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ORIGINAL SUBMISSION

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February 8, 2001

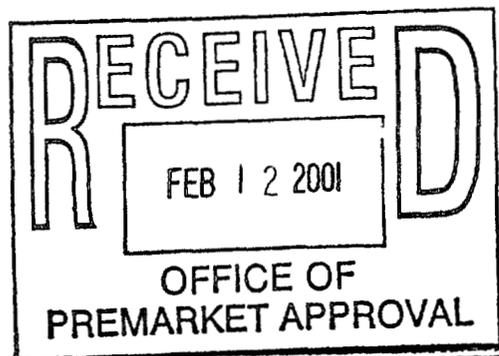
Alan Rulis, Ph.D.
Office of Premarket Approval
(HFF-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

Dear Dr. Rulis:

In accordance with proposed 21 CFR § 170.36 (Notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the agent to the notifier, Thixo Limited, 2 Hashaked Street, Ness Ziona, 74104 Israel, a GRAS notification of behenic acid for use as a texturizer in certain, specified fats and oils, a GRAS panel report setting forth the basis for the GRAS determination and CV's of the members of the GRAS panel for review by the agency.

Sincerely, 

W. Gary Flamm, Ph.D., F.A.C.T., F.A.T.S.



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BEHENIC ACID NOTIFICATION

I. GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR § 170.36 (c)(1)

Behenic acid has been determined to be generally recognized as safe, and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

Date Feb 8, 2001

W. Gary Flamm, Ph.D., F.A.C.T., F.A.T.S.

Agent for:

Thixo Limited
2 Hashaked Street
Ness Ziona, 74104 Israel

BEHENIC ACID NOTIFICATION

B. Name and Address of Notifier

W. Gary Flamm, Ph.D., F.A.C.T., F.A.T.S.
Flamm Associates
622 Beachland Blvd.
Vero Beach, Florida 32963
Telephone: 561-234-0096
Facsimile: 561-234-0026

C. Common Name of the Notified Substance

Behenic acid.

D. Conditions of Use

Behenic acid is intended to be used as an oil structuring and solidifying agent (texturizer as defined in CFR § 170.3(o)(32)) in margarine, shortening and foods typically requiring the use of semi-solid and solid fats at levels of up to 8% of the oil mass of the food item. The estimated mean and 90th percentile intake of behenic acid by the total population from all proposed food uses of behenic acid in the United States was determined to be 0.68 and 1.36 g/person/day.

Background exposure to behenic acid has been estimated at 0.3 g behenic acid/person/day on the basis of 1987 *per capita* consumption data for behenic acid-containing foods (peanuts, peanut butter, peanut oil, hydrogenated and superglycerinated hydrogenated rapeseed oil, and hydrogenated and partially hydrogenated menhaden oil) (FASEB, 1991). In addition, bohenin, a behenic acid-containing triglyceride, is GRAS for use as a tempering aid and as an anti-bloom agent in the manufacture of chocolate and chocolate coatings and has an estimated 90th percentile exposure of 396 mg/person/day for the "all-ages" group and 644 mg/person/day for the 2 to 5 year old group (GRN 000050).

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, behenic acid has been determined GRAS by scientific procedures for its intended conditions of use. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of substance used as ingredients in food. The safety of behenic acid is supported by a number of published studies on behenic acid-containing triglycerides including metabolic studies, acute, subchronic and chronic toxicity studies in experimental animals and clinical studies investigating the nutritional effects of behenic acid. This determination is further supported by the GRAS Notice No. GRN 000050 for bohenin and the published expert panel evaluation of the health aspects of caprenin, a behenic acid rich triglyceride. (See attached – EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE STATUS OF BEHENIC

BEHENIC ACID NOTIFICATION

ACID FOR USE IN SHORTENING, MARGARINE, AND FOODS TYPICALLY CONTAINING SEMI-SOLID AND SOLID FATS).

F. Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the offices of:

W. Gary Flamm, Ph.D.
Flamm Associates
622 Beachland Blvd.
Vero Beach, Florida 32963
Telephone: 561-234-0096
Facsimile: 561-234-0026

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Dr. Flamm.

II. Detailed Information About the Identity of the Substance

A. Identity

Behenic acid, a long-chain fatty acid, is a clear solid with a light odour. It has a melting point of 80 to 82 °C, a boiling point of 306 °C (at 60 mm Hg) and is soluble in both ethanol and ether.

Common or Usual Name: Behenic acid

Chemical Name: n-docosanoic acid

Chemical Abstracts Service (CAS) Number: 112-85-6

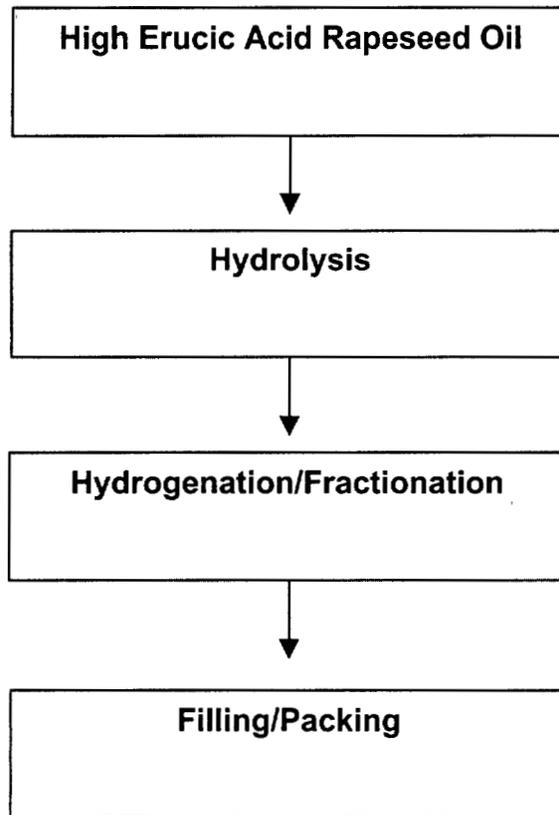
Empirical Formula and Formula Weight: C₂₂H₄₄O₂ Molecular weight 340.5884

Structural Formula: CH₃(CH₂)₂₀COOH

B. Method of Manufacture

Behenic acid is manufactured by hydrolysis of high erucic acid rapeseed oil at a high temperature (at least 200°C) under steam pressure, and subsequent hydrogenation of erucic acid to behenic acid in the presence of a nickel catalyst (See Figure 1). Nickel is a commonly used catalyst for hydrogenation reactions in the production of food (21 CFR § 184.1537). The materials involved are appropriate for food use, and the manufacturing procedures are commonly used in the edible fat industry.

Figure 1. Manufacturing Scheme for Behenic Acid



C. Specifications for Food Grade Material

Specification and Analytical Methods for Behenic Acid		
Specification Parameter	Specification	Analysis Method
Acid value	163-168	ISO 660 [International Organization for Standardization; Animal and vegetable fats and oils - determination of acid value and acidity]
Iodine value [Wijs]	Not more than 2	ISO 3961 [Animal and vegetable oils and fats - determination of iodine value]
Titer (°C)	75-78	ISO 935 [Animal and vegetable oils and fats - determination of titre]
Colour, Lovibond 5¼"	3.5 red 0.8 red	BSI BS 684 [British Standard Institute; British standard method of analysis of fats and oils - determination of colour]
Saponification value	163-169	ISO 3657 [Animal and vegetable fats and oils - determination of saponification value]
Water content (%)	Not more than 0.2	ISO 760 [Determination of water - Karl Fischer method]
Unsaponifiable matter (%)	Not more than 2	ISO 3596-1 [Animal and vegetable fats and oils - determination of unsaponifiable matter]
Residue on ignition (sulphated ash)	Not more than 0.01%	Limit tests; Section 2.4.14 of the European Pharmacopoeia
Heavy metals (as Pb)	Not more than 10 ppm	Limit Tests; Section 2.4.8 of the European Pharmacopoeia (Method D)
Lead	Not more than 1 ppm	Limit tests; Section 2.4.10 of the European Pharmacopoeia
Chain distribution (%)		ISO 5508 [Animal and vegetable fats and oils - analysis by gas-liquid chromatography of methyl esters of fatty acids]
< C19	Not more than 5	
C 20	Not more than 12	
C 22	Not less than 85	
> C 22	Not more than 4	

III. Self-Limiting Levels of Use

At varying levels exceeding 8% of the oil mass of certain food items, the characteristics of the food item would likely be altered. For example, some foods may become too hard at use levels higher than 8% and the texture, mouth feel, melting point, etc. of the product may be altered.

IV. Basis for GRAS Determination

The determination that behenic acid is GRAS is on the basis of scientific procedures. See attached - EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE STATUS OF BEHENIC ACID FOR USE IN SHORTENING, MARGARINE, AND FOODS TYPICALLY CONTAINING SEMI-SOLID AND SOLID FATS).

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF BEHENIC ACID FOR USE IN SHORTENING, MARGARINE, AND FOODS TYPICALLY CONTAINING SEMI-SOLID AND SOLID FATS

January 26, 2001

Introduction

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Panel), qualified by their scientific training and relevant national and international experience in evaluating the safety of food and food ingredients, were requested by Thixo Limited to conduct a comprehensive review of the pertinent data and information to determine whether specified uses of behenic acid in food would be Generally Recognized As Safe (GRAS) in accordance with 21CFR§170.30, 21CFR§170.35 and proposed 21CFR§170.36. Attachment 1 contains the *curriculum vitae* documenting the expertise of the Panel.

The Panel critically evaluated 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 Thixo Limited. This included information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, and exposure estimates.

Following independent, critical evaluation of the data and information, the Panel concluded that behenic acid, meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practices, is "Generally Recognized As Safe" (GRAS) based on scientific procedures for the conditions of intended use described herein. A summary of the basis for this conclusion is provided below.

Background

Semi-solid and solid fats are typically produced through hydrogenation of vegetable oils, which results in the formation of saturated fats and *trans* fatty acids, both of which are associated with elevated serum LDL cholesterol levels and increased risk of heart disease. These fats are also present in certain animal and plant-derived fats. Behenic acid ($\text{CH}_3(\text{CH}_2)_{20}\text{COOH}$) is a clear solid with a melting point of approximately 80-82 °C. Given the physical properties of the acid, a limited addition of behenic acid to oil permits the production of semi-solid and solid fats without the need for hydrogenation.

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Manufacturing and Specifications

Behenic acid is manufactured by hydrolysis of high erucic acid rapeseed oil at a high temperature (at least 200°C) under steam pressure, and subsequent hydrogenation of erucic acid to behenic acid in the presence of a nickel catalyst. Nickel is a commonly used catalyst for hydrogenation reactions in the production of food (FCC, 1996). The manufacturing process for behenic acid complies with Good Manufacturing Practices (GMP), the procedures are commonly used in the edible fat industry, and the materials involved are all appropriate for food use. Specifications are provided in attached Table 1.

Current and Proposed Uses

Behenic is a component of a number of GRAS affirmed products including hydrogenated and partially hydrogenated menhaden oil (21CFR184.1472), hydrogenated and superglycerinated hydrogenated rapeseed oil (21CFR184.1555), peanut oil and hydrogenated soybean oil migrating from cotton packaging to dry foods (21CFR182.70) and glyceryl behenate (21CFR184.1328). Behenic acid is also a component of the tempering aid and anti-bloom agent bohenin (GRN 000050, August 31, 2000). Based on 1987 *per capita* consumption data, exposure to behenic acid from the consumption of peanuts, peanut butter, peanut oil, hydrogenated and superglycerinated hydrogenated rapeseed oil, and hydrogenated and partially hydrogenated menhaden oil has been estimated at 0.3 g behenic acid/person/day.

Behenic acid is intended for use as an oil structuring and solidifying agent (texturizer) in margarine, shortening, and foods typically requiring the use of semi-solid and solid fats, at levels of up to 8% of the oil mass of the food item.

Estimated Exposure

The consumption of behenic acid from the intended uses was estimated using published information on 1-day nutrient (total fat) intake data, and published survey data indicating that (1) the consumption of added fats and oils constitutes up to 47.6% of total fat consumption, and (2) that the intake of margarine and baking and frying fats contributes 47.8% of total added fats and oils consumption. The use of behenic acid will compete with technologies that have already been developed to lower the *trans* fat content of foods and; therefore, will not capture 100% of the replacement market for hydrogenated fats. For example, TransEND® trans-free solid shortenings have been developed for use in baked goods, muffins, spreads, cakes, doughnuts, granolas, crackers, pies, *etc.*, and low or *trans*-free margarines and spreads such as Promise, Smart Beat, Fleischmann's lower fat margarine, and Spectrum Naturals spread are also widely available in the market. Furthermore, future industry initiatives to continually reduce the *trans* fat content of the diet are highly likely given the known adverse health effects associated with a high *trans* fat diet. In addition, many hydrogenated products will remain on the market. An over-estimated market share of 50% of the replacement market for hydrogenated fats in these uses was used in estimating exposure to behenic acid. The estimated mean and 90th percentile intake of behenic acid by the total population from all proposed food uses of behenic acid in the

United States was determined to be 0.68 and 1.36 g/person/day. A summary of behenic acid consumption under the intended uses in food is provided in attached Table 2.

Safety

The Expert Panel critically evaluated the existing metabolic, toxicological and nutritional studies relating to the safety of behenic acid.

Metabolism

In a fat-balance study, behenic acid absorption was reported to be 7% in male rats (Carroll, 1957). Behenic acid has also been reported to be poorly absorbed (3-19% absorption) in animal studies using behenic-acid containing fats such as superglycerinated hydrogenated rapeseed oil and caprenin (Nolen, 1981; Webb and Sanders, 1991; Webb *et al.*, 1991) while absorption from peanut oils is reported to be as high as 59% (Bezard and Sawadago, 1983; Tso *et al.*, 1984). Absorption in a 5-day fat-balance study in 20 healthy adult humans with caprenin was reported to be 29% (Peters *et al.*, 1991).

Absorbed behenic acid can either undergo -oxidation for use as an energy source or follow an anabolic path to be incorporated into wax esters, sphingolipids, glycolipids or acylglycerols (Bernhard and Vischer, 1946; Nicolaidis, 1974; Max *et al.*, 1978; Alexson and Cannon, 1984). Alexson and Cannon (1984) reported very low -oxidation rates for behenic acid and other very long (C20-C22) chain acids. In contrast, Bernhard and Vischer (1946) reported that rats fed a diet containing either 5% deuterated ethyl behenate and 5% olive oil or 10% deuterated ethyl behenate alone absorbed 40% of the behenate and attributed the labeled C18, C16 and C14 fatty acids present in the lipids of the rat carcasses to -oxidation of the behenic acid.

Toxicological Studies

Data on the subchronic and chronic toxicity of behenic acid are lacking; however, numerous toxicity studies on behenic acid-containing fats, including 4 pivotal toxicological studies in which behenic acid was present in the test diet at concentrations ranging from 6 to 13% (Webb *et al.*, 1991, 1993) have been conducted. A summary of these pivotal studies is provided in the table below.

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SUMMARY OF THE PIVOTAL RAT AND HAMSTER TOXICOLOGICAL STUDIES ON BEHENIC ACID-RICH TRIGLYCERIDES, AS COMPARED TO THE ESTIMATED INTAKE OF BEHENIC ACID IN HUMANS

Number of Animals	Exposure Period	No-Observed-Adverse-Effect Level for Behenic Acid (g/kg body weight/day)	Ratio of Experimental Dose/Human Intake ^{A,B,C}	Reference
hamster	28-days	4.36	145	Webb <i>et al.</i> , 1991
rat	23-days	7.13	238	Webb <i>et al.</i> , 1991
rat	28-days	4.04/4.86	162	Webb <i>et al.</i> , 1991
rat	91-days	5.94/6.57	219	Webb <i>et al.</i> , 1993

^A based on 90th percentile consumption of 0.03 g/kg body weight/day¹.

^B ratio of experimental dose/estimated daily human intake

^C highest dose used in all calculations

Three groups of 30 male Sprague-Dawley rats were fed diets containing 25.8% fat as either corn oil, a medium-chain triglyceride (MCT) or behenic medium-chain triglyceride (BMCT; 51% behenic acid) for 23 days (Webb *et al.*, 1991). Significant decreases in growth in rats fed the MCT and BMCT diets were attributed to lower feed intake and decreased fat absorption, respectively. Carcass fat analysis demonstrated that only 0.78 g of the absorbed behenic acid was stored in the rat [14.7% of the total amount absorbed (5.3 g)].

Three groups of 9 adult male golden Syrian hamsters were fed diets containing 84.8% pelleted rodent chow, 0.2% cholesterol, and 15% of BMCT or MCT oil for 28 days (Webb *et al.*, 1991). A control group received chow without added fat (5.6% total fat and 0.02% cholesterol). Significant increases in body weight gain and gross feed efficiency were reported in rats fed the BMCT diet in comparison to controls due to the lower caloric density of the control diet. Behenic acid was poorly absorbed in this study (3 to 4% absorption).

Four groups of 30 CrI:CD@BR rats (15 male and 15 female) were fed semi-purified diets containing 0, 5, 10, or 15% BMCT for 28 days (Webb *et al.*, 1991). Corn oil was added to maintain total fat content at 18% and to provide a source of essential fatty acids. All diets containing BMCT resulted in significantly lower male body weights attributed to lower fat and energy absorption. Similarly, a significant increase in relative testes-to-terminal body weight ratios resulted from reduced growth.

Sporadic differences in hematology and serum chemistry parameters were not dose related or consistent across sexes and were within the normal range of historical reference values, with

¹ Estimated 90th percentile intake of behenic acid on a per kilogram basis assuming an average body weight of 52 kg for the total population. This body weight was determined using mean children and adult body weights (EPA, 1997) and assumed equal contribution of all age groups to the population body weight.

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the exception of serum alanine aminotransferase (ALAT). ALAT was elevated in mid- and high-dose caprenin female groups, and in the high-dose males, with only the high-dose female values falling outside of the normal historical range for this sex and species. Given the lack of alteration in serum aspartate aminotransferase, alkaline phosphatase and bilirubin levels and the absence of any histopathological findings in the liver, the increase in serum ALAT is not considered to be treatment related but rather an adaptation to the diet. Behenic acid was poorly retained by both sexes in this study with concentrations of BMCT at 1.7% in any depot site for either sex, at any level of BMCT intake. ALAT values in rats have previously been correlated with dietary protein intake, particularly in female rats (Knox and Greengard, 1965), and to weight-restrictive diets (Clapp, 1980), high sucrose diets (Porikos and Van Itallie, 1983) and high fat diets (Krajcovicova-Kudlackova and Dibak, 1985). In a subsequent 91-day rat feeding study with caprenin, test diets were prepared to provide 4,000 kcal/kg and the same number of calories from fat, protein and carbohydrate. In this study, no statistically significant increase in ALAT was reported in males and although significant increases were reported in mid- and high-dose females, all values were reported to be within historical control ranges. The panel concluded that the increase in serum ALAT is a consequence of a physiological adaptation to the diet. Furthermore, the increases reported here occurred only at very high doses of caprenin (approximately 10-11g caprenin/kg body weight/day). These intake levels correspond to approximately 4-5 g behenic acid/kg body weight/day; levels which are 130 to 160 times that of the 90th percentile exposure for behenic acid from its intended uses.

The no-observed-adverse-effect level (NOAEL) is >15% in the diet (approximately 9.60 and 11.5 g caprenin/kg body weight/day, for male and female rats, respectively); the highest dose tested. This equates to a NOAEL of approximately 4.04 and 4.86 g behenic acid/kg body weight/day for male and female rats, respectively.

Twenty-five weanling Sprague-Dawley rats/sex/group were administered a semi-purified diet containing caprenin [behenic acid (45%)] at dietary concentrations of 5.23, 10.23 or 15.00%, for 91 days (Webb *et al.*, 1993). Corn oil (12.5%) and a blend of medium chain triglyceride oil plus corn oil (11.21 and 3.13%, respectively; MCT group) were used as controls. Each of the diets was prepared to provide 4,000 kcal/kg and the same percentage of calories from fat, protein, and carbohydrate. An additional 5 rats/sex/group were added to the study to investigate the potential storage of behenic acid in the heart, liver or perirenal fat at the end of the study.

No treatment-related deaths, clinical signs or ocular abnormalities were reported nor any significant differences in body weights gains. Significantly lower feed efficiency values occurred in high-dose males due to a significant increase in food consumption attributed to the decreased caloric value of the caprenin in the high-dose diet (less than 5 kcal/g) and to incomplete absorption of behenic acid.

Significant differences between the caprenin and control groups in relative kidney and spleen weights were considered to be unrelated to treatment because they were slight, limited only to relative organ weights, and not dose related.

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Rats fed caprenin had a tendency to have a lower liver weight in comparison to controls. The significance of this finding is not known given the inconsistency of the effect across sexes and with respect to both absolute and relative measurements of liver weight and due to the inverse relationship it displayed with respect to the caprenin doses. The decreased fat deposition in the caprenin-treated groups may have contributed to this finding. Absolute and relative colon weights were significantly higher in the mid- and high-dose male caprenin groups and relative colon weights were significantly increased in all caprenin fed female groups. The increased colon weight is considered to be an adaptive, reversible response to a diet causing an increased fecal mass due to the presence of unabsorbed behenic acid in the colon.

Although dose-related changes occurred in alkaline phosphatase in treated males, ALT in males and females, and total protein, albumin and globulin in females, the values for each parameter were still reported to be within historical control ranges and were not accompanied by adverse histopathological changes.

Results of this study support those of the 23- and 28-day rat feeding studies reported by the same group in which behenic acid was present in the diet at concentrations ranging from 5 to 26% and of the dietary studies where behenic acid was present at lower concentrations (0.3 to 4.59% of the diet; Gopalan *et al.*, 1974; Mattson and Streck, 1974; Svaar *et al.*, 1980; Nolen, 1981). The NOAEL for this study is >15% (w/w in the diet) or >13.2 g caprenin/kg body weight/day for male rats and >14.6 g caprenin/kg body weight/day for females rats. This equates to a NOAEL of 5.94 g behenic acid/kg body weight/day for males and 6.57 g behenic acid/kg body weight/day for females.

Nutritional Studies

The Panel is aware that saturated fatty acids such as palmitic, lauric and myristic acid have long been associated with increased serum cholesterol levels and considered studies relating the intake of behenic acid to serum total, HDL- and LDL-cholesterol levels. Variable results have been reported in these studies; however, collectively they provide evidence that behenic acid is not strongly or definitively associated with an increase in cholesterol levels. Given that the poor absorption of behenic acid could possibly lead to interactions with cationic minerals to form insoluble soaps that would be excreted in the feces, consideration also was given to the possible effects of behenic acid on the absorption of minerals and fat-soluble vitamins.

Ten men were fed liquid-formulated diets containing a mixture of behenic acid-substituted medium-chain triacylglycerol (BMCT) and soybean oil (80:20) as 40% of total energy, for 6 days (Swift *et al.*, 1991). Participants received the diet in a quantity determined to meet their normal maintenance energy requirements as determined from measured metabolic rates using an indirect calorimetry system (these quantities were not reported). Plasma HDL cholesterol in the BMCT and soybean oil group was reported to decrease significantly from 1.06 mmol/L to 0.91 mmol/L.

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In 2 randomized, double-blind studies, 7-17 hypercholesterolemic men consumed baseline diets enriched with either palm oil/palm kernel oil or butter for 3 weeks and then consumed either a caprenin-rich diet (31% behenic acid and 13% capric and 13% caprylic acid) or continued to consume the baseline diet for 6 weeks (Wardlaw *et al.*, 1995). The first study sought to compare the effects of a total substitution of caprenin for the palm/kernel oil fatty acids in 17 men (average caprenin intake of 71 g/day). The second study compared the effects of a gram for gram substitution of caprenin for the 12:0 to 16:0 fatty acids in the butter in 7 men (average caprenin intake of 56 g/day).

Five out of 17 men in study 1 and 2 out of 7 men in study 2 consuming the caprenin diet reported gastrointestinal effects (stomach aches, flatulence and/or loose stool) that were mild to moderate in nature. None of these individuals discontinued their participation in the study. In the first study, total HDL cholesterol and HDL₂ and HDL₃ cholesterol were significantly lower (16, 33, and 16% reductions, respectively) at the end of the study compared to baseline values in the caprenin-fed group and the ratio of total cholesterol to HDL cholesterol increased by 19%.

The absence of a decrease in total cholesterol, LDL cholesterol or apo B-100 at the end of the study in the caprenin-fed group compared to baseline values may be due to one or more of the 3 primary fatty acids present in caprenin (capric, caprylic and behenic acid) contributing to hypercholesterolemia. However, very high doses of caprenin (average intake of 71 g/day) were used in this study. In addition, findings from experimental hamster studies indicate that the cholesterol potential suggested for caprenin may be due to the presence of fatty acids other than behenic acid (Jandacek *et al.*, 1993). In an experimental hamster study using behenic acid-substituted medium chain triacylglycerol oil (BMCT; 40.8% behenic acid) and a triglyceride synthesized from behenic acid and long chain fatty acids (BLCT; 26.8% behenic acid), total and LDL plasma cholesterol were reported to be comparable to those resulting from consumption of an oleic acid-rich triglyceride and lower than those resulting from consumption of triglycerides rich in linoleic and palmitic acid (Jandacek *et al.*, 1993). In an additional study, hamsters consuming BLCT in their diet were reported to excrete 75% of the cholesterol ingested over a 10-day faecal collection period suggesting that behenic acid-rich triglycerides significantly reduce plasma total and LDL cholesterol in comparison to linoleate and palmitate-containing triglycerides by altering cholesterol absorption (Jandacek *et al.*, 1993). Furthermore, the level of behenic acid consumed in this study (approximately 22 g behenic acid/person/day) is 16 times that of the 90th percentile exposure estimates for behenic acid from its intended use in food.

Fifteen men from each group of 17 men in the Wardlaw *et al.* (1995) study participated in a postprandial study (Snook *et al.*, 1996). Following 3 weeks of a baseline diet and 4 weeks on the test diets (caprenin and baseline diets) the men fasted overnight, had their blood sampled, and then consumed a breakfast high in their respective test fat. Four hours after the meal, the chylomicron fatty acid concentrations of 8:0, 10:0, 22:0 and 24:0 were significantly higher, and the 12:0, 14:0 and 20:0 concentrations were significantly lower, in the caprenin group compared to the palm oil/palm kernel oil group. However, the behenic acid concentration in the test meal

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was 5 times greater than that detected in the chylomicrons. No difference was reported between the 2 groups in total serum cholesterol. Based on these findings, a low uptake of the fatty acids C8:0, 10:0, and, in particular, 22:0 into chylomicrons was concluded.

Studies in which rats were fed a behenic acid-rich flour did not report interference between behenic acid and the absorption of either zinc or iron (Hettiarachchy and Erdman, 1984). The low prospected consumption level of behenic acid also reduces any possible adverse effect that behenic acid could have on the absorption of minerals.

Three groups of 6 male rats received an emulsion of either capric, palmitic or behenic acid containing 3 mg of dissolved vitamin A by oral gavage (Blaskovits *et al.*, 1987). A fourth group served as the control group. Blood samples were collected prior to introducing the emulsion and then 1, 2, 3, 4 and 6 hours after. In a second experiment, the rats were grouped and treated as above and then bled for determination of the liver vitamin A concentration. Vitamin A absorption occurred rapidly with peak absorption levels occurring within the first hour, particularly in the behenic acid emulsion group. Liver vitamin A content was increased by approximately 45% in the behenic acid group compared to the control group. These findings indicate a negligible effect of behenic acid on fat-soluble vitamins. Furthermore, given that behenic acid is not capable of serving as a solvent for fat-soluble vitamins, it is less likely to prevent their absorption by carrying them into the feces.

As indicated in the study summaries above, the results of studies investigating the effect of behenic acid intake on cholesterol levels have indicated somewhat variable findings. However, the weight of evidence from the available studies on behenic acid-containing fats indicates that behenic acid is not strongly or definitively associated with higher blood cholesterol levels. Furthermore, the intended level of use of behenic acid is a small fraction of the levels used in the studies showing moderate effects on cholesterol levels. With the reduced level of consumption at the intended use levels of behenic acid, increases in plasma cholesterol are not anticipated. Thus, the presence of low levels of behenic acid in the diet in replacement of hydrogenation and the consumption of *trans* and saturated fat, which has demonstrable effects on cholesterol levels, is favorable. Behenic acid is also unlikely to adversely affect the absorption of minerals or fat-soluble vitamins.

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Conclusion

Based on critical, independent, and collective evaluation of the available data and information, we, as members of an Expert Scientific Panel, conclude that behenic acid, meeting appropriate food grade specifications and manufactured in accordance with current Good Manufacturing Practices, is "Generally Recognized As Safe" ("GRAS") based on scientific procedures for its intended use in food.

W. Garv Flamm, Ph.D., F.A.C.T.

Date

Feb 8, 2001

Ian C. Munro, Ph.D., F.A.T.S., FRCPath

Date

Jan 26/01

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Table 1 Specification and Analytical Methods for Behenic Acid		
Specification Parameter	Specification	Analysis Method
Acid value	163-168	ISO 660 [International Organization for Standardization; Animal and vegetable fats and oils - determination of acid value and acidity]
Iodine value [Wijs]	Not more than 2	ISO 3961 [Animal and vegetable oils and fats - determination of iodine value]
Titer (°C)	75-78	ISO 935 [Animal and vegetable oils and fats - determination of titre]
Colour, Lovibond 5¼"	3.5 red 0.8 red	BSI BS 684 [British Standard Institute; British standard method of analysis of fats and oils - determination of colour]
Saponification value	163-169	ISO 3657 [Animal and vegetable fats and oils - determination of saponification value]
Water content (%)	Not more than 0.2	ISO 760 [Determination of water - Karl Fischer method]
Unsaponifiable matter (%)	Not more than 2	ISO 3596-1 [Animal and vegetable fats and oils - determination of unsaponifiable matter]
Residue on ignition (sulphated ash)	Not more than 0.01%	Limit tests; Section 2.4.14 of the European Pharmacopoeia
Heavy metals (as Pb)	Not more than 10 ppm	Limit Tests; Section 2.4.8 of the European Pharmacopoeia (Method D)
Lead	Not more than 1 ppm	Limit tests; Section 2.4.10 of the European Pharmacopoeia
Chain distribution (%)		ISO 5508 [Animal and vegetable fats and oils - analysis by gas-liquid chromatography of methyl esters of fatty acids]
< C19	Not more than 5	
C 20	Not more than 12	
C 22	Not less than 85	
> C 22	Not more than 4	

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Table 2 Summary of Estimated Daily Per Person Consumption of Behenic Acid from Proposed Uses, in the US by Population Group

Group	Age Group (Years)	Consumption of Margarine and Baking/Frying Fats	Behenic Acid Consumption
		Mean (g/day)	Mean (g/day)
Infant	1 - 2	11.0	0.44
Children, male and female	3 - 5	13.2	0.53
Children, female	6 - 11	15.2	0.61
Children, male	6 - 11	17.1	0.68
Teenagers, female	12 - 19	15.9	0.64
Teenagers, male	12 - 19	23.6	0.94
Adults, female	20 and older	13.9	0.56
Adults, male	20 and older	21.3	0.85
All individuals	<1 and older	17.1	0.68

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EDUCATION

- 1970 Ph.D., Toxicology and Pharmacology, Queen's University, Kingston, Ontario, Canada
1967 M.Sc., Nutrition, McGill University, Montreal, Canada
1962 B.Sc., McGill University, Montreal, Canada

ACCREDITATION

- 1999 Fellow of The Academy of Toxicological Sciences
1988 Fellow of Royal College of Pathologists, London, England

EMPLOYMENT HISTORY

- 1999-Present **University of Toronto**, Department of Nutritional Sciences, Faculty of Medicine.
Toronto, Ontario. Professor.
- 1999-Present **CANTOX HEALTH SCIENCES INTERNATIONAL**, Mississauga, Ontario.
President.
- 1985-1999 **CanTox Inc.**, Mississauga, Ontario, Consultants in Health and Environmental Sciences.
Consultant Toxicologist & Principal.
- 1983-1992 **Canadian Centre for Toxicology**, Guelph, Ontario, Canada.
Director.
- 1981-1983 **Health and Welfare, Canada**, Food Directorate, Health Protection Branch. Ottawa,
Canada. Director General.
- 1976-1981 **Health and Welfare, Canada**, Bureau of Chemical Safety, Food Directorate, Health
Protection Branch, Ottawa, Canada. Director.
- 1975-1976 **Health and Welfare, Canada**, Bureau of Chemical Safety, Health Protection Branch,
Ottawa, Canada. Chief, The Division of Toxicology.
- 1974-1976 **Health and Welfare, Canada**, Bureau of Chemical Safety, Health Protection Branch.
Ottawa, Canada. Section Head, The Division of Toxicology.
- 1963-1974 **Health and Welfare, Canada**, Health Protection Branch, Ottawa, Canada. Research
Scientist.

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COMMITTEE MEMBERSHIPS

- 2000- Member, Georgetown Dialogue Science Council, Georgetown University Center for Food and Nutrition Policy (CFNP)
- 2000- Consultant, FEMA Expert Panel
- 1999 Center for Food Safety and Applied Nutrition (CFSAN) Research Program Committee, Food and Drug Administration
- 1998 Member, Minister's Advisory Board, Canadian Food Inspection Agency
- 1996 Chairman, Institute of Medicine, Subcommittee on Upper Safe Reference Levels of Nutrients
- 1996 Member, Ad Hoc Expert Panel, Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB)
- 1993- Member FAO/WHO Expert Committee on Food Additives
- 1989 Chairman, Expert Group to Develop a Threshold of Regulation for Indirect Food Additives
- 1989-1991 Member, Scientific Committee, International Food Biotechnology Council
- 1985-2000 Member, FEMA Expert Panel
- 1985 Member ILSI-NF, Nutrition and Safety Committee (FNSC)
- 1985 Member, NAS, Committee on Carcinogenicity of Cyclamates.
- 1984 Member, Committee on Food Chemicals Codex.
- 1983-1984 Member, Panel of Chemical Carcinogenesis Testing and Evaluation (National Toxicology Program)
- 1983 Member, The Nutrition Foundation Project on the Use of Mouse Hepatoma Data.
- 1981-1983 Expert Committee on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, The Nutrition Foundation, Inc.
- 1981-1982 Expert Advisory Committee to The Nutrition Foundation, Inc., on the Assessment of the Safety of Lead and Lead Salts in Foods.
- 1981 Chairman, International Committee on Hazards Associated with Dioxin in the Great Lakes.
- 1981 Chairman, WHO Ad Hoc Meeting on the Future of Joint Expert Committees in the Context of the International Program on Chemical Safety, Geneva.
- 1980-1983 Chairman, Health Protection Branch/Food Industry Liaison Committee.
- 1980-1983 Chairman, Interdepartmental Committee on Canning Regulations.
- 1980 Member, Federal Interdepartmental Salmonella Committee.
- 1980 Member, Senior Level Committee (U.S., U.K., Canada).
- 1980 Member, International Life Sciences Institute Experts in Pathology and Toxicology.
- 1980 Member, Technical Committee: WHO International Program on Chemical Safety.
- 1978-1980 Expert Committee on Food Safety - Agriculture Canada
- 1978-1980 Food Safety Council, Social and Economic Committee.
- 1978-1979 U.S. National Academy of Sciences, Subcommittee on Risk Assessment - Safe Drinking Water Committee.
- 1978 Chairman, Tripartite Toxicology Committee (U.S., U.K., Canada).
- 1977-1981 International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC), subcommittee 3.
- 1977-1979 U.S. National Cancer Institute, Cause and Prevention Scientific Review Committee.
- 1976-1984 WHO/FAO Joint Expert Committee on Food Additives.
- 1976-1980 Food Safety Council, Toxicology Committee.
- 1976-1979 Canadian Council on Animal Care.
- 1976-1979 Interdepartmental Committee on Toxicology Needs in Canada.
- 1976-1978 National Research Council Task Force on Mercury and Captan.
- 1975-1976 U.S. National Academy of Sciences Committee on Toxicology
- 1975-1976 WHO/FAO Committee on Criterion Documents on the Toxicology of Environmental Chemicals.

EDITORIAL RESPONSIBILITIES

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

PROFESSIONAL AFFILIATIONS

Professional Society Memberships:

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

Contributions to Professional Societies:

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

AWARDS

1998	International Society of Regulatory Toxicology and Pharmacology "International Achievement Award" for his guiding role as Chairman of the Expert Panel of Members – "Interpretive Review of the Effects of Chlorinated Organic Chemicals".
1975	Society of Toxicology "Achievement Award" for outstanding contributions to the science of toxicology by an individual 35 years of age or younger.

SCIENTIFIC PUBLICATIONS AND MONOGRAPHS

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Tryphonas, H., and Munro, I.C. 1984. Risk-Benefit Assessment in Immunotoxicology. In: Mullen, P.W. (Ed.) NATO ASI Series, Vol. G2 Immunotoxicology.

Clayson, D., Krewski, D., and Munro, I.C. 1984. The power and interpretation of the carcinogenicity bioassay. Regul Toxicol Pharmacol 3:329-348.

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Munro, I.C. 1978. Chapter on ADI Concept. Prepared for the Safe Drinking Water Committee, National Academy of Sciences.

Munro, I.C. 1978. Detecting and Measuring Carcinogens. Presented at the Law and Public Affairs Seminar on Government Regulation of Cancer-Causing Chemicals, December, Washington, DC.

Munro, I.C. 1978. Environmental Contaminants and Food Safety. Presented at the XI International Congress of Nutrition Conference, September, Rio de Janeiro, Brazil.

Munro, I.C. 1978. Reproductive Toxicity and the Problems of *In Utero* Exposure. Presented at the International Symposium on Chemical Toxicology of Food, June, Milan, Italy.

Munro, I.C. 1978. Environmental Contaminants. Presented at the Symposium on Principal Hazards in Food Safety and Their Assessment, FASEB Annual Meeting, April, Atlantic City, New Jersey.

Munro, I.C. 1977. Regulatory Applications of Short-Term Tests for Carcinogenicity. Presented at the Gordon Research Conference, August, Meriden, New Hampshire.

Munro, I.C. 1977. Overview - Dose Selection. Presented at the Toxicology Forum Meeting, July, Aspen, Colorado.

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Munro, I.C. 1977. The Importance of Specifications for Substances in Their Safety Evaluation in Foods. Prepared for the Scientific Committee of the Food Safety Council.

Munro, I.C. 1977. Working Papers for 34 Food Colors. Prepared for Joint FAO/WHO Expert Committee, Geneva.

Charbonneau, S.M., Munro, I.C., and Nera, E. 1977. Chronic Toxicity of Methylmercury in the Adult Cat. Proc. X Symposium on Trace Substances in Environmental Health, Columbia, Missouri.

Munro, I.C. 1976. Considerations in Chronic Toxicity Testing: The Chemical, The Dose, The Design. Presented at the Status of Predictive Tools in Application to Safety Evaluation Conference, November, Little Rock, Arkansas.

Munro, I.C. 1975. Working Paper on Nitrates, Nitrites and Nitrosamines. Prepared for the World Health Organization.

Grice, H.C., DaSilva, Stoltz, D.R., Munro, I.C., Clegg, D.J., and Abbatt, J.D. Testing of Chemicals for Carcinogenicity, Mutagenicity, Teratogenicity.

Munro, I.C. 1974. Chemicals that Cause Food Poisoning. Proc. of Symposium on Food Poisoning and its Significance in the Food Service Industry. Department of National Health and Welfare.

Stavric, B, Lacombe, R., Munro, I.C., and Grice, H.C. 1973. Studies on Chemical Impurities in Commercial Saccharin (Interim Report). Submitted to NRC Committee on Artificial Sweeteners of the National Academy of Sciences of the United States.

Munro, I.C., Moodie, C.A., and Grice, H.C. 1973. An Evaluation of the Carcinogenicity of Commercial Saccharin. Submitted to NRC Committee on Artificial Sweeteners of the national Academy of Sciences of the United States.

Munro, I.C., Charbonneau, S.M., and McKinley, W.P. 1973. Studies on the Toxicity of Methylmercury. Commission of the European Communities, Luxembourg.

Grice, H.C., DaSilva, T., Stoltz, D.R., Munro, I.C., Clegg, D.J., and Abatt, J.D. 1973. Testing of Chemicals, Mutagenicity and Teratogenicity. Department of National Health and Welfare.

Munro, I.C., Hasnain, S., Salem, F.A., Goodman, T., Grice, H.C., and Heggveit, H.A. 1972. Cardiotoxicity of Brominated Vegetable Oils. Myocardiology Volume I. Recent Advances in Studies on Cardiac Structure and Function. p 588.

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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

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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.

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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.

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.

Predocctoral 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, 1978-1979
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,

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

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

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

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

Chairman, Subcommittee on Mutagenesis of NAS committee to revise Publication No. 1138, 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

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, 1968.

"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.

"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, 1969.

"Structure and Function of Repetitive DNA", Duke University, Durham, North Carolina, 1969.

"Satellite DNAs in Rodent Species", University of Chicago, Chicago, Illinois, 1969.

"Synthesis of DNA Following Alkylation", Temple University, Philadelphia, Pennsylvania, 1970.

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

"Repetitive Sequences of Higher Organisms", University of Nebraska, Lincoln, Nebraska, 1970.

"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, 1971.

"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.

"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.

"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 II", 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.

"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.

"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.

"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.

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