicologist* 11 149 (#521), 1991

Weiner, M L , Steinberg, M., Borzelleca, J F , Enters, EX, Hager, D F., Kinoshita, F.K., Loper, A., Mitchell, D B and Tamulinas, C.B Proposed safety evaluation guidelines for new excipients. *Toxicologist* 13 213 (#796), 1994

Borzelleca, J F The safety evaluation of macronutrient substitutes IFT Annual Meeting Abstracts #15-2, 1994

Borzelleca, J F Fat replacers ACS meeting, 1995

Rice, R G , Graham, D M , Glaze, W.H , Pariza, M W., Newell, G W., Erdman, J.W., and Borzelleca, J F. Ozone preservation of Foods and Foodstuffs 13th Ozone World Congress, October 1997, Kyoto, Japan

Lien, E , Boyle, F , Perry, Thompson, C , Borzelleca, J F , and Wrenn, J.. Comparison of AIN-76A and AIN-93G Diets in Rats, a 13 Week Study. *Fed. Proc* , 1998

Munro, E C , Berndt, W O , Borzelleca, J.F , Flamm, G , Lynch, B.S., Kennepohl, E., Bar, A. and Modderman, J Erythritol An Interpretive Summary of Biochemical, Metabolic, Toxicological and Clinical Data *Toxicologist* 38: 1999

000063

## BOOKS and BOOK CHAPTERS

Skalsky, H L , Lane, R W and Borzelleca, J F "Excretion of carbaryl into saliva of the rat and its effect on cholinesterase" In. Toxicology and Occupational Medicine (W.B. Deichman, ed.), p 349, 1979

Borzelleca, J F. and Carmines, E L.. "New drug evaluation safety assessment". In: Program for Applied Research on Fertility Regulation, 1980.

Hayes, J F and Borzelleca, J F "Biodisposition of environmental chemicals by animals". In: Animal Products in Human Nutrition (D Beitz and R. Hansen, eds ), Chap 11, p. 225. Academic Press, New York, 1982

Borzelleca, J F "Neurobehavior toxicological testing". Pharmacodependence and neurobehavioral toxicology Quo Vadis ?, Symposium "Quo Vadis ?", Sanofi Group, Montpellier, France, p 115, 1983

Schwartz, S L and Borzelleca, J F "Toxicology of polyvinylpyrrolidone". Proceedings of the International Symposium on Povidone (G A Digenis, Ed.), College of Pharmacy, University of Kentucky, Lexington, KY, p. 234, 1983

Borzelleca, J F , Hallagan, J and Reese, C. "Food, Drug and Cosmetic Colors. Toxicological Considerations " ACS Symposium Series, No 234, Xenobiotics in Foods and Feeds. (Finley, J W and Schwass, D E , eds.), Chap. 20, p.31-41 ACS, Washington, D.C., 1983

Borzelleca, J F "Extrapolation of animal data to man". In: Toxicology Laboratory Design and Management for the 80's and Beyond (Tegeris, A.S , Ed); Vol 1 of Concepts in Toxicology, Homburger, F , Series Ed.), 1984

Borzelleca, J F "Current concepts in reproductive toxicology". In: Clinics in Laboratory Medicine, Symposium on Environmental and Occupational Health Hazards, Vol 4 (R.V. Blanke, ed ), W B Saunders Co , Philadelphia, 1984

Borzelleca, J F , Condie, L W., and Hayes, J R : "Toxicological evaluation of selected chlorinated phenols" In Water Chlorination, Chemistry, Environmental Impact and Health Effects. (R.L. Jolley, R J Bull, W P Davis, S Katz, M H. Roberts, Jr., V A Jacobs). Volume 5, Chap. 26, p 331 Lewis Publishers, Inc , Ann Arbor, Michigan, 1985.

Robinson, B V , Sullivan, F M , Borzelleca, J F. and Schwartz, S.L.: PVP. A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone). Lewis Publishers, Inc , Ann Arbor, Michigan 1990

Borzelleca, J F and Hallagan, J B : "Safety and Regulatory Status of Food, Drug, and Cosmetic Colors " ACS Symposium Series, No 484, Food Safety Assessment. (Finley, J.W , Robinson, S F , and Armstrong, D J., eds ), Chap 31, p 377 ACS, Washington, DC 1992

Borzelleca, J F "Foods of the Future: What Will We Be Eating in the Next Century?" In Practical Handbook of Nutrition in Clinical Practice (Kirby, D F and Dudrick, S.J., eds.), Chap. 16, p.279. CRC Press, Inc , Boca Raton, Fl. 1994

Borzelleca, J F . "History of Toxicology " In Principles and Methods of Toxicology (Hayes, A W., editor), edition 3, Chap. 1, p 1-18, Raven Press, New York, NY 1994

000064

Matt, D W and Borzelleca, J.F "Toxic Effects on the Female Reproductive System During Pregnancy, Parturition, and Lactation " In *Reproductive Toxicology* (Witorsch, R.J., editor), edition 2, chapter 10, p 175 Raven Press, New York, NY. 1995

Borzelleca, J F "Food-Borne Health Risks: Food Additives, Pesticides and Microbes." In *Nutrition Policy in Public Health* (Bronner, F., editor). Chap. 3, p.33, Springer Publishing Co New York, NY 1997

Rice, R G , Graham, D M., Glaze, W H , Pariza, M W , Newell, G W., Erdman, J.W , and Borzelleca, J F Ozone Preservation of Foods and Foodstuffs. 13th Ozone World Congress, Kyoto, Japan, October 1997

Borzelleca, J F and Weiner, M L "Development of Safety Evaluation Guidelines." In *Excipient Toxicity and Safety* (Weiner, M L and Kotkoskie, L. A., editors). Chapter 5, p.101. Marcel Dekker, Inc , New York, N Y 1999

**Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)**

Research Office, Federation of American Societies of Experimental Biology (FASEB):

Evaluation of the health aspects of iron and iron salts as food ingredients. 1973.

Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient 1973.

Evaluation of the health aspects of certain zinc salts as food ingredients 1973.

Evaluation of the health aspect of pulps as they may migrate to food from packaging materials. 1973

Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients 1973

Evaluation of the health aspects of alginates as food ingredients 1973.

Evaluation of the health aspects of agar-agar as a food ingredient. 1973.

Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973

Iodine in foods chemical methodology and sources of iodine in the human diet. 1974.

*Evaluation of the health aspects of aconitic acid as a food ingredient 1974.*

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974

*Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycyrrhizin as food ingredients 1974*

Evaluation of the health aspects of Gaprylic acid as a food ingredient. 1974

**000065**

Evaluation of the health aspects of sorbose as a food ingredient 1974.

Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients. 1974.

Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients 1975

Evaluation of the health aspects of dextran as food ingredients. 1975

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975

Evaluation of the health aspects of succinic acid as a food ingredient 1975.

**Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)**

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients 1975

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients 1975.

Evaluation of the health aspects of phosphates as food ingredients. 1975

Evaluation of the health aspects of the tocopherols and  $\alpha$ -tocopheryl acetate as food ingredients. 1975

Evaluation of the health aspects of sorbic acid and its salts as food ingredients 1975.

Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975

Evaluation of the health aspects of inositol as a food ingredient 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

**000066**

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials 1976

Evaluation of the health aspects of hydrosulfites as they may migrate to foods from packaging materials 1976

Evaluation of the health aspects of gum guaiac as a food ingredient 1976.

**Contributing authorship on the following publications of the Life Science Research Office, Federation of American Societies of Experimental Biology (FASEB)**

Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients 1976

Evaluation of the health aspects of sucrose as a food ingredient 1976

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

Evaluation of the health aspects of magnesium salts as food ingredients. 1976. Evaluation of the health aspects of sodium hydroxide and potassium hydroxide as food ingredients. 1976.

Evaluation of the health aspects of adipic acid as a food ingredient. 1976.

Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient

Evaluation of the health aspects of formic acid, sodium formate, and ethyl formate as food ingredients 1976

Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials 1976

Evaluation of the health aspects of pyridoxine and pyridoxine hydrochloride as food ingredients. 1977

Evaluation of the health aspects of papain as a food ingredient 1977.

Evaluation of the health aspects of hypophosphites as food ingredients 1977.

Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they migrate to food from packaging materials, and linoleic acid as a food ingredient 1977

Evaluation of the health aspects of pectin and pectinates as food ingredients 1977.

Evaluation of the health aspects of tannic acid as a food ingredient 1977

**000067**

Evaluation of the health aspects of rennet as a food ingredient 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. 1977

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of corn silk as a food ingredient. 1977.

Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients. 1977

Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977.

Evaluation of the health aspects of lactic acid and calcium lactate as food ingredients. 1978.

Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl alcohol as food ingredients 1978.

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient 1978

Evaluation of the health aspects of certain glutamates as food ingredients 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978.

Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients 1978

Evaluation of the health aspects of urea as a food ingredient 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients 1978

Evaluation of the health aspects of biotin as a food ingredient 1978

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients 1979.

Evaluation of the health aspects of casein, sodium Caseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

000068

**Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)**

Evaluation of the health aspects of soy protein isolates as food ingredients 1979

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient 1979

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods 1979

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979

Evaluation of the health aspects of starch and modified starches as food ingredients 1979.

Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979

Evaluation of the health aspects of certain silicates as food ingredients. 1979

Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients 1979

Evaluation of the health aspects of hydrochloric acid as a food ingredient 1979

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient 1981

**000069**

Evaluation of the health aspects of methyl polysilicones as food ingredients 1981

**Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)**

Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

Evaluation of the health aspects of smoke flavoring solutions and smoked yeast flavoring as food ingredients 1981.

Evaluation of the health aspects of corn mint oil as a food ingredient. 1981

Evaluation of the health aspects of a mixture Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients 1981

Evaluation of the health aspects of peptones as food ingredients. 1981

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients 1981.

Evaluation of the health aspects of oat gum, okra gum, quince seed gum, and psyllium seed husk gum as food ingredients. 1982

**Contributing Authorship on the Following Publications of the National Academy of Sciences**

Principles and Procedures for Evaluating the Toxicity of Household Substances. Committee for the Revision of NAS Publication 1138, Committee on Toxicology, Assembly of Life Sciences National Research Council, National Academy of Sciences National Academy Press, Washington, D C 1977

Drinking Water and Health Safe Drinking Water Committee, Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, National Academy of Sciences Volume 1, 1977; Volume 2, 1980, Volume 3, 1980 National Academy Press, Washington, D C

Estimating Consumer Exposure to Food Additives and Monitoring Trends in Use. Food Additives Survey Committee, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences National Academy Press, Washington, D C. 1992

Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods Pariza, M W , Borzelleca, J F , Cassens, R G., Filer, L J , and Kritchevsky, D , CAST Issue Paper Number 8, November 1997

000070

CURRICULUM VITAE

**W. GARY FLAMM, Ph.D., F.A.C.T., F.A.T.S.**

Former Director, Office of Toxicological Sciences  
U S Food and Drug Administration

**EDUCATION:**

Doctor of Philosophy (Biological Chemistry, University of Cincinnati, Cincinnati, Ohio, 1959-1962.

Master of Science (Pharmaceutical Chemistry), University of Cincinnati, Cincinnati, Ohio, 1957-1959

Bachelor of Science (Pharmacy), University of Cincinnati, Cincinnati, Ohio, 1953-1957.

**PROFESSIONAL POSITIONS:**

Consultant, Flamm Associates, 1988-present

Director, Office of Toxicological Sciences, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (US FDA), 1984-1988

Associate Director for Toxicological Sciences, Bureau of Foods, US FDA, 9/82 - 3/84

Acting Associate Director for Toxicological Sciences, Bureau of Foods, US FDA, 5/82 - 9/82.

Acting Associate Director for Regulatory Evaluation, Division of Toxicology, Bureau of Foods, US FDA, 10/81 - 5/82

Deputy Associate Commissioner for Health Affairs, US FDA, 5/81 - 10/81

Acting Deputy Associate Commission for Health Affairs, US FDA, 7/80 - 7/81

Associate Director for Regulatory Evaluation, Division of Toxicology, Bureau of Foods, US FDA, 11/78 - 7/80

Assistant Director for Division of Cancer Cause and Prevention, National Cancer Institute, NCI, 9/74 - 10/77

Chief, Genetic Toxicology Branch, Bureau of Foods, US FDA, 9/72 - 9/74

Head, Somatic Cell Genetics Section, National Institute of Environmental Health Sciences, National Institutes of Health, 1/72- 9/72

Research Chemist, Cell Biology Branch, National Institute of Environmental Health Sciences, National Institute of Health 6/68 - 1/72

**000071**

Sr Research Fellow, Dept of Zoology, University of Edinburgh, Edinburgh, Scotland, 9/66 -7/68

Research Chemist, National Cancer Institute, National Institute of Health, 7/64 - 9/66.

Research Fellow, California Institute of Technology, 6/62 - 7/64.

Predoctoral Fellow, Department of Biochemistry, University of Cincinnati, 9/59 - 6/62.

**PROFESSIONAL SOCIETIES AND HONORS:**

Fellow, Academy of Toxicological Sciences, 1999 -present

American College of Toxicology (Charter Member) 1977-present

President, 1984-1985

Fellow of the American College of Toxicology, since 1986

Chairman, Program Committee 1983,1984

Membership Committee, 1979,1981

Program Committee, 1984-1985

Nominee Committee, 1982-1983

Council, 1982-1984

Publications Committee, 1983-1984

Environmental Mutagen Society (EMS) (Charter Member) 1969-present

Treasurer, 1973-1974

Council, 1974-1976, 1978-1981

Executive Board, 1975-1976

Chairman, Program Committee, 1974

Chairman, Nomination Committee, 1978-979

Finance Committee, 1979-1980

Long-Range Planning Committee, 1979-1980

Society for Risk Analysis (Charter Member & Co-Founder) 1980-present

Secretary 1992-1997

Council 1988-1990

Program Committee, 1981-1982

President's Advisory Committee, 1981-1982

Membership Committee, 1988-1990

International Society for Regulatory Toxicology and Pharmacology, 1985-present

President, 1990-1992

Vice President, 1988-1990

The Toxicology Forum

Member 1992-present

Program Planning Committee 1980-1994

Sigma Xi

Member, Federal Executive Institute Alumni Association, 1982

Former Member, American Chemical Society, Genetics Society of America,

000072

Former Biophysical Society, American Pharmaceutical Association, Biochemical Society,

Former American Association for the Advancement of Science, New York Academy of Science,  
American Forestry Association

George Scott Memorial Award, Toxicology Forum, 1988

U S FDA Senior Executive Performance Award for Outstanding Performance during fiscal years  
1980,1982,1983,1984

Environmental Mutagen Society's Recognition Award, 1981. "For his accomplishments both in  
research and the administration of toxicology programs, especially for his untiring efforts to establish  
genetic toxicology as an essential component of chemical safety evaluation."

U S Department of Health, Education and Welfare Superior Service Award, 1977. "For vigorous  
leadership in reshaping the philosophy and methods for assessing environmental carcinogenic hazard  
to humans on a national and international scale.

Elected Class Representative to Senior Executive Training Program, 1980

U S Public Health Service Predoctoral Fellowships, 1962, 1963, 1964

Sigma Xi - honorary graduate

U S Public Health Service Predoctoral Fellowships, 1959, 1960, 1961, 1962

Rho Chi - honorary Pharmaceutical Society, 1958

Otto Mooseburger Award in Pharmacy, 1957

#### **ADDITIONAL TRAINING:**

Radiation Biology, University of Sao Paulo, Brazil, 1971

Molecular Biology, University of Edinburgh, Scotland, 1966-1968

Biochemical Genetics, National Institutes of Health, 1965-1966

Molecular Biology, Biophysics, California Institute of Technology, Pasadena, California, 1962-1964

Senior Executive Training Program, Federal Executive Institute, 1980

#### **COMMITTEES, CHAIRMANSHIPS AND RESPONSIBILITIES:**

Special Foreign Assignment to the University of Edinburgh, Edinburgh, Scotland, 1967-1968

Testimony before US Senate on "Chemicals and the Future of Man," 92nd Congress, Subcommittee  
on Executive Reorganization and Government Research, Washington, D.C., 1971

000073

Organizer and Chairman "Methods for the Detection of Somatic Mutations in Man," NIEHS/NIH, Research Triangle Park, North Carolina, 1972

Executive Secretary - Subcommittee on Carcinogen Laboratory Standards, DHEW, 1973-1975  
Chairman - Subcommittee on Carcinogenicity of NTA, Committee to Coordinate Toxicology and Related Programs, DHEW, Bethesda, Maryland, 1974-1975

Executive Secretary - National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis, Bethesda, Maryland, 1975-1977

Chairman - Working group to develop document on "Approach to Determining the Mutagenic Properties of Chemical Substances," CCTRP, DHEW, 1975-1977

Preparation of testimony and hearing statements before NIH appropriation subcommittees of the Congress on cancer prevention for the National Cancer Institute, 1975, 1976

Preparation of testimony and appearance before U S. Senate Health Subcommittee on Diethylstilbestrol Hearings, 1975

Member, DHEW Subcommittee on polychlorinated biphenyls, Bethesda, Maryland, 1975 Coordinated and participated in the interdepartmental HEW study on the toxicology and health effects of polybrominated biphenyl, 1975-1977

Chairman, Carcinogenesis Coordinating Committee, National Cancer Institute, Bethesda, Maryland, 1976-1977

Member of the FDA interagency committee to evaluate carcinogenicity of FD&C Red No. 40, Washington, D C., 1976-1978

Testimony before a U S Congress on saccharin, House Health Subcommittee, 1977

Commissioner's Task Force on the 1977 National Academy of Sciences report on the National Center for Toxicologic Research, Rockville, Maryland, 1977-1978

Chairman, Cancer Assessment Committee, FDA/Bureau of Foods, Washington, D.C., 1978-1988

Chairman, Mutagenicity Working Group on Risk Evaluation, U.S. Environmental Protection Agency, 1978-1980

Chairman, Health Effects of Diesel Fuel Emission, U.S. Environmental Protection Agency, 1978

Testimony before U S House of Representatives, Committee on Science and Technology on Use of Animals in Medical Research and Testing, 1981

Member of Working Group on methods for the integrated evaluation of risks for progeny associated with prenatal exposure to chemicals - WHO/International Program for Chemical Safety 1981

Working Group on Carcinogen Principles, White House Office of Science Technology Policy, 1982

Testimony before a U S House of Representatives, Committee on Science and Technology, hearing on Hazards of Chemicals to Human Reproduction, 1982

000074

Member, Risk Management Working Group, Interagency Risk Management Council, 1984, 1985

Co-chairman, U.S. FDA, Health Hazard Evaluation Board, 1982-1988

Chair, Session on Mutagenesis, Annual Meeting of the American College of Toxicology, 1980

Chairman, Food and Risk Assessment, Mechanisms of DNA Damage and Repair: Implications for Carcinogenesis and Risk Assessment, 1985

Chair, Session on DeMinimus Risk, International Society of Regulatory Toxicology and Pharmacology, 1987

Chairman, Approaches to Validation, In Vitro Toxicology, sponsored by the Johns Hopkins Center for Alternatives to Animal Testing, 1986

Chair, Risk Analysis and the Food and Drug Administration, Society for Risk Analysis, Annual Meeting, 1988

Chair, Risk Assessment in the Federal Government Managing the Process, Toxicology Forum, 1983

Chair, Program Committee, Annual Meeting of the International Society of Regulatory Toxicology and Pharmacology, 1987, 1988, 1989

Chair, Risk Assessment, Toxicology Forum, 1990

Ad Hoc Chair of Expert Panels on Generally Recognized as Safe Substances from 1990-present

#### **FACULTY APPOINTMENTS:**

Adjunct Associate Professor, Department of Zoology, University of North Carolina, Chapel Hill, North Carolina, 1968-1972

Visiting Professor of Biochemistry, University of Sao Paulo, Brazil, 1970 and 1971

Adjunct Professor of Genetics, George Washington University, Washington, D.C., 1972-1974

Visiting Professor, European Molecular Biology Organization, University of Zurich, Zurich, Switzerland, 1973

Visiting Professor, University of Concepcion, Chile, 1979

#### **EDITORIAL AND ADVISORY ACTIVITIES.**

Manuscript review for numerous journals, e.g., Biochem Biophys. Acta, Science, Proc Natl. Acad Sci, J Mol Biology, J. Biochem, Genetics, Biochemical Journal, Expt Cell Research, Cancer Research, J Natl Cancer Institute, Mutation Research, Radiation Research, Food and Chemical Toxicology, J Toxicology and Environ, Health, Genetic Toxicology, CRC Reviews in Toxicology

Associate Editor, Journal of Environmental Health and Toxicology, 1974-1978

000075

Section Editor, Journal of Environmental Pathology and Toxicology, 1978-1982

North American Field Editor, Teratogenesis, Carcinogenesis and Mutagenesis, 1994-present

Editorial Board, Genetic Toxicology, 1975-1978

Editorial Board, Food and Chemical Toxicology, 1977-1988

Editorial Board, Biomedical and Environmental Sciences, 1988-present

Sec Ed , Journal of the American College of Toxicology, 1982-1996

Member of Editorial Board, Journal for Risk Analysis, 1982-1986

Member of Editorial Board, Regulatory Toxicology and Pharmacology, 1986-present

Co-editor, Advances in Modern Toxicology- Mutagenesis, 1976-1978

Co-editor, Carcinogenesis & Mutagenesis, Princeton Scientific Publishers, 1979-1981

Member, Genetics Program Committee, George Washington University, Washington, D.C., 1972-1975

Member, Joint Subcommittee on Mutagenicity, Pharmaceutical Manufacturers Association - Food and Drug Administration, Washington, D C , 1972-1974

Member, Faculty Group, European Molecular Biology Organization, Geneva, Switzerland, 1973

Member, US/USSR Delegation to Moscow, Environmental Health Agreement, DHEW, 1974

Member, Scientific Advisory Board, National Center for Toxicological Research (NCTR), Jefferson, Arkansas, 1975-1978

Chairman, Subcommittee on Mutagenesis, Science Advisory Board, National Center for Toxicological Research, Jefferson, Arkansas, 1975-1978

Chairman, Subcommittee on Genetic and Environmental Influences on Carcinogenesis (*matrix*) Sci. Adv Board, National Center for Toxicological Research, Jefferson, Arkansas, 1975-1978

Member, Toxicology Advisory Committee, Food and Drug Administration, Rockville, Maryland, 1975-1978

Member, National Academy of Sciences, Committee to Develop Principles for Evaluating Chemicals in the Environment, Washington, D C , 1975

Chairman, Subcommittee on Tissue Culture Resources, Sci. Adv. Board, National Center for Toxicologic Research, Jefferson, Arkansas, 1976-1978

Member, National Academy of Sciences Committee to Revise Publication No. 1138, Toxicologic Evaluation of Household Products, Washington, D C., 1976-1977

000076

Chairman, Subcommittee on Mutagenesis of NAS committee to revise Publication No 138, Washington, D C., 1976-1977

Member, National Academy of Sciences Visiting Committee to Review the Food and Nutrition Board, Washington, D C , 1976-1977

Consultant, Organization of American States, Office of Scientific Affairs, Sao Paulo, Brazil, 1971

Consultant, National Science Foundation, Structure and Function of Human Chromosome, Washington, D C., 1971

Advisor, National Science Foundation, Developmental Biology - Cell Biology, Washington, D C 1971-1972, 1978.

Consultant, World Health Organization, consultant group on anti-schistosomal agents, Geneva, Switzerland, 1972

Consultant, National Cancer Institute, Carcinogenesis Program, Bethesda, Maryland, 1972-1974

Consultant, Environmental Protection Agency, Washington, D.C. 1972-1973, 1976-1977

Consultant, Bureau of Drugs, Safety Evaluation, Rockville, Maryland, 1972-1974

Consultant, Consumer Product Safety Commission, 1973-1975, 1977

Consultant, National Institute on Drug Abuse, Rockville, Maryland, 1976-1977

Member, Faculty Group - International Course on Methods for the Detection of Environmental Mutagens, Concepcion, Chile, 1979

Chairman of the FDA's Recombinant DNA Coordinating Committee, 1980-1981

Co-Chairman Joint Committee on Agency-Wide Quality Assurance Criteria (FDA), 1980-1981

Chairman, Scientific Advisory Research Associates Program (FDA), 1980-1981

Chairman, International Visiting Scientific Program (FDA), 1980-1981

Chairman, Agency-Wide Research Review and Planning Group (FDA), 1981

Ex-Officio Member National Cancer Advisory Board, 1980-1981

Member, Interagency Regulatory Liaison Group on 1-Mutagenesis; 2-Cancer Risk, 1979-1981

Organizing Committee for First World Congress on Toxicology and Environmental Health, 1983

Organizing Committee for "Symposium on Health Risk Analysis", 1981

Chairman, Toxicology Committee, National Conference for Food Protection, 1985-1986

Member, NAS Committee on Biomedical Models, 1983-1985

000077

### INVITED PRESENTATIONS:

"Kinetics of Homogentisate Oxidase", Federation of American Societies of Experimental Biology Atlantic City, New Jersey, 1961

"Histone Synthesis", invited speaker, First International Conference on Histone Chemistry and Biology, Santa Fe, California, 1963

"Free and Bound Ribosomes", FASEB, Chicago, Illinois, 1963

"Histone Synthesis" Seminar, California Institute of Technology, Pasadena, California, 1963.

"Association and Dissociation of RNP particles" Seminar, University of Cincinnati, Cincinnati, Ohio, 1963

"Ribosome Synthesis", California Institute of Technology, Pasadena California, 1964.

"Protein and Nucleic Acid Biosynthesis", University of California, Santa Barbara, California, 1964

Biosynthesis and Assembly of Ribosomes", Dupont Laboratories, Wilmington, Delaware, 1964.

"Isopycnic Density Gradient Centrifugation", University of Pennsylvania, Institute for Cancer Research, Philadelphia, Pennsylvania, 1965

"Use of fixed-angle rotors" Seminar, Carnegie Institution of Washington, Washington, D C., 1965.

"Conversion of 23S to 16S RNA", Biophysical Society, Boston, Massachusetts, 1965.

Participant at Gordon Conference on Cell Structure and Function, Meriden, New Hampshire, 1965

"Turn-Over of Mitochondrial DNA" Seminar, National Cancer Institute, Bethesda, Maryland, 1966.

"Isolation and Fractionation of DNA", invited speaker, Symposium on Subcellular Fractionation, London, England, 1967

"Isolation and Properties of Satellite DNA", University of Edinburgh, Scotland, 1967.

Properties of Mouse Satellite DNA", University of Glasgow, Glasgow, Scotland, 1967.

"Isolation of Complementary Strands from Mouse Satellite", Oxford University, Oxford, England 1967.

"Highly Repetitive Sequences of DNA", St. Andrews University, St. Andrews, Scotland,

"Repetitive Sequences in Rodents", Department of Molecular Biology, University of Edinburgh, Edinburgh, Scotland, 1968

"Satellite DNA from the Guinea Pig", Newcastle University, Newcastle, England, 1968

"Isolation, Preparation, and Fractionation of DNA", Imperial Cancer Research Fund, London, England, 1968

000078

"Properties and Possible Role of Satellite DNAs", Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1968

"Highly Repetitive DNA", Yale University, New Haven, Connecticut, 1968

"Structure and Function of Repetitive DNA", invited speaker at Conference on Satellite DNA, American Association for the Advancement of Science, Chicago, Illinois, 1968.

"Properties of Guinea Pig DNA", Symposium on Hybridization of Nucleic Acids, Biochemical Society, Newcastle, England, 1968

"Complementary Strands of Satellite DNAs", Biophysical Society Meeting, Los Angeles, California, 1969

Participant at Gordon Conference on Cell Structure and Function, Hanover, New Hampshire, 1969.

"Classes of DNA in Mammals", University of North Carolina, Chapel Hill, North Carolina,

"Structure and Function of Repetitive DNA", Duke University, Durham, North Carolina,  
"Satellite DNAs in Rodent Species", University of Chicago, Chicago, Illinois, 1969

"Synthesis of DNA Following Alkylation", Temple University, Philadelphia, Pennsylvania,

"Repetitive DNA", Case Western Reserve University, Cleveland, Ohio, 1970.

"Repetitive Sequences of Higher Organisms", University of Nebraska, Lincoln, Nebraska,

"Alkylation of DNA", Biophysical Society Meeting, Baltimore, Maryland, 1970

"Structure and Function of Mammalian DNA", University of Texas, Austin, Texas, 1971

"Repair of Human DNA", National Institute for Environmental Health Sciences, 1971

"Alkylation and Repair of DNA", Oak Ridge National Laboratory, Oak Ridge, Tennessee,

"Repetitive Sequences of DNA", Brooklyn College, New York, New York, 1971

"A Gene Mutational Assay in Mouse Cells", North Carolina State University, Raleigh, North Carolina, 1971

"Lectures on Chemical Mutagenesis", University of Sao Paulo, Sao Paulo, Brazil, 1971 "Lectures and Demonstrations on Ultracentrifugation", University of Sao Paulo, Sao Paulo, Brazil, 1971.

"Chemical Mutagens in the Biosphere", Environmental Mutagen Society, Washington, D.C., 1971

"Molecular Mechanisms of Mutagenesis", invited participant in Workshop on Chemical Mutagens as Environmental Contaminants, sponsored by the Fogarty International Center, Bethesda, Maryland, 1971

"Lectures on Chemical and Radiation Biology", Winter Biochemistry Course, sponsored by Organization of American States, 1971

000079

"Structure and Function of Human Chromosomes", National Science Foundation, Boulder, Colorado, 1971

Chairman of Workshop on "Somatic Cell Mutagenesis", sponsored by National Institute of Environmental Health Sciences, 1972

"Repetitive DNA, Chromosome Defects and Neoplasia", sponsored by National Science Foundation, Minneapolis, Minnesota, 1972.

"Mutagenesis in Mammalian Cells", Duke University, Durham, North Carolina, 1972.

"Mutagenicity of Hycanthone", University of Sao Paulo, Sao Paulo, Brazil, 1972.

"Gene Mutations at the Thymidine Kinase Locus", John Hopkins University, Baltimore, Maryland, 1972

"Repetitive Sequences and Neoplasia", University of Minnesota, Minneapolis, Minnesota, 1972.

"Mutagenicity of Chemical Substances", George Washington University, Washington, D.C., 1973.

"Test Systems for Measuring Mutagenicity", Howard University, Washington, D.C., 1973

"Lectures on Molecular Biology", University of Zurich, Zurich, Switzerland, 1973.

"Mutagenesis and Repair", Swiss Institute for Experimental Cancer Research, Lucerne, Switzerland, 1973

"Mutagenic Test Systems", Food and Drug Administration, Washington, D.C., 1973.

"Relationship of DNA Repair to Mutagenesis", invited participant to Workshop on Mutagenic Test Methods, sponsored by National Institutes of Health, Research Triangle Park, North Carolina, 1973.

"A Tier System Approach to Mutagen Testing", invited speaker at International Conference on Chemical Mutagens, Asilomar, California, 1973

"Lectures on Molecular Genetics", Symposium on Molecular Hybridization, Zurich, Switzerland, 1973

"A New approach to Mutagen Testing", invited speaker at Symposium on Chemical Mutagenesis, Moscow, USSR, 1974

"Introduction to Toxicology", Chairman of Symposium on Collaborative Studies in Toxicology, sponsored by Society of Toxicology and the Association of Official Analytical Chemists, Washington, D C , 1974

"Relevance of Mutagenicity Tests in Toxicology", Saratoga Conference on Molecular Biology and Pathology, Saratoga Springs, New York, 1974.

"Test Systems for Assessing Mutagenic Potential", invited speaker at Symposium on Collaborative Studies in Toxicology, sponsored by SOT and AOAC, Washington, D.C., 1974.

"Use of Gene Mutational Assays as a Model for Risk Assessment", Symposium on Risk Assessment, sponsored by NIH, Wrightsville Beach, North Carolina, 1974.

000080

"Tier System Approach to Mutagen Testing", National Institute of Health, Research Triangle Park, North Carolina, 1974

"Carcinogenesis and Mutagenesis", Procter and Gamble Co , Cincinnati, Ohio, 1975.

"The Need to Quantify Risk", National Cancer Advisory Board, Bethesda, Maryland, 1975

"Mechanisms of Mutagenesis", General Foods Corporation, New York, New York, 1975

"Problems in Carcinogenesis", Worcester Foundation for Experimental Biology, Worcester, Massachusetts, 1975.

Chairman of Workshop for Developing a Document on "Mutagenic Test Procedures", Ocean City, Maryland, 1975

"Mutagenesis as a Toxicologic Problem", Chairman of Gordon Conference Session on Mutagenesis, Meriden, New Hampshire, 1975

"Open Meeting on Mutagenesis", sponsored by National Institutes of Health, Bethesda, Maryland, 1975

"Mutagenic Test Systems", Chairman of Session on Short-Term Test, Symposium entitled, "Toxicology and the Food Industry," Aspen, Colorado, 1975

Session Chairman, Symposium on In Vitro Mutagenicity Tests, Environmental Mutagen Society Miami, Florida, 1975

Workshop on "Principals for Evaluating Chemicals in the Environment", sponsored by the National Academy of Sciences, San Antonio, Texas, 1975

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1976

"Carcinogenicity Assays, Problems, and Progress", Gordon Conference on Toxicology and Safety Evaluation, Meriden, New Hampshire, 1976

"Value of Short-Term Tests in Carcinogenesis", Toxicology Forum, Aspen, Colorado, 1976.

"Presumptive Tests", Symposium on Risk Assessment entitled, "Extrapolation 11", sponsored by DHEW, Pinehurst, North Carolina, 1976.

"Programs of the National Cancer Institute", invited speaker on cancer, sponsored by the American Association of Science, Boston, Massachusetts, 1976

"Assessment of Risks from Carcinogenic Hazard", invited speaker to Symposium on Toxicology, sponsored by Synthetic Organic Chemists Manufacturing Association, Atlanta, Georgia, 1976.

Chairman of Session on Short-Term Tests, Symposium on "Status of Predictive Tools in Application to Safety Evaluation", Little Rock, Arkansas, 1976

"Relevance of Carcinogenicity Testing to Humans", invited speaker at Origins of Human Cancer Cold Spring Harbor Symposium, 1976.

000081

"Human Genetic Disease Versus Mutagenicity Assays", Symposium sponsored by Pharmaceutical Manufacturers Association, Sea Island, Georgia, 1976.

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1976

"Role of the NCI in the National Cancer Program on Environmental Carcinogenesis", invited speaker at Conference on Aquatic Pollutants and Biological Effects with Emphasis on Neoplasia, New York Academy of Sciences, New York, New York, 1976

"Genetic Disease in Human and Mutagenic Test Systems", Albany Medical School, Albany, New York, 1976

"Statistical Problems in Carcinogenesis", University of California, Berkeley, California, 1976.

"Carcinogenesis and Animal Bioassay", Grocery Manufacturers of America, Washington, D.C. 1976

"Problems and Needs in Assessing Carcinogenicity Data", National Clearinghouse for Environmental Carcinogens, 1976

"Carcinogenesis and Cancer Prevention", University of Eastern Virginia Medical College, Norfolk, Virginia, 1977

"Overview of Mutagenesis", Food and Drug Administration, Washington, D.C., 1977.  
Workshop on Carcinogenicity of Aromatic Amines and Hair Dyes, International Agency for Research in Cancer, Lyon, France, 1977

"Strengths and Weaknesses of Current Approaches in Carcinogenesis", session Chairman and speaker on "Federal Regulation of Environmental Carcinogens," Center for Continuing Education, Washington, D.C. 1977

"Program in Carcinogenesis", Cancer Research Safety, NIH, Dulles Airport, Virginia, 1977.

"Predictive Value of Short-Term Tests", invited speaker at Animal Health Institute, Lake Tahoe, Nevada, 1977

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1977.

"Risk Evaluation", in the Federal Regulation of Environmental Carcinogens, sponsored by Center for Continuing Education, Washington, D.C., 1977 "Statistical Considerations of the Dominant Lethal and Heritable Translocation Test", The Washington Statistical Society, 1978.

"Testing Short-Term", 3rd Toxic Substances Control Conference, Government Institutes, Inc. Washington, D.C., 1978

"The Degree of Concern as Defined by Short-Term Carcinogenicity Assays", Pharmaceutical Manufacturers Association, Point Clear, Alabama, 1978.

"Short-Term Predictive Tests", Pharmaceutical Manufacturers Association, Lincolnshire, Illinois, 1978

Chairman of Scientific Review Meeting on the U.S. Environmental Protection Agency Diesel Emission Health Effects Research Program, U.S., EPA, Washington, D.C., 1978.

000082

"Strengths and Weaknesses of Tests for Mutagenesis", Banbury Center of the Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1978

"Detecting and Measuring Carcinogens", Seminar on Government Regulation of Cancer Causing Chemicals, National Center for Administrative Justice, Washington, D.C , 1978.

Workshop on "Chemical Scoring Systems", Interagency Testing Committee (TSCA), San Antonio, Texas, 1978

"Needs for Regulatory Utility of Short-Term Test Data", International Update on Short-Term Tests, The Toxicology Forum, Washington, D C , 1979.

"Proposed Application of Short-Term Tests", International Update on Short-Term Tests, The Toxicology Forum, Washington, D C., 1979

"Current and Proposed Use of Short-Term Tests", Cosmetic, Toiletry and Fragrance Association, Washington, D C , 1979

"Application of Mutagenicity Testing on SOM Food Animal Drugs", Subcommittee on Environmental Mutagenesis, DHEW/CCTRP, 1979

"Application of Mutagenicity Testing in Cyclic Review of Food Additives", Subcommittee on Environmental Mutagenesis, DHEW/CCTRP, 1979

"Recent Developments on Sorbate/Nitrite", Tripartite (U S , Canada, U.K ), Annapolis, Maryland, 1979.

"What is Risk?", International Course on the Detection of Environmental Mutagens, Concepcion, Chile, 1979

"Status of Regulations and Proposed Regulation Covering Environmental Mutagens", International Course on the Detection of Environmental Mutagens, Concepcion, Chile, 1979.

"Food Safety Guidelines", Tripartite (U.S , Canada, U K.), Ottawa, Canada, 1980

"History and Progress in Carcinogenesis", Society of Cosmetic Chemists, 1978.

"Introduction and History of Mutagenicity Testing", Annual Meeting of the American College of Toxicology, 1980

Mutagenicity and Neoplastic Transformation Assays, Course on "Identification and Quantification of Environmental and Occupational Carcinogenic Risks", sponsored by the American College of Toxicology, 1980

Lectured on Molecular Mechanisms at the American College of Toxicology's course on "Identification of Environmental and Occupational Carcinogenic Risks " "Introduction and History of Environmental Mutagenesis", Second Annual Meeting of the American College of Toxicology.

"Risk-Benefit Considerations in Toxicology", The Toxicology Forum, 1981 Winter Meeting,

"Trends in Biosassay Methodology", 75th Anniversary of the Food and Drug Act, Sponsored by the Animal Health Institute

000083

"Relationship Between Science & Regulation", Food and Drug Administration Risk Assessment for Carcinogenic Food Ingredients - EPA, 1982.

FDA Experience with Risk Assessment for Carcinogens in Foods, Food and Drug Law Institute, 1982.

Practical Applications of Risk Analysis, The Food, Drug and Law Institute Conference, 1982

The Future of Carcinogen Testing Implications for Food Safety, A Symposium on Food Safety Laws-Delaney and Other Dilemmas, sponsored by Boston University, 1982

Regulatory Use of Genetic Toxicity, Tests, Society of Toxicology - Mid Atlantic Chapter Meeting on Genetic Toxicology/Predictive or Not, 1983.

Aerosol Spray Adhesives, A Workshop on Principles and Applications of Cytogenetic, Sister Chromatid Exchange, Gene Damage to Problems of Human Health, sponsored by the American College of Toxicology, 1982

Food and Drug Administration Viewpoint on Problem Tumor, Toxicology Forum, Winter Meeting, 1983.

Food-Borne Carcinogens, Second International Conference on Safety Evaluations and Regulations of Chemicals, sponsored by Boston University, 1983

Carcinogenicity of Hair Dyes, Formaldehyde, Nitrates and Beryllium, Symposium on Interpretation of Epidemiological Evidence, sponsored by International Agency for Research on Cancer, 1983.

Use of Acute Toxicity Studies in the Bureau of Foods, Acute Toxicity Workshop, sponsored by the Food and Drug Administration, 1983.

Critical Issues on Science, Technology and Future, The Brookings Institution, 1983.

Challenge to Animal Testing, Chemical Manufacturers Association, 1983.

Regulatory Significance of Workshop Recommendation on Alternatives to Animal Testing, Workshop on Acute Toxicity Testing - Alternative Approaches, sponsored by Johns Hopkins University, 1983.

Role of Mathematical Models in Assessment of Risk and in Attempts to Define Management Strategy, Safety Assessment The Interface Between Law and Regulation, sponsored by International Life Science Institute, 1983

Impact of Short-Term Tests on Regulatory Actions, Conference on Cellular Systems for Toxicity Testing, sponsored by New York Academy of Sciences, 1984.

Requirements of Pre-Market Evaluation, Toxicology Forum, April Meeting, 1984

Use of Short-Term Tests in Risk Assessment, Workshop on RA/RM: Carcinogenesis, sponsored by Society for Risk Analysis, 1986.

A Regulator's Viewpoint, Workshop on Risk Assessment, sponsored by The Procter and Gamble Co., 1986

000084

Risk Assessment, Sensitivity Analysis, GMA Technical Committee Food Protection Meeting, Grocery Manufacturers of America, 1986

Update on Current Approaches in Addressing Threshold of Regulations and DeMinimus Risk, Toxicology Forum, Winter Meeting, 1986

Toxicity Update on BHA/BHT, Toxicology Forum, Aspen Meeting, 1985.

Food Regulatory Issues, Washington Chemical Society, 1984

Issues in Decision Making, Interdisciplinary Discussion Group in Carcinogenicity Studies, sponsored by ILSI, 1986

Recent Developments in Risk Assessment, Medical Issues in Toxic Tort Cases: Risk Assessment, Cancer, and Immunological Injuries, sponsored by the American Bar Association, 1987.

Replacement of the LD50 Tests at the Food and Drug Administration, Workshop on Alternative Tests, sponsored by Mobil Oil, 1987

Risk Assessment/Oncology and Regulatory Issues, The American College of Toxicology, Annual Meeting, 1987

The Need for Situational Analysis and Scientific Judgment in Assessing the Risk from Chemical Carcinogens, New York Academy of Sciences, 1987

Summary of "Workshop on the Role of Liver Enzyme Induction in Carcinogenesis and Drug Interaction", sponsored by Merk, Sharp and Dohme Laboratories, 1988.

Issues and Directions for the Future, Society for Risk Analysis, Annual Meeting, 1988

Pros and Cons of Quantitative Risk Analysis, Institute for Food Technology, Basic Symposium, 1988

Threshold of Regulation for Indirect Food Additives, Workshop on DeMinimus Risk, 1985.

Possible Mechanisms of BHA Carcinogenicity in the Rat, Food Antioxidants: International Perspectives, sponsored by ILSI, 1986

In Vitro Toxicology, General Principles and Concepts in Toxicology and Toxicologic Pathology, Course sponsored by University of Cincinnati, 1987.

Risk Assessment in Product Regulation, Prevention 85, sponsored by the American College of Preventive Medicine, 1985

Establishment of Acceptable Limits of Intake, Second National Conference for Food Protection, 1984.

Use of Short-Term Test Data in Cancer Risk Assessment, Society of Toxicology Annual Meeting (Course), 1988

Critical Assessment of Carcinogen Risk Policy, International Society of Regulatory Toxicology and Pharmacology, 1988

000085

The Food and Drug Administration Procedures and Policies to Estimate Risks of Injury to the Male Reproductive System, Sperm Measures and Reproductive Success, sponsored by Georgetown University, 1988

Risk Assessment of Food and Color Additives, United States-Japan Workshop on Risk Assessment/Risk Management sponsored by The Environmental Protection Agency and Osaka University, 1988.

How Molecular Data is Used in Risk Assessment, Banbury Conference on New Directions in the Quantitative and Qualitative Aspects of Carcinogen Risk Assessment, 1988.

How has the Delaney Clause Impacted on The Food and Drug Administration and Public Health, Food and Drug Law Institute Symposium on The Delaney Clause, 1988.

Presentations at the Toxicology Forum 1989-1994

American College of Toxicology -Annual Meeting "Does the Term Carcinogen Send the Wrong Message", Dec 1998

#### PUBLICATIONS:

Shirkey, H C , Schmidt, G C , Miller, R G , and Flamm W.G , "Animal Sera and Specific Enzymes in the Treatment of Poisoning", Journal of Pesticides, 60 711, 1962.

Flamm, W G , and Crandall, D I , "Evidence for the Existence of Ferrous Mercaptans in the Active Center of Homogentisate Oxidase", Federation Proc., 21:250, 1962

Flamm, W G , and Crandall, D I , "Purification of Mammalian Homogentisate Oxidase and Evidence for the Existence of Ferrous Mercaptans in the Active Center", J Biol. Chem., 238 389,1963.

Flamm, W G , "Purification of Homogentisate Oxidase and an Investigation of its Properties and Active Center", Dissertation Abstracts, 23:1503, 1962

Flamm, W G , Birnstiel, M L., and Filner, P , "Protein Synthesis in Isolated Nuclei of Exponentially Dividing Cells", Biochem Biophys Acta., 76:110, 1963

Flamm, W G , and Birnstiel, M L , "Studies on the Metabolism of Nuclear Basic Proteins in Nucleohistones," In Bonner, J , and Ts'o, P. (Ed ) : The Nucleohistones, San Francisco, Holden-Day, Inc , 1964, pp 230-41

Flamm, W G , and Birnstiel, M L , "Nuclear Synthesis of Ribosomes in Cell Cultures", Biochem. Biophys Acta , 87-101, 1964

Flamm, W G , and Birnstiel, M L , "Inhibition of DNA Replication and its Effect on Histone Synthesis", Experimental Cell Research, 33 616, 1964

Birnstiel, M L , Chipchase, M I H., Flamm, W.G , "The Chemical Composition and Organization of Nucleolar Proteins", Biochem Biophys Acta , 87:111, 1964

Nicholson, M , and Flamm, W G , "The Fate of Functional Ribosomes in Tobacco Cell Cultures", Federation Proc., 23 316, 1964

000086

Birnstiel, M L , and Flamm, W G , "On the Intranuclear Site of Histone Synthesis", *Science*, 145:1435, 1964

Flamm, W G , and Nicholson, M , "Synthesis of RNA in Cultured Tobacco cells", *Biology*, Pasadena, California Institute of Technology, 1964, pp. 136-41

Nicholson, M , and Flamm, W G , "Properties and Significance of Free and Bound Ribosomes from Cultured Tobacco Cells", *Biochem Biophys Acta.*, 108-266, 1965

Flamm, W G , Counts, W B , and Banerjee, M R., "Inhibition of RNA Synthesis in Mouse Skin by actinomycin D and 7,12-dimethylbenz(a)anthracene", *Nature*, 210:541, 1966.

Flamm, W G , Banerjee, M R., and Counts, W.B., "Topical Application of Actinomycin D on Mouse Skin Effect on the Synthesis of RNA and Protein", *Cancer Research*, 26-1349, 1966

Counts, W B , and Flamm, W G , "An Artifact Associated with the Incorporation of Thymine into DNA Preparations", *Biochem. Biophys Acta.*, 114:628, 1966

Flamm, W G , Counts, W B , and Bond, E , "Conversion of 23S to 16S RNA. Evidence of Heterogeneity within the 23S Fraction", *Abstracts Biophysical Society*, 10:7, 1966.

Banerjee, M R , Flamm, W G , and Counts, W.B., "Effect of Actinomycin D on RNA and Protein Synthesis in Mouse Skin", *Proc of the Amer. Assn for Cancer Research*, 7 5, 1966

Bond, E , Flamm, W G , and Burr, H.E., "Intracellular Location and Metabolism of Satellite DNA in Mouse Liver", *American Zoologist*, 6 308, 1966.

Flamm, W G , Bond, E , and Burr, H E , "Density Gradient Centrifugation of DNA in a Fixed-Angle Rotor A Higher Order of Resolution", *Biochem Biophys. Acta* , 129:310, 1966.

Flamm, W G , Bond, E , Burr, H E , and Bond S , "Satellite DNA Isolated from Mouse Liver: Some Physical and Metabolic Properties", *Biochem Biophys Acta.*, 123-652, 1966

Bond, E , Flamm, W G , Burr, H E , and Bond, S., "Mouse Satellite DNA. Further Studies on its Biological and Physical Characteristics and its Intracellular Localization", *J. Mol. Biol.*, 27:289, 1967.

Flamm, W G , McCallum, M , and Walker, P M B , "The Isolation of Complementary Strands from a Mouse DNA Fraction", *Proc. Natl. Acad Sci* , 57:1729, 1967.

Flamm, W G , McCallum, M , and Walker, P M.B , "Isolation of Complementary Strands from Mouse Satellite DNA", *Biochemical J* , 104:38-9, 1967

Flamm, W G , "Use of Fixed-Angle Rotors for the Banding of DNA in CsCl Density Gradients", *Measuring & Scientific Equipment Ltd , Newsletters (London)- A2*, 1967

Flamm, W G., Birnstiel, M L , and Walker, P M.B , "Preparation, Fractionation and Isolation of Single Strands of DNA by Isopycnic Ultracentrifugation in Fixed-Angle Rotors", In: Birnie, G D. (Ed.), *Subcellular Components* London, England, Butterworth Publishing Co , 1968, p 125

000087

Walker, P M B., Flamm, W G., and McLaren, A "The Problem of Highly Repetitive DNA in Higher Organisms", In Lima-De-Faria, A. (Ed.), Handbook of Molecular Cytology. Amsterdam, North Holland Publishing Co., 1969

Flamm, W G , McCallum, M., and Walker, P.M B., "Guinea Pig Satellite DNA Renaturation Characteristics and Strand Separation", Biochemical J., 108:42, 1968.

Flamm, W G , Walker, P M B , and McCallum, M , "Some Properties of the Single Strands Isolated from the DNA of the Nuclear Satellite of the Mouse (mus musculus)", J. Mol. Biol., 40:423, 1969.

Flamm, W G , McCallum, M , and Walker, P M B , "On the Properties and the Isolation of Individual Complementary Strands of the Nuclear Satellite of Guinea Pig DNA", J. Mol. Biol., 42:441, 1969.

Adam, K M G , Blewett, D A , and Flamm, W G., "The DNA of Acanthamoeba- A Method for Extraction and Its Characterization", J Protoz, 16 6, 1969

Flamm, W G , Walker, P M B., and McCallum, M , "Satellites from Nuclear DNA- Large Variation in Properties Among the Genera of Rodentia", Biophysical Journal, 13-219, 1969

Fishbein, L , Flamm, W G , and Falk, H L , Chemical Mutagens in Man's Environment. New York, Academic Press, 1970, p. 360

Flamm, W G , Bernheim, N J., and Spalding, J , "Selective Inhibition of the Semiconservative Replication of Mouse Satellite DNA", Biochem Biophys Acta., 195 273, 1969.

Brubaker, P E , Flamm, W G , and Bernheim, N J., "Effect of Y Chlordane on Synchronized Lymphoma Cells Inhibition of Cell Division", Nature 226:548, 1970

Flamm, W G , Bernheim, N J , and Fishbein, L , "On the Existence of Intrastrand Crosslinks in DNA Alkylated with Sulfur Mustard", Biochem Biophys Acta., 223:657, 1970.

Flamm, W G , Bernheim, N J , and Brubaker, P.E., "Density Gradient Analysis of Newly Replicated DNA from Synchronized Mouse Lymphoma Cells", Experimental Cell Research, 64:97, 1971

Flamm, W G , Birnstiel, M L , and Walker, P M.B., "Isopycnic Centrifugation of DNA- Methods and Applications", In. Birnie, G D (Ed ), Subcellular Components London, England, Butterworth Publishing Co , 1968, pp 279-310.

Flamm, W G , "Chemical Mutagenesis", In Chemical and the Future of Man, Hearings before the Subcommittee on Executive Reorganization and Government Research. U.S. Senate U.S Government Printing Office, April, 1971, pp 27-31

Flamm, W G , "Highly Repetitive Sequences of DNA in Chromosomes", International Review of Cytology, 32 1-55, 1972.

Clive, D , Flamm, W G , and Machesko, M , "Mutagenicity of Hycanthone in Mammalian Cells", Mutation Research, 14 262, 1972.

Flamm, W G , and Drake, J , "The Molecular Basis of Mutation", In. Sutton, H.E., and Harris, M., (Ed ), Mutagenic Effects of Environmental Contaminants New York, Academic Press, 1972, pp. 15-26.

000088

Clive D , Flamm, W G , Macesko, M R., and Bernheim, N J , "A Mutational Assay System Using the Thymidine Kinase Locus in Mouse Lymphoma Cells", Mutation Research, 16:77-87, 1972.

Clive, D , Flamm, W G , Machesko, M R , and Bernheim, N J , "An In Vitro System for Quantitating Mutations at the Thymidine Kinase Locus in L5178Y Mouse Lymphoma Cells", Mutation Research, 21 7-8, 1973

Clive, D , Flamm, W G , and Patterson, J , "Specific Locus Mutational Assay Systems for Mouse Lymphoma Cells", In Hollaender, A (Ed ) Chemical Mutagens, Volume 111. New York, Plenum Press, 1973, 790

Fishbein, L , and Flamm, W G , "Potential Environmental Chemical Hazards, Part Drugs", The Science of the Total Environment, 1. 15-30, 1972

Fishbein, L , and Flamm, W G., "Potential Environmental Chemical Hazards, Part 11. Feed Additives and Pesticides", The Science of the Total Environment, 1 31-64, 1972

Fishbein, L , and Flamm, W G., "Potential Environmental Chemical Hazards, Part 111. Industrial and Miscellaneous Agents", The Science of the Total Environment, 1:117-140, 1972

Brandt, W , Flamm, W G , and Bernheim, N.J , "The Value of HU in assessing Repair Replication of DNA in HeLa Cells", Chernico-Biological Interactions, 5:327-339, 1972

Flamm, W G , and Fishbein, L , "Mutagenic Agents", Science, 175:980, 1972

Legator, M S , and Flamm, W G , "Chemical Mutagenesis and Repair", In Snell, E.E. (Ed. Annual Review of Biochemistry Palo Alto, California, Annual Reviews, Inc , 1973, pp 683-708

Flamm, W G , "The Role of Repair in Environmental Mutagenesis", Environmental Health Perspectives, 215-220, 1973

Flamm, W G , "A Tier System Approach to Mutagen Testing", Mutation Research, 26,329-333, 1974.

Flamm, W G., "Test System for Assessing Mutagenic Potential", J. Amer. Assn. of Analytical Chemists, 58- 668-671, 1975

Flamm, W G , "Introduction Need for Collaborative Studies", J Amer. Assn. of Analytical Chemists, 58, 1975

Drake, J W , and Flamm, W G , "Environmental Mutagenic Hazards", Science, 187:503-514, 1975.

Wilson, J , Brent, R , Flamm, W G , Rice, J , Salhanick, H.A , Spyker, J , and deSerres, F.J., "Environmental Chemicals as Potential Hazards to Reproduction", Principles for Evaluating Chemicals in the Environment Washington, D C., National Academy of Sciences, 1975, pp. 156-197

Mayer, V , and Flamm, W G , "Legislative and Technical Aspects of Mutagenicity Testing", Mutation Research, 29 295-300

Flamm, W G , Guest Editorial, "The Need for Quantifying Risk from Exposure to Chemical Carcinogens", Preventive Medicine, 5 4-6, 1976

000089

Dybas, R A , Hite, M , and Flamm, W G , Chapter, "Detecting Mutagens - Correlation Between the Mutagenicity and Carcinogenicity of Chemicals", In: 1977 Annual Reports in Medicinal Chemistry, 12.234-248, 1977

Green, S , Moreland, F M , and Flamm, W G., "A New Approach to Dominant Lethal Testing", Toxicology and Applied Pharmacology, 39 549-552, 1977.

Flamm, W G , "Role of the National Cancer Institute in the National Cancer Program of Environmental Carcinogens", Ann N Y Acad Sci , 298 593, 1977. ~

Green, S , Sauro, F , and Flamm, W G , "A Modified Dominant Lethal Test", 6th Annual Meeting, Environmental Mutagen Society, 1975

Rauscher, F J , and Flamm, W G., "Etiology of Cancer Introduction", In. Holland, J.F and Frei, E (Ed ), Cancer Medicine Lea & Febiger, Philadelphia

Sheu, C W , Moreland, F M., Oswald, E J , Green, S , and Flamm, W G., "Heritable Translocation Test on Random-Bred Mice with Prolonged Triethylenemelamine Treatment", Mutation Research, 50-241, 1978

Mayer, V M , and Flamm, W G , book chapter in Principles and Practice of Industrial Toxicology, A.L. Reeves (Ed ), Wiley-Interscience, 1975.

Flamm, W G , deSerres, F , Fishbein, L , Green, S., Malling, H , Pertel, R., Prival, M , Roy, V , Rodricks, T , Wolff, G., Valcovic, L., and Zeiger, E., "Approaches to Determining the Mutagenic Properties of Chemicals", Journal of Pathology and Toxicology, 1, No. 2:302-352, 1978.

Flamm, W G , Brusick, D J , Drake, J.W , and Green, S., "Mutagenicity Test, Principles and Procedures for Evaluating the Toxicity of Household Substances", National Academy of Science Report, Washington, D.C , 1978, pp 134-154.

Flamm, W G , and Mehlman, M., editors, Advance in Modern Toxicology, Mutagenesis. Hemisphere Publishing Corporation, Washington, D C., 1978

Flamm, W G , Preface, In. Flamm, W G , and Mehlman, M (Ed.), Advances in Modern Toxicology. Mutagenesis Hemisphere Publishing Corporation, Washington, D.C , 1978.

Flamm, W G , "Genetic Diseases in Humans versus Mutagenicity Test Systems", Advances in Modern Toxicology, Hemisphere Publishing Corporation, Washington, D C , 1978

Flamm, W G , In Hart, R W , A Rational Evaluation of Pesticidal vs Mutagenic/Carcinogenic Action, DHEW Publication No 78-1306, pp 119, Washington, D.C , 1976.

Kimbrough, R , Buckley, J , Fishbein, L , Flamm, W.G , Kasza, L., Marcus, W , Shibko, S., and Teske, R , Animal Toxicology, Environmental Health Perspective, 24.173, 1978.

Sontag, J M , and Flamm, W G , Safety Considerations and Carcinogen Bioassay, Workshop on Cancer Research Safety Proceedings, National Institutes of Health, pp. 35-47, 1977

000090

Flamm, W G , "Strengths and Weaknesses of Tests for Mutagenesis", In: McElheny, V., and Abraham, S , Banbury Report 1, Assessing Chemical Mutagens: The Risk to Humans, Cold Spring Harbor Laboratory, 27-46, 1979

Nightingale, S , and Flamm, W G , "Caffeine and Health. Current Status," Nutrition Update, (Weininger, Briggs, Ed ), Wiley Pub , New York, 3-19, 1982.

Flamm, W G , U S Approaches to Regulating Carcinogens and Mutagens in Food, In. Stich, H.F (Ed ), Carcinogens and Mutagens in the Environment CRC Press, pp. 275-282, 1982.

Tardiff, R , Flamm, W G , Rodricks, J., (Ed ), Actual Versus Perceived Risks, Plenum Publishers, 1982.

Flamm, W G , "Food-Borne Carcinogens," in Homburger, Marquis, (Eds.), Chemical Safety Regulation and Compliance Karger Publishers, Basel Seitzerland, 3-10, 1985

Flamm, W G , and Dunkel, V C , "Impact of Short-Term Test on Regulatory Action," Ann N.Y. Acad. of Sci , 407 395, 1983

Scheuplein, R J , Blumenthal, H , and Flamm, W G , "New Approaches to the Regulation of Carcinogens in Food," J Am. Oil Ch. 61 (4)- 643, 1984

Flamm, W G , and Winbush, J S , "Role of Mathematical Models in Assessment of Risk and in Attempts to Define Management Strategy," Fundamental and Applied Toxicology, 4 S395-S401 1984.

Miller, S A , Flamm, W G , Krewski, D , "Risk Assessment and Risk Management Panel Discussion," Fundamental and Applied Toxicology, 4S402-S407, 1984.

Flamm, W G , "Regulatory Implications of Acute Toxicity Testing," In Goldberg, A M. (Ed ), Acute Toxicity Testing- Alternative Approaches, pp. 283-292, 1984

Kokoski, C J , and Flamm, W G , "Establishment of Acceptable Limits of Intake," Proc. of Second National Conf for Food Protection, pp. 61-72, 1984.

Flamm, W G , "Hair Dyes Laboratory Evidence," In Wald, N J. and Doll, R. (Eds. Interpretation of Negative Epidemiological Evidence for Carcinogenicity, IARC Scientific Publications No. 65, 53-56, Lyon, France, 1985

Flamm, W G , and Frankos, V , "Formaldehyde Laboratory Evidence," In Wald, N.J., and Doll, R., (Eds ), Interpretation of Negative Epidemiological Evidence for Carcinogenicity, IARC Scientific Publications No. 65, 85-90, Lyon, France, 1985.

Flamm, W G , "Nitrates Laboratory Evidence," In Wald, N.J., and Doll, R., (Eds.), Interpretation of Negative Epidemiological Evidence of Carcinogenicity, IARC Scientific Publications No 65, 181-182, Lyon, France, 1985

Flamm, W G , "Beryllium Laboratory Evidence," In Wald, N J , and Doll, R., (Eds.), Interpretation of Negative Epidemiological Evidence for Carcinogenicity, IARC Scientific Publications No 65, 199-201, Lyon, France, 1985

Flamm, W G , and Lorentzen, R (Eds ), Mechanisms and Toxicities of Chemical Carcinogens and Mutagens, 1985.

000091

Flamm, W G , and Lorentzen R , (Eds ) , "Mechanisms and Toxicities of Chemical Carcinogens and Mutagens," Introduction VII-XII Princeton Scientific Publishing Co , Inc., 1985

Flamm, W G , Lorentzen, R , "The Use of In Vitro Methods in Safety Evaluation," *In Vitro Toxicology*, 1: 1-4, 1986

Flamm, W G , "Risk Assessment Policy in the United States", *Risk and Reason: Risk Assessment in Relation to Environmental Mutagen and Carcinogens*, Alan R. Liss, Inc., 141149, 1986.

Flamm, W G , and Scheuplein, R.J., "Use of Short-Term Test Data in Risk Analysis of Chemical Carcinogens," In: Curtis Travis (Ed.), *Carcinogen Risk Assessment, Contemporary Issues in Risk Analysis*, Plenum Publishing New York, N.Y pp 37-48, 1988.

Flamm, W G , Lake, L R., Lorentzen, R J , Rulis, A M , Schwartz, P.S , and Troxell, T.C., "Carcinogenic Potencies and Establishment of a Threshold of Regulation for Food Contact Substances", *Plenum Publishing Corporation, New York, New York*, 87-92, 1988.

Flamm, W G , Editorial on Carcinogenesis, *Regulatory Toxicology and Pharmacology*, 1988.

Flamm, W G , Lorentzen, R L , "Quantitative Risk Assessment (QRA): A Special Problem in Approval of New Products", In: Mehlman, M. (Ed ), *Risk Assessment and Risk Management*. Princeton Scientific Publishing Co , Inc , Princeton, New Jersey, p 91-108, 1988.

Flamm, W G , "Regulatory Implications," In: Alan Goldberg (Ed ) *Acute Toxicity Testing: Alternative Approaches*, Volume 2, Mary Ann Liebert Publishers, New York, 1984.

Flamm, W G , "Issues in Decision Making in Carcinogenesis" (ILSI Monograph Series) Springer Verlag Publishers, pp 241-247, 1988

Flamm, W G , "Pros and Cons of Risk Assessment "in J Taylor and R. Scanlan (Eds ) *Food Toxicology A Perspective on the Relative Risks*," Marcel Dekker Publ. pg. 429-446, 1989.

Scheuplein, R J , and Flamm, W.G., "An Historical Perspective on FDA's Use of Risk Assessment." In: Philip Shubik and Roger Middlekauf (Eds) *International Food Regulation Handbook*, Marcel Dekker, Inc pg 27-51, 1989

Flamm, W G , "Quantitive Risk Analysis of Chemical Carcinogens: Prospects for the 90's and Beyond", *Risk Analysis*, in press

Flamm, G , and Dunkel, V.C , "FDA Procedures and Policies to Estimate Risks of Injury to the Male Reproductive System " In: E Burger and R. Tardiff (Eds ), *Sperm Measures and Reproductive Success*, Alan R Liss Publ pg 21-32, 1989.

Flamm, W G , "Critical Assessment of Carcinogen Risk Policy", *Regulatory Toxicology and Pharmacology*, 9, 216-224 (1989).

Flamm, W G , "Commentary on Risk Assessment" In: Banbury Report 31 -. *Carcinogen Risk Assessment New Directions in the Qualitative and Quantitative Aspects*, Cold Spring Harbor Laboratory, pg 171-174, 1990

000092

Flamm, W G , and Lehman-McKeeman, "The Human Relevance of the Renal Tumor-Inducing Potential of d-Limonene in Male Rats Implications for Risk Assessment" Reg. Tox. and Pharmacol. 13,70-86, 1991.

God, G , and Flamm, W.G , "How Sick A Patient? Report on Workshop on Cancer Risk Assessment" Regulatory Tox and Pharmacol 14, 1-8, 1991

Ashby, J , Doerrler, N G , Flamm, W G , et al "A Scheme for Classifying Carcinogens" Regulatory Tox. and Pharmacol. 12, 270-295, 1990.

Flamm, W G , "Introduction to Safety Testing of Transesterified Fat" J Am. College of Toxicology 13, 51-52, 1994

Shimoda, T , Mandella, R C , Izumi, T , Kitagawa, M , and Flamm, W G "Twenty-Eight-Day Toxicity Study of a Lipase Protease Enzyme From *Rhizopus Niveus* Fed to Rats" J Am. College of Toxicol 13, 53-59, 1994.

Flamm, W G , Kotsonis, F N , and Hjelle, J J "Threshold of Regulation: A Unifying Concept in Food Safety Assessment" In F Kotsonis, M Mackey and J. Hjelle (Eds ) Nutritional Toxicology, Raven Press, pg 223-234, 1994

Kotsonis, F N , Burdock, G A and Flamm, W.G "Food Toxicology" In. C D Klaassen Casareft and Doull's Toxicology, 5th Edition, McGraw Hill Publisher, pg. 909-949, 1996

Flamm, W G , and Hughes, D.H , "Does the Term Carcinogen Send the Wrong Message?", Cancer Letters, 117, 189-194, 1997

Munro, I C , Bernt, W O , Borzelleca, J F , Flamm, W G , et al. "Erythritol. An Interpretative Summary of Biochemical, Metabolic, Toxicological and Clinical Data" Food and Chemical Toxicol. 36, 1139-1174, 1998

Burdock, G A , and Flamm, W G "A Review of the Studies of the Safety of Polydextrose in Food" Food and Chemical Toxicol 37, 233-264, 1999.

WALTER H. GLINSMANN, M.D.

Center for Food and Nutrition Policy  
Georgetown University Graduate School of Public Policy

EDUCATION

1956 BA - Columbia College, New York, NY  
1960 M.D - Columbia College of Physicians and Surgeons, NY  
1960-1965 Internship and Residency in Medicine - New York Hospital (Cornell Medical School), New York, NY – Dept. of Metabolism, Walter Read Army Medical Center

LICENSE

1961-Present New York State Physician, No. 086359.

EMPLOYMENT HISTORY

1998 President, GLINSMANN, INC. Evaluations of safety and health effects of foods, the development of nutritional products, and food-related claims. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University. Member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. Scientific Advisor to the Technical Committee on Food Components for Health Promotion ("Functional Foods"), International Life Sciences Institute, North America. Scientific Advisor to U.S. and International Food Companies.

1995-1997 President, GLINSMANN, INC.. Fellow and Adjunct Professor, Georgetown Center for Food and Nutrition Policy, Graduate School of Public Policy, Georgetown University. Advisor to the Committee on Revision (1995) and member, Expert Panel on Nutrition and Electrolytes, United States Pharmacopeial Convention, Inc. Scientific Advisor to the Technical Committee on Food Components for Health Promotion, International Life Sciences Institute, North America. Expert Consultant, Office of the Deputy Director for Programs, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration (FDA).

1993-1994 Expert in Nutrition, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services (DHHS) Managing Editor for a Surgeon General's Report on Dietary Fat and Health. Provided management/technical support for nutrition and dietary guidance-related activities. Visiting Fellow, Center for Food and Nutrition Policy and The Ceres Forum, Georgetown University.

000094

1992-1993 Director, Nutrition Policy Staff, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Public Health Service (PHS), DHHS. Provided leadership and coordination among DHHS agencies for Nutrition Policy Board functions; implementation of year 2000 nutrition objectives; development of dietary guidance with U.S. Department of Agriculture; and initiatives in food labeling, safety, and fortification: included program coordination for nutrition monitoring and related research; international nutrition conferences; interagency nutrition research initiatives; and preparation of nutrition and health reports and briefing materials.

1987-1991 Associate Director for Clinical Nutrition, Division of Nutrition, CFSAN, FDA. Provided program direction for human clinical and population-based research on: food safety; special dietary use and medical food products; novel food ingredients; health impacts of dietary behaviors of select populations; nutrient imbalances that relate to human morbidity and mortality; and techniques for assessing and monitoring nutritional status and adverse reactions to foods, food additives, and contaminants. Chaired the Center's Health Hazard Evaluation Board and Task Force for developing Guidelines for Clinical Testing for Food Additives and served as senior Center medical officer for developing Medical Foods Regulations. Represented Center or Agency interests and positions and provided guidance on human food safety evaluations to industry.

1983-1987 Chief, Clinical Nutrition Branch, Division of Nutrition, CFSAN, FDA. Developed and managed clinical nutrition activities, human food safety assessments, and the nutrition monitoring program. Special assignments included: FDA Research in Human Subjects Committee; CFSAN Health Hazards Evaluation Board; primary responsibility for Center programs dealing with Clinical Nutrition, Clinical Investigations, Foods for Special Dietary Use, and Health-and Injury-Related Surveillance; Chairperson, Task Forces on Medical Foods Regulation and Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners; and member Task Forces on Biotechnology, Food Monitoring Systems, and Nutrition and Toxicology Research Priorities.

1978-1983 Chief, Experimental Nutritional Branch and Director of Research, Division of Nutrition, CFSAN, FDA. Developed, managed, conducted research based on CFSAN priorities; Special assignments included: FDA Research Involving Human Subjects Committee; Center/FDA Science Liaison; Center Health Hazards Evaluation Committee; and Task Forces on Nitrates-Nitrosamines, Research and Research Facilities Plans, Medical Foods Regulations, and Coordinated Use of Databases to Estimate Exposures.

1968-1978 Chief, Section on Physiological Controls, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, Maryland. Developed and managed research, Chief Intramural Research Contracts Officer; Institute Safety Officer; Member/Chair of Clinical Research Review and Grants and Contracts Review Committees.

1967-1968 Senior Research Investigator, Laboratory of Biomedical Sciences, NICHD, NIH.

1966-1967 Guest Investigator, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, NIH.

000095

1965-1966 Medical Officer - Research Planning and Program Development, Growth and Development Program, NICHD, NIH.

1962-1965 Assistant Chief, Department of Metabolism and Attending Physician in Medicine, Walter Reed Army Hospital, and Senior Investigator, Walter Reed Army Institute of Research, Washington, D.C.

#### PROFESSIONAL MEMBERSHIPS

American Institute of Nutrition, renamed American Society of Nutritional Sciences (Membership Committee, 1986-1991)

American Society for Clinical Nutrition (Membership Committee, 1986-1994: Chair, Publications Management Committee, American Journal of Clinical Nutrition, 1994-1996)

American Physiological Society

New York Academy of Sciences

#### AWARDS

DHHS Secretary's Award for Excellence in Public Service, Implementing the Food Labeling Initiative, 1993.

PHS Citation for exemplary and creative work as a management clinician in nutrition research and investigative matters, 1989

FDA Award of Merit for Leadership, Health Hazard Evaluations, 1988

PHS Unit Commendation, Food Irradiation Safety Evaluation, 1988

PHS Citations for Outstanding Management Performance in Clinical Nutrition and Food Safety Evaluations, 1986-91

PHS Meritorious Service Medal for sustained high quality leadership and outstanding contributions to Nutrition and Food Safety, 1986

FDA Award of Merit for Leadership, Aspartame Clinical Investigation Team, 1986

FDA Commissioner's Special Citation to the Research Involving Human Subjects Committee for unique and outstanding performance to the Food and Drug Administration by promoting research while ensuring the protection of the human subjects involved, 1984

PHS Commendation Medal for sustained high quality leadership and professional accomplishments in planning, implementing, and evaluating nutrition research at the Food and Drug Administration, 1982

000096

#### INVITED LECTURES AND SEMINARS

August 3, 2000 *Communicating Benefits to the Consumer: FTC, FDA, and Claim Substantiation*  
Warner-Lambert-Pfizer Nutrition Symposium, Morris Plains, NJ

Jan. 27, 2000 *Concepts, Standards, and Substantiation of Effects of Functional Foods*

Workshop on Functional Foods, Kappel am Albis, Switzerland

- June 14, 1999 *Scientific Concepts, Standards, and Substantiation*  
American Association of Cereal Chemists Annual Meeting, Functional Foods –  
Strategies for the Food Industry, Newport Beach, CA
- March 30, 1999 *Distinguishing a Nutrient from a Drug*  
Ceres Forum® on What is a Nutrient? Georgetown University Conference  
Center,  
Washington, DC
- June 19, 1998 *The Role of Clinical Investigations in Establishing Safety and Efficacy for  
Functional Foods*  
Course: A Global Perspective on Regulatory Approval for Food Ingredients,  
Nutraceuticals, and Dietary Supplements. Institute of Food Technologists  
Annual Meeting '98, Atlanta, GA
- April 18, 1998 *Functional Foods: Regulatory Considerations*  
Symposium: Functional Foods for Health Promotion: A Public Health  
Opportunity? Experimental Biology '98, San Francisco, CA
- Oct. 27, 1997 *Functional Foods: Regulatory Considerations*  
Panel: Are Consumers Ready for Functional Foods? American Dietetic  
Association Annual Meeting, Boston, MA
- March 13, 1997 *Overview of Research on Health Benefits from Specific Phytochemicals*  
Panel on Demystifying Functional Foods, Public Voice 20th Annual National  
Food Policy Conference, Washington, DC
- Nov 28, 1996 *Dietary Guidance and the U.S. Food Supply: Focus on Infants and Young  
Children*  
Health Visitors Association Centenary Conference, Harrogate, England
- Oct. 17, 1996 *U.S. Health Claims: Rational and Lessons Learned*  
Symposium on Health Claims for Foods in Canada, U. Toronto, Ontario, Canada
- Feb 26, 1996 *Statements of Nutritional Support: Claim Substantiation*  
Symposium on the New Structure/Function Claims Frontier Under DSHEA,  
National Nutritional Foods Association, Washington, DC
- Feb. 9, 1996 *Regulatory Framework: United States*  
Workshop on Antioxidants, ILSI-Europe, Brussels, Belgium
- Jan. 24, 1996 *Perspective on the Future of Designer and Functional Foods: Definitions,  
Regulatory Perspective, and Health Claims*  
Annual Meeting, ILSI, Cancun, Mexico
- Oct. 2, 1995 *Food Labeling and Food Safety Requirements in the United States and  
Oct 3 International Developments in Food Fortification, Foods for Special Dietary Use,  
and Functional Foods, Doosan Technical Center, Seoul, Korea*
- Sept. 26, 1995 *Functional Foods in North America*  
Sept 28 *Regulatory Aspects of Functional Foods*  
First International Conference on East-West Perspectives on Functional Foods,

000097

ILSI-Southeast Asia, Singapore

- Sept.14, 1995 *Adverse Events Associated with Chemical Food Components*  
Safety Forum: Population Subgroups Requiring Special Food Safety Attention  
National Center for Food Safety and Technology, Argo-Summit, IL
- July 12-13, 1995 *Health Benefits vs. Safety Concerns When Developing "Functional" Foods and Regulation of Food Components for Health Promotion and Disease Prevention*  
Nutracon '95: Nutraceuticals and Functional Foods, Las Vegas, NV
- June 20, 1995 *Dietary Guidelines for Infants and Young Children*  
Public Voice Children and Nutrition Conference, Washington, DC

#### PUBLICATIONS

Carpenter, M B , Glinsmann, W H., Fabrega, H. Effects of secondary striatal lesions upon cerebella dyskinesia. *Neurology*. 8: 352, 1958.

Carpenter, M.D., Fabrega, H., Glinsmann, W.H. Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. *J. Neurophysiol.* 22: 22, 1959.

Fiala, S., Glinsmann, W.H., Fiala, A.E. Deoxyribonucleotidase activity during carcinogenesis in rat liver *Naturwiss.* 46: 635, 1959

Swank, R.L., Glinsmann, W.H., Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. *Surgery, Gynecology and Obstetrics* 110: 9, 1960.

Fiala, S., Fiala, A E , Glinsmann, W.H. Deoxycytidylic deaminase in carcinogenic rat liver. *Naturwiss*, 47: 45, 1960.

Fiala, S., Glinsmann, W.H. Acid soluble ribonucleotides in adrenal tissue after hormonal stimulation. *Endocrinology* 68: 479, 1961

Fiala, S , Fiala, A., Glinsmann, W.H. Mechanism of carcinogenesis and proliferation of tumor cells in rat liver. *Pathologie-Biologie* 9: 613, 1961.

Fiala, S., Glinsmann, W.H. A unified concept of cancerogenesis. *Neoplasma* 10: 1, 1963.

Glinsmann, W.H. Renal micropuncture studies during exsanguination hypotension. *Clin. Res.* 12: 252, 1964.

Ericsson, J.L.E., Glinsmann, W.H. Focal degenerative cytoplasmic alterations in liver cells induced by hypoxia Electron microscopic observations. *Acta Path. Microbiol. Scand.* 64: 151, 1965.

Ericsson, J.L.E., Glinsmann, W.H. Observations on the subcellular organization of hepatic parenchymal cells I. golgi apparatus, cytosomes, and cytosomes in normal cells. *Lab. Invest* 15: 750, 1966.

Glinsmann, W.H., Ericsson, J L.E. Observations on the subcellular organization of hepatic parenchymal cells II. Evolution of reversible alterations induced by hypoxia. *Lab. invest.* 15: 762, 1966.

Glinsmann, W.H., Mertz, W Effect of trivalent chromium on glucose tolerance. *Metabolism* 15:

000098

510, 1966.

Glinsmann, W.H., Feldman, F.J., Mertz, W. Plasma chromium during glucose loading. *Science* 152: 1243, 1966.

Mortimore, G., Mondon, C E., King, E., Glinsmann, W.H. Effect of insulin on alterations in liver glycogen. *Am. J. Physiol.* 212: 179, 1967.

Glinsmann, W.H., Mertz, W. Studies on the relationship between chromium and glucose tolerance in man. *Proc. VIIth Internat. Cong. Nutrition*, Vol. 5, p. 714, 1967.

Glinsmann, W.H., Mortimore, G.E. Influence of glucagon and 3', 5'-AMP on insulin responsiveness of the perfused rat liver. *Am. J. Physiol.* 216: 698, 1969

Glinsmann, W.H., Hern, E.P., Linarelli, L.G., Farese, R.V. Similarities between effects of adenosine 3', 5'-monophosphate and guanosine 3', 5'-monophosphate on liver and adrenal metabolism. *Endocrinology* 85: 711, 1969.

Farese, R.V., Linarelli, L.G., Glinsmann, W.H., Ditzion, B.R., Paul, M.I., Pauk, G.L. Persistence of the steroidogenic effect of adenosine-3', 5'-monophosphate *in vitro*: Evidence for a third factor during the steroidogenic effect of ACTH. *Endocrinology* 85: 867, 1969.

Linarelli, L.G., Weller, J.L., Glinsmann, W.H. Stimulation of fetal rat liver tyrosine aminotransferase activity *in utero* by 3', 5'-cyclic nucleotides. *Life Sciences* 9: 535, 1970.

Klein, D.C., Berg, G.R., Weller, J., Glinsmann, W.H. Pineal gland: dibutyl cyclic adenosine monophosphate stimulation of labelled melatonin production. *Science* 167: 1738, 1970.

Glinsmann, W.H., Pauk, G., Hern, E. Control of rat liver glycogen synthetase and phosphorylase activities by glucose. *Biochem. Biophys. Res. Comm.* 39: 774, 1970.

Berg, G., Glinsmann, W.H. Cyclic AMP in depression and mania. *Lancet* 1: 834, 1971.

Sherline, P., Lynch, A., Glinsmann, W.H. Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. *Endocrinology* 91: 680, 1972.

Eisen, H.J., Glinsmann, W.H., Sherline, P. Effect of insulin on glycogen synthesis in fetal rat liver in organ culture. *Endocrinology* 92: 584, 1973.

Zieve, F.J., Glinsmann, W.H. Activation of glycogen synthetase and inactivation of phosphorylase kinase by a single phosphoprotein phosphatase. *Biochem. Biophys. Res. Comm.* 50: 872, 1973.

Eisen, H.J., Goldfine, I.E., Glinsmann, W.H. Regulation of hepatic glycogen synthesis during fetal development: roles for hydrocortisone, insulin receptors. *Proc. Nat. Acad. Sci. (U.S.A.)* 70: 759, 1973.

Sherline, P., Eisen, H., Glinsmann, W.H. Acute hormonal regulation of cyclic AMP content and glycogen phosphorylase activity in fetal liver in organ culture. *Endocrinology* 94: 935, 1974.

Glinsmann, W.H., Eisen, H.J., Lynch, A., Chez, R.A. Glucose regulation by isolated near-term fetal monkey liver. *Pediat. Res.* 9: 600, 1975.

Eisen, H.J., Glinsmann, W.H. Partial purification of glucocorticoid receptor from rat liver using DNA-cellulose. *J. Steroid Biochem.* 6: 1171, 1975.

000099

Huang, K. P., Huang, F.F., Glinsmann, W.H., Robinson, J.C. Regulation of glycogen synthetase activity by two kinases. *Biochem. Biophys. Res. comm.* **65**: 1163, 1975.

Huang, F.L., Glinsmann, W.H. Inactivation of rabbit muscle phosphorylase phosphatase by cyclic AMP-dependent kinase *Proc. Nat. Acad. Sci. (U.S.A.)* **72**: 3004, 1975.

Sparks, J.W., Lynch A , Glinsmann, W.H. Regulation of rat liver glycogen synthesis and activities of glycogen cycle enzymes by glucose and galactose. *Metabolism* **25**: 47, 1976.

Sparks, J.W., Lynch A., Chez, R A., Glinsmann, W.H. Glycogen regulation in isolated perfused near-term monkey liver. *Pediat Res.* **10**: 51, 1976.

Huang, F L., Glinsmann, W.H. A second heat-stable protein inhibitor of phosphorylase phosphatase from rabbit muscle. *FEBS Lett.* **62**: 326, 1976.

Eisen, H.J., Glinsmann, W H. Partial purification of the glucocorticoid receptor from rat liver: a rapid two-step procedure using DNA-cellulose. *Biochem, Biophys, Res. Comm.* **70**: 367, 1976.

Huang, K. P., Huang, F.L , Glinsmann, W H., Robinson, J.C Effect of limited proteolysis on activity and phosphorylation of rabbit muscle glycogen synthetase. *Arch. Biochem. Biophys.* **173**: 6, 1976.

Huang, F.L., Glinsmann, W H. Separation and characterization of two phosphorylase phosphatase inhibitors from rabbit skeletal muscle. *European J Biochem.* **70**: 419, 1976.

Nakai, C., Glinsmann, W.H. Effects of polyamines on nucleosidediphosphate kinase activity. *Biochem Biosphys. Res. Comm.* **74**: 1419, 1977.

Nakai, C., Glinsmann, W.H. Inhibition of rabbit skeletal muscle phosphorylase phosphatase by spermine. *Molec. Cellular Biochem.* **15**: 141, 1977.

Nakai, C , Glinsmann, W.H. Protein inhibitors of phosphorylase phosphatase and cyclic AMP-dependent protein kinase from rabbit muscle. *Molec. Cellular Biochem.* **15**: 133, 1977.

Glinsmann, W.H., Huang, F.L., Tao, S., Nakai, C. Control of rabbit muscle phosphorylase phosphatase activity *Proc. FEBS Congress, Copenhagen.* Elsevier Press, 1977.

Huang, F., Tao, S., Glinsmann, W.H. Multiple forms of protein phosphatase inhibitors in mammalian tissues. *Biochem. Biophys. Res. Comm.* **78**: 615, 1977.

Eisen, H J , Glinsmann, W.H. Maximizing purification of the activated glucocorticoid receptor by DNA-cellulose chromatography. *The Biochem. J., Molecular Aspects,* **17**: 1977.

Nakai, C., Glinsmann, W.H. Interaction between polyamines and nucleotides. *Biochemistry* **16**: 5636, 1977

Buffone, G.J., Sparks, J.W , Johnson, J., Iosefsdin, M., Lewis, S.A., Glinsmann, W.H. Evaluation of an immobilized enzyme electrode system for the monitoring of therapeutic galactose concentrations in neonates. *Clin. Chem.* **23**: 1166, 1977.

Tao, S.H , Huang, F L., Lynch, A , Glinsmann, W.H. Control of rat skeletal muscle phosphorylase activity by adrenalin. *Biochem. J.* **176**: 347, 1978.

Simpkins, R.A., Eisen, H.J., Sparks, J.W., Glinsmann, W.H. Development of gluconeogenesis from galactose by fetal liver explants in organ culture. *Devel. Biol.* **66**: 353, 1978.

000100

Simpkins, R.A., Eisen, H.J., Glinsmann, W.H. Functional integrity of fetal rat liver explants cultured in a chemically defined medium *Devel. Biol.* **66**: 344, 1978.

Sparks, J.W., Avery, G.B., Fletcher, A.B., Simmons, M.A., Glinsmann, W.H. Parenteral galactose therapy in the glucose-intolerant premature infant. *The J. of Pediatrics* **100**: 255, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Urinary chromium excretion of human subjects; effects of chromium supplementation and glucose loading. *Amer. J. Clin. Nutr.* **36**: 1184, 1982.

Anderson, R.A., Polansky, M.M., Bryden, N.A., Roginski, E.E., Mertz, W., and Glinsmann, W.H. Chromium supplementation of human subjects: effects on glucose, insulin, and lipid variables. *Metabolism* **32**: 894, 1983

Anderson, R.A., Polansky, M.M., Bryden, N.A., Patterson, K.Y., Veillon, C., Glinsmann, W.H. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. *J. Nutr.* **113**: 276, 1983.

Yetley, E.A., Glinsmann, W.H. Regulatory issues regarding iron bioavailability. *Food Technol.* **37**: 121, 1983.

Archer, D.L., Glinsmann, W.H. Hypothesis: Intestinal infection and malnutrition initiate acquired immune deficiency syndrome (AIDS). *Nutrition Research* **5**: 9, 1985.

Archer, D.L., Glinsmann, W.H. Enteric infections and other co-factors in AIDS: Possible intervention points from a historical perspective. *Immunology Today* **6**: 292, 1985.

Glinsmann, W.H., Irausquin, H., Park, Y.K. Evaluation of health aspects of sugars contained in carbohydrate sweeteners, report of task force 1986. *J. Nutr.* **116** - supplement 11: S1-216, 1986.

Glinsmann, W.H., Tollefson, L.K., Hattan, D.G. Evaluation of adverse reactions reported to be associated with the use of aspartame-containing products. *Proc. International Aspartame Workshop*, Ed. P.B. Dews Publ. Int'l Life Sci. Inst. - Nutr. Found., Washington, D.C., 1987.

Tollefson, L.K., Barnard, R.J., Glinsmann, W.H. Monitoring of adverse reactions to aspartame. *Proc. First International Meeting on Dietary Phenylalanine and Brain Function*. Ed. R.J. Wurtman and E. Ritter-Walker, p. 347-72, Publ. Ctr. for Brain Sciences and Metabolism Charitable Trust, Cambridge, Massachusetts, 1987.

Glinsmann, W.H., L.K. Tollefson, Park, Y.K. Regulatory status and health aspects of sweeteners. In *Sweeteners: Health Effects*, Ed. G.M. Williams, p. 263-74, Princeton Sci. Publ. Inc., Princeton, New Jersey, 1988.

Glinsmann, W.H., Dennis, D.A. Regulation of nonnutritive sweeteners and other sugar substitutes. In *Sweeteners*, Eds. N. Kretchmer and C. Hollenbeck, p. 257-85, CRC Press, Boca Raton, Florida, 1991.

Glinsmann, W.H. Usefulness of clinical studies in establishing safety of food products. In *ACS Symposium Series, No 484, Food Safety Assessment*, Eds. J.W. Finley, S.F. Robinson, and D.J. Armstrong, p. 105-13, Amer. Chem. Society, 1992.

Vanderveen, J.E., Glinsmann, W.H. Fat substitutes: a regulatory perspective. In *Ann. Rev. Nutr.*, Vol. 12, Eds. R.E. Olsen, D.M. Bier, and D.B. McCormick, p. 473-87, Annual Reviews Inc., Palo Alto, California, 1992.

000101

*Workshop on Dietary Fatty Acids and Thrombosis*, March 1991, Proceedings Eds. J.C. Hoak, W.H. Glinsmann, J.T. Judd. *Amer. J. Clin. Nutr.* 56 - supplement 4: 7835-8265, 1992.

Hyman, F.N , Sempos, E., Saltsman, J., Glinsmann, W.H. Evidence for success of caloric restriction in weight loss and control: summary of data from industry. *NIH Technology Assessment Conference on Methods for Voluntary Weight Loss and Control.* *Ann. Int. Med.* 119: 681-87, 1993.

Glinsmann, W.H., Bowman, B. Public health significance of dietary fructose. In *Health Effects of Dietary Fructose*, Eds. A.L. Forbes and B.A. Bowman. *Amer. J. Clin. Nutr.* 58 - Supplement 5:820-23, 1993.

Glinsmann, W H , Park, Y.K. Perspective on the 1986 FDA assessment of the safety of carbohydrate sweeteners; uniform definitions and recommendations for future assessments. *Amer. J. Clin. Nutr.* 62 (suppl): 161S-9S, 1995.

Shank, F.R., Carson, K., Glinsmann, W.H Putting things in perspective: building on our experience. (1995 Ceres Forum: *Fortifying Policy with Science - The Case for Folate*) *J. Nutrition* 126 (suppl): 781-87S, 1996.

Glinsmann, W. Focus on substitutes that alter gastrointestinal physiology. (*Proceedings of the Workshop on Safety and Regulatory Aspects of Macronutrient Substitutes*, Nov. 1994, Washington, D.C ) *Regulatory Toxicol. and Phamacol.* 23(suppl): S27-30, 1996.

Glinsmann, W. H., Bartholmay, S.J , Coletta, F. Dietary guidelines for infants: a timely reminder. *Nutrition Reviews* 54:50-57, 1996.

Glinsmann, W.H. Functional foods in North America. In *Proceedings of First International Conference on Functional Foods*, Singapore, September 1995. Eds. F.M. Clydesdale and S.H. Chan. *Nutrition Reviews*, Vol. 54, No. 11, Part II, S33-37, 1996.

Glinsmann, W H Perspective on functional food development and commercialization. *J Nutraceuticals, Functional & Medical Foods*, 1:89-93, 1997.

Glinsmann, W H. Functional foods: an overview of regulatory status. *Nutrition Today*, 34:1-4, 1999.

Glinsmann, W. Functional Foods. Special Considerations in the Pediatric Diet. *Pediatric Basics*, 92:2-15, 2000.

000102

SUBMISSION END

000103