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Original Submission

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**Fuji Foods USA**™  
CREATIVE FLAVORS AND SEASONINGS™

January 14, 2003

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

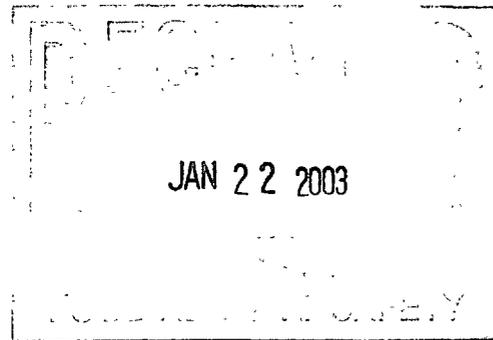
Dear Dr. Rulis,

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 18937-18964), I am submitting in triplicate, as the representative of the notifier, Fuji Foods Inc., 6206 Corporate Park Drive, Browns Summit, NC 27214, a GRAS notification of *Laminaria japonica* broth and extract powder for use as a flavoring agent at levels up to 0.8% in marinade or at final level up to 800 ppm in meat products, poultry, fish products, soups, gravies and seasonings. 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 are also enclosed.

Sincerely,

[Redacted signature box]

Michael Russell  
Chief Operating Officer  
Fuji Foods USA



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**1. GRAS Exemption Claim**

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

*Laminaria japonica* broth and extract powder 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 1/14/03

Michael Russell  
Chief Operating Officer  
Fuji Foods Inc.,  
6206 Corporate Park Drive,  
Browns Summit, NC 27214

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**(i) Name and Address of the Notifier**

Michael Russell  
Chief Operating Officer  
Fuji Foods Inc.,  
6206 Corporate Park Drive,  
Browns Summit, NC 27214

Telephone: 336-375-3111  
Facsimile: 336-375-3663

**(ii) Common Name of the Notified Substance**

*Laminaria japonica* (Kelp; Brown kelp) broth, extract

**(iii) Conditions of Use**

*Laminaria japonica* liquid broth is intended to be used as a flavoring agent and adjuvant [defined in 21 CFR § 170.3(o)(12)] as part of marinade system for meat products, poultry and fish products. *L. japonica* extract powder will be used as part of soup mix or liquid soup base and in gravies. Additionally, the liquid broth will be used as seasoning and flavor. The purpose of these additions is to enhance the flavor. The liquid broth concentration in the marinade flavoring will be used at levels up to 0.8%. The USDA allows 8% marinade flavoring in meat and poultry products. In the 8% marinade flavoring, a maximum of 1% of kelp broth will be used. This would result in 0.08% of the broth in the final 100 g soaked product. For other uses such as soups, gravies and seasonings & flavors a maximum of 800 ppm of the extract will be used in the final product. The estimated mean and 90<sup>th</sup> percentile intake of *L. japonica* broth and extract by the total population from all proposed uses at the maximum use levels as a broth and extract in the United States was determined to be 50 and 150 mg/person/day, respectively.

**(iv) Basis of GRAS Determination**

Pursuant to 21 CFR § 170.3, *Laminaria japonica* broth and extract has been determined GRAS by scientific procedures for its intended conditions of use. The safety of *L. japonica* is supported by its use as a foodstuff in Far East countries (particularly Japan) for millennia and animal and clinical studies. 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.

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**(v) 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 office of:

Michael Russell  
Chief Operating Officer  
Fuji Foods Inc.,  
6206 Corporate Park Drive,  
Browns Summit, NC 27214

Telephone: 336-375-3111  
Facsimile: 336-375-3663

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

**2. Detailed Information About the Identity of the Notified Substance**

**A. Identity**

*L. japonica* liquid broth and powdered extract is prepared from dehydrated seaweed (kelp) obtained from the species *L. japonica* by extracting in water. The product contains only the soluble solids from the kelp. The kelp broth is a brown liquid and has a characteristic salty taste. General description of *L. japonica* broth is presented in Table 1.

Common or Usual Name: *Laminaria japonica* Broth/Extract

**Table 1. General description and analytical information of *L. japonica* broth**

Botanical source	<i>Laminaria japonica</i>
Physical description	Kelp broth is a brown liquid
Packaging	37.47 pounds (17 kg)/plastic bag in a plastic tube
Storage	Store in a cool, dry environment at a constant temperature
Labeling	Kelp broth, salt
Functional use in food	Flavoring ingredient

**B. Composition**

Approximately 1 kg of dry leaves of *L. japonica* will yield about 0.876 kg of the product at about 39% soluble solids and 61% moisture. The broth/extract contains approximately 13% inorganic salts. The remaining soluble solids (26%) of the total liquid are composed of amino acids, sugars and other organic and inorganic materials. But, it is emphasized that all constituents are also present in edible *L. japonica* used generally as

food. Chemical composition of the broth is summarized in Table 2. Amino acid composition of the broth and extract is presented in Table 3. Among the amino acids, glutamate and aspartate are found in relatively high concentrations. Although these levels are relatively high, their consumption from the proposed use levels of broth and extract is very small compared to current permissible levels.

**Table 2. Chemical analysis of *L. japonica* broth**

Chemical analysis	Value
Moisture	61.0 ± 2.5%
Salt	13.0 ± 3.0%
pH	5.2 ± 0.5
Protein	N/A
Fat	N/A
Iodine	1607 ppm
Sodium	1.60%
Potassium	6.71%
Calcium	940 ppm
Magnesium	1852 ppm
Iron	1.85 ppm
Zinc	0.88 ppm

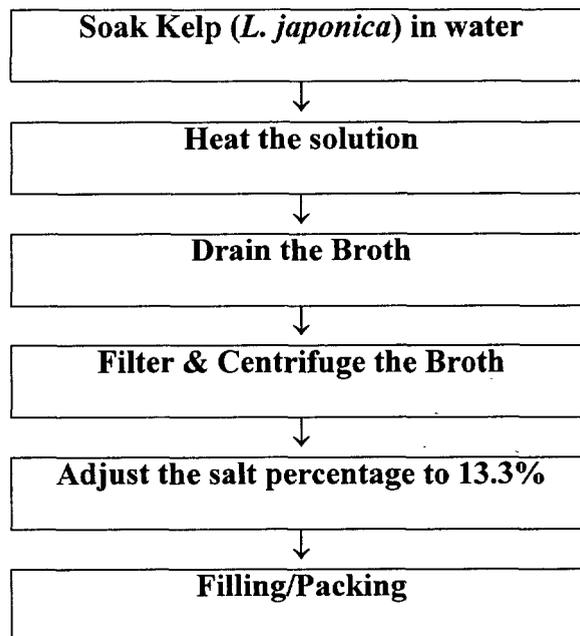
**Table 3. Amino acid composition of *L. japonica* broth and extract**

Amino acid	Broth (mg/100 g)	Extract (mg/100 g)
Aspartate	906	609
Serine	0	14
Glutamate	2276	1719
Alanine	107	82
Ammonia	12	8
Proline	237	230
Threonine	0	0
Serine	0	0
Glycine	0	0
Valine	0	0
Cystine	0	0
Methionine	0	0
Isoleucine	0	0
Leucine	0	0
Tyrosine	0	0
Phenylalanine	0	0
Ornithine	0	0
Lysine	0	0
Histidine	0	0
Arginine	0	0
<b>Subtotal</b>	<b>3538</b>	<b>2662</b>
Other amino acids	44	21
<b>Total all amino acids</b>	<b>3582</b>	<b>2641</b>

### C. Method of Manufacture

The broth and powdered extract is prepared by extraction of dehydrated seaweed (kelp) from the species *Laminaria japonica* in water. The kelp is soaked in water for at least 16 hours. The soaked solution is heated to approximately 190°F for a short while. The broth is drained, filtered and centrifuged. The time of centrifugation is approximately 10 seconds and the gravitational-force applied for centrifugation is approximately 5500 G. The broth is heated to 185°F for at least 5 minutes and salt is added, if necessary, to adjust the salt percentage to approximately 13%. The product contains only the soluble solids from the kelp. The kelp leaves are discarded. For some uses the kelp broth is used to make kelp extract powder. This is done by mixing a carrier such as malto-dextrin into the broth and then spray dried.

Figure 2. Manufacturing Scheme for *L. japonica* Broth



#### D. Specifications for Food Grade Material

<b>Specifications and Analytical Methods</b>		
<b>Specification Parameter</b>	<b>Specification</b>	<b>Analysis Method</b>
Appearance	Brown liquid	
Arsenic	<3 mg/kg (as As, inorganic)	FCC (1996) 209, 756 (modified)
Ash (total)	14-18%	
Heavy metals	0.61 mg/kg (Pb+Hg)	
Iodine content	Not more than 1607 mg/kg	Internal HPLC
Lead	0.56 mg/kg	AOAC 984.27*
Mercury	<0.05 mg/kg	EPA 7471
Cadmium	0.34 mg/kg	AOAC 984.27*
Salt	13-14%	AOAC 935.47*
Brix	36-38%	
Specific gravity	9.99 – 10.06 lbs/gallon	
<b>Microbiological analysis</b>		
Aerobic Plate Count	<100,000	
Coliform	<10	
*Official Methods of Analysis of the AOAC International		

### **III Self Limiting Levels of Use**

At high levels (exceeding 800 ppm) certain food items may acquire an undesirable taste.

### **IV Basis of GRAS Determination**

The determination that *Laminaria japonica* broth/extract is GRAS is on the basis of scientific procedures. See attached- EXPERT PANEL REPORT ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *Laminaria japonica* AS A FLAVORING AGENT

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**EXPERT PANEL REPORT**  
**ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS**  
**OF *Laminaria japonica* BROTH AND EXTRACT POWDER**  
**AS A FLAVORING AGENT**

January 06, 2003

Panel Members

Joseph F. Borzelleca, Ph.D., F.A.T.S.

George A. Burdock, Ph.D., D.A.B.T.

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

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# EXPERT PANEL REPORT ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *Laminaria japonica* BROTH AND EXTRACT POWDER AS A FLAVORING AGENT

## 1. INTRODUCTION

The undersigned, an independent panel of recognized experts (hereafter referred as Expert Panel)<sup>1</sup>, qualified by their scientific training and relevant national and international experience in evaluating the safety of food and food ingredients, was convened to determine the Generally Recognized As Safe (GRAS) status in accordance with 21 CFR § 170.30, 21 CFR § 170.35 and proposed 21 CFR § 170.36, of *Laminaria japonica* broth and extract powder for use as a flavoring agent at levels up to 0.8% in marinade flavoring or at final level up to 800 ppm in meat products, poultry, fish products, soups, gravies and seasonings. A comprehensive search of the scientific literature for safety and toxicity information, specifically on *Laminaria japonica* and on *Laminaria* spp. in general, was conducted through November 2002 and made available to the Expert Panel. The Expert Panel independently and critically evaluated materials submitted by the Fuji Foods USA and other materials deemed appropriate or necessary. Following an independent, critical evaluation of the data and information, the Expert Panel concluded that *L. japonica* broth and extract, meeting appropriate food grade specifications and produced 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.

### 1.1. General Background

*Laminaria japonica* is also known as “giant sea kelp” or *kombu* (Kiple and Ornela, 2000). The giant kelp is a perennial plant with an average life of 8 to 10 years. The mature stipes range in length from 50 to 200 feet. It grows in water 25 to 80 feet deep in areas having a rocky bottom and strong currents and is attached to the ocean floor by a hold-fast or root-like structure (Burdock, 1997). *Laminaria* species are prevalent in the cold waters of the North Atlantic and North Pacific oceans (Burdock, 2002b). In recent years, *L. japonica* has been extensively cultured and different strains are bred for strain selection to improve its production for commercial uses (Li *et al.*, 1999). The entire plant, except the root, is used. General descriptive parameters and properties of kelp and *L. japonica* are summarized in Table 1.

In the informational database (*Everything Added to Food in the United States*) maintained by the FDA, CFSAN has assigned two numerical code numbers (assigned to those substances that do not have a CAS Registry Number) to additives or preparations of this type: one for Kelp (977001-75-4) and other for Brown Algae Extract (977161-38-8). These products also have separate FEMA numbers, 2606 and 2014, respectively. Neither of these two numbers (CFSAN as well as FEMA) cites *L. japonica* specifically, but references all *Laminaria* species as “*Laminaria* spp”. Although not specified, *Laminaria* spp. in general, are included under the name “brown algae extract” (Clydesdale, 1997) and “algin” (Hall and Oser, 1965; Burdock, 2002b). In

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<sup>1</sup>Modeled after that described in section 201(s) of the Federal Food, Drug, and Cosmetic Act, As Amended. See also attachments (curriculum vitae) documenting the expertise of the Panel members.

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addition, FDA has recognized several forms of alginates (derivatives of kelp) for specific food uses, including ammonium alginate, calcium alginate, potassium alginate, sodium alginate and propylene glycol alginate prepared from brown algae, for specific food uses. Algin is a collective term for the hydrophilic colloidal substance isolated from certain brown algae, including *Laminaria*.

**Table 1. General description of *Laminaria japonica* extract or kelp**

Botanical source	<i>Laminaria japonica</i>
Botanical order	<i>Laminariales</i>
Botanical family	<i>Laminariaceae</i>
Synonyms	Kelp; Brown algae; Giant sea kelp; Horsetail; Sea girdles
CFSAN No.	977001-75-4 (kelp) or 977161-38-8 (brown algae extract)
NAS No.	2606
FEMA No.	2606 (kelp)
Storage	Store in a cool, dry environment at a constant temperature
Labeling	Kelp broth, salt
Functional use in food	Dietary supplement; Flavoring ingredient

Bhattacharya *et al.* (1991) conducted restriction enzyme analysis of ribosomal DNA sequence variation in *Laminaria* spp. to differentiate among various species of this genus. In a previous study, these authors found that genotypes are quite similar as DNA reassociation kinetics are not effective in discriminating species of *Laminaria*. Further studies with restriction fragment length polymorphism (RFLP) analysis of nuclear DNA could discriminate the genotypes, with differences in restriction sites occurring in the gene and spacer regions of rDNA from six *Laminaria* species. In this study, identical RFLPs were observed in half of the species. These studies indicate that many of the *Laminaria* spp. are virtually indistinguishable by RFLPs.

### 1.1.1. Chemistry of kelp

In the crude state, *Laminaria* spp. dry matter contains approximately 8% protein, 8% crude fiber, 55% nitrogen free extract (carbohydrates) and 27% minerals (Adrian, 1985). Kelp contains several polysaccharides such as algin, laminarin and fucoidans. Only 4-5% of these carbohydrates are simple glucosides (glucides) that can undergo hydrolysis. Algin (approximately 15-25% dry weight), a high molecular weight polysaccharide forms viscous colloidal solutions or gels in water. Sodium alginate has been isolated from *Laminaria japonica* (Abdussalam, 1990). Elyakova and Zvyagintseva (1974) studied the structure of laminarins [ $\beta$ -(1 $\rightarrow$ 3)-linked D-glucans] from some Far-Eastern brown seaweeds, including *L. japonica*. Inagawa *et al.* (1992) reported detection of lipopolysaccharide (LPS) (14  $\mu$ g/g) in *L. japonica* thallus. *L. japonica* is very sensitive to environmental temperature. Sanina *et al.* (2000) reported a relation between thermotrophic behavior and the fatty acid unsaturation of lipids of *L. japonica*.

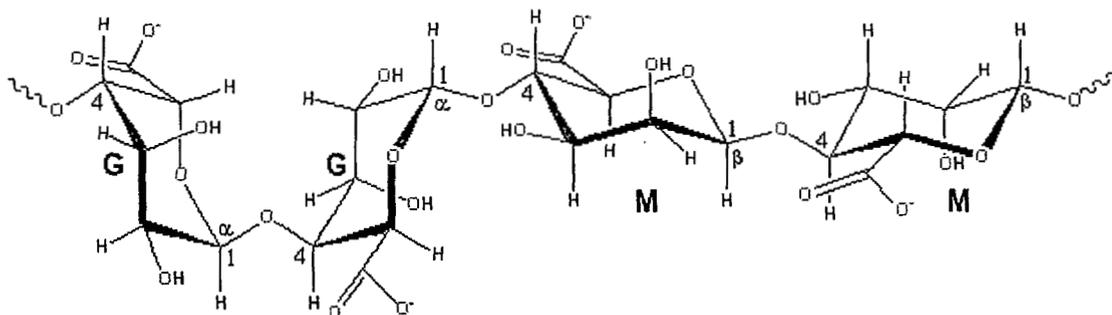


Figure 1. Chemical structure of alginates from brown algae.

Alginate (Fig. 1) is the main cell wall component of Laminariales. Alginates are linear unbranched polymers containing  $\beta$ -(1 $\rightarrow$ 4)-linked D-mannuronic acid (M) and  $\alpha$ -(1 $\rightarrow$ 4)-linked L-glucuronic acid (G) residues. These monomers may be arranged in homopolymeric [polymannuronate (M block) or polyglucuronate (G block)] or heteropolymeric block (MG) structures. Kupper *et al.* (2001) reported oligosaccharides derived from alginate elicit a marked oxidative burst in the cortical cells of *L. digitata* sporocytes, sufficient to control populations of epiphytic bacteria. Honya *et al.* (1993) investigated the monthly variations in alginate content and D-mannuronic acid (M) and L-glucuronic acid (G) residues ratios along with the variations in mannitol and some minerals such as calcium, magnesium, iron and phosphorus in *Laminaria japonica* cultivated at Date Bay, Hokkaido. The relative content of the MG block of alginate varied only slightly from March to October in pattern similar to the total alginate content. During summer, the M block increased with the growth of kelp, while G block was reduced. The variations in mannitol content resembled that of the M block. Inorganic elements varied with characteristic patterns, except for calcium, which resembled changes in M block towards autumn.

Kajiwara *et al.* (1988) studied the volatile components of *L. japonica* by gas chromatographic mass spectra. The major components detected were cubenol (sesquiterpene alcohol), myristic acid and palmitic acid. Flavor evaluation determined that sesquiterpene alcohol was an important contributor to kelp flavor. The composition of volatiles identified in *L. japonica* essential oils is presented in Table 2. Patterson (1968) reported detection of fucosterol, 24-methylene cholesterol, cholesterol, saringosterol and desmosterol in two species of *Laminaria* (*L. faerosensis* and *L. digitata*).

Yoshida *et al.* (1983) reported that arsenic present in *L. japonica* can be easily extracted (>90%) with water:methanol (4:1) mixture and the arsenic soluble compounds in this extract have low molecular weight (MW 500-1000). The arsenic compounds in *L. japonica* were eluted in activated charcoal chromatography with water:methanol (4:1) mixture, but not with water (article in Japanese with English abstract).

**Table 2. Volatiles identified in *Laminaria japonica* essential oil (Kajiwara *et al.* 1988)**

Compound	Peak area (%)	Compound	Peak area (%)
Hexanal	0.05	$\beta$ -Cyclocitral	0.06
(E)-2-Hexenal	0.13	$\beta$ -Homocyclocitral	0.03
(E)-2-Hexenol	0.07	(E)-2-Decenol	0.12
Hexanol	0.03	(E,E)-2,4-Decadienal	0.13
Xylene	0.06	$\beta$ -Ionone	0.66
1-Octen-3-ol	0.05	Pentadecane	0.45
(E,E)-2,4-Heptadienal	0.07	Epicubenol	0.05
Butylbenzene	0.03	Cubenol	16.10
(E)-2-Octenal	0.10	Myristic acid	38.40
(E)-2-Octenol	0.05	Dibutyl phthalate	0.99
(E,E)-2,4-Octadienal	0.02	$\omega$ -Hexadecenoic acid	3.10
(E,Z)-2,6-Nonadienal	0.18	Palmitic acid	10.79
(E)-2-Nonenol	0.19	Phytol	2.11
$\alpha$ -Terpineol	0.04	$\beta$ -Homocyclocitral	0.03

## 1.2. Identity, Composition & Manufacturing Process

*L. japonica* liquid broth and powdered extract is prepared from dehydrated seaweed (kelp) obtained from the species *L. japonica* by extracting in water. The product contains only the soluble solids from the kelp. The kelp broth is a brown liquid and has a characteristic salty taste. Approximately 1 kg of dry leaves of *L. japonica* yields about 0.876 kg of the product at about 39% soluble solids and 61% moisture. The broth/extract contains approximately 13% inorganic salts. The remaining soluble solids (26%) of the total liquid are composed of amino acids, sugars and other organic and inorganic materials. But, it is emphasized that all constituents are also present in edible *L. japonica* used generally as food. Chemical composition of the broth is summarized in Table 3. Amino acid composition of the broth and extract is presented in Table 4. Among the amino acids, glutamate and aspartate are found in relatively high concentrations. Although these levels are relatively high, their consumption from the proposed use levels of broth and extract is very small compared to current permissible levels.

**Table 3. Chemical analysis of *L. japonica* broth**

Chemical analysis	Value
Moisture	61.0 $\pm$ 2.5%
Salt	13.0 $\pm$ 3.0%
pH	5.2 $\pm$ 0.5
Protein	N/A
Fat	N/A
Iodine	1607 ppm
Sodium	1.60%
Potassium	6.71%
Calcium	940 ppm
Magnesium	1852 ppm
Iron	1.85 ppm
Zinc	0.88 ppm

Dehydrated seaweed (kelp) obtained from the species *L. japonica* is soaked in water, heated and the broth is drained, filtered and centrifuged. The broth is heated and salt is added, if necessary, to adjust the salt content to approximately 13%. The product contains only the soluble solids

from the kelp. The kelp leaves are discarded. The kelp broth is a brown liquid and has a characteristic salty taste. For some uses, the kelp broth is dried to a powder (Kelp Extract Powder) and mixed with maltodextrin.

**Table 4. Amino acid composition of *L. japonica* broth and extract**

Amino acid	Broth (mg/100 g)	Extract (mg/100 g)
Aspartate	906	609
Serine	0	14
Glutamate	2276	1719
Alanine	107	82
Ammonia	12	8
Proline	237	230
Threonine	0	0
Serine	0	0
Glycine	0	0
Valine	0	0
Cystine	0	0
Methionine	0	0
Isoleucine	0	0
Leucine	0	0
Tyrosine	0	0
Phenylalanine	0	0
Ornithine	0	0
Lysine	0	0
Histidine	0	0
Arginine	0	0
<b>Subtotal</b>	<b>3538</b>	<b>2662</b>
Other amino acids	44	21
<b>Total all amino acids</b>	<b>3582</b>	<b>2641</b>

Specifications of kelp from FCC (1996) and of *Laminaria japonica* extract from Fuji Foods USA are summarized in Table 5.

**Table 5. Kelp and *Laminaria japonica* broth specifications**

Characteristic	FCC (1996)	Fuji Foods USA
Appearance	Brown	Brown liquid
Arsenic	Not more than 3 mg/kg (as As, inorganic)	<3 mg/kg (as As, inorganic)
Ash (total)	Not more than 45%	14-18%
Heavy metals	Not more than 0.002% (20 mg/kg) (as Pb)	0.61 mg/kg (Pb+Hg)
Iodine content	Between 0.1 and 0.5% (1000 - 5000 mg/kg)	Not more than 1607 mg/kg
Lead	Not more than 10 mg/kg	0.56 mg/kg
Loss on drying	Not more than 13%	
Mercury		<0.05 mg/kg
Cadmium		0.34 mg/kg
Salt		13-14%
Brix		36-38%
Specific gravity		9.99 - 10.06 lbs/gallon

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### 1.3. Summary of Approved and other Uses

#### 1.3.1. Approved uses of kelp

*L. japonica* is also used in the production of alginates, which are cell-wall constituents of brown algae. Alginates are frequently used as stabilizers in ice cream, giving a smooth texture and body, and also as a suspending agent in milk shakes. The Flavor and Extract Manufacturers' Association (FEMA) has approved kelp *Laminaria* spp. (*L. digitata*; *L. saccharina* and *Macrocystis pyrifera*) (FEMA No. 2606) as Generally Recognized As Safe (GRAS) for use in food as a flavoring ingredient (FEMA, 1965). FEMA has also recognized algin (FEMA No. 2014) from *Laminaria* spp. and other kelp as GRAS.

The FDA has approved brown algae, including *Laminaria japonica*, as GRAS for use as a flavoring agent and adjuvant in spices, seasonings and flavorings at levels not to exceed current good manufacturing practice under 21 CFR § 184.1120. This regulation refers only to dried, chopped and ground *Laminaria japonica*. In accordance with §184.1(b)(2), the ingredient is used in food with the following specific limitations: Category of food: Spices, seasonings, and flavorings as cited under 170.3(n) (26); Maximum use level: not to exceed current good manufacturing practice; and Functional use as flavor enhancer as cited under 170.3(o)(11) and 170.3(o)(12). The proposed use does not exceed Good Manufacturing Practice.

Kelp is used in food as a source of the essential mineral iodine (21 CFR § 172.365). The intended use of *Laminaria japonica* in this submission is not supported by this regulation, it is included to show that other species of *Laminaria* are accepted. Secondly, this regulation is cited in support of the amount of iodine intake permitted and that the proposed use of *Laminaria japonica* would not result in those limits being exceeded (Refer to section 1.7 Iodine Exposure).

In addition to these uses of kelp, *Laminaria* spp. is also GRAS for animal use (21 CFR § 582.30 and 582.40). Approvals for use of kelp and brown algae extract by FDA and FEMA are summarized in Table 6. *Laminaria japonica* is also listed in Herbs of Commerce (HOC, 1992). FEMA reported approved uses of algin are summarized in Table 7.

**Table 6. Regulatory status of kelp and brown algae extract**

Agency	Citation/Comments	Food category	Permitted functionality	Use limits
FDA	21 CFR § 172.365 Food additives permitted for direct addition to food for human consumption. Subpart D – Special dietary and nutritional additives	See below*	(20) Nutrient supplements	Confined to species listed below*
FDA	21 CFR § 184.1120 Direct food substances affirmed as GRAS	(26) Spices, seasonings and flavorings	(11) Flavor enhancer (12) Flavor adjuvant	cGMP**
FEMA	2606, GRAS 3		Flavor ingredient	

\*Kelp may be safely added to a food as a source of the essential mineral iodine, provided the maximum intake of the food as may be consumed during a period of one day, or as directed for use in the case of a dietary supplement, will not result in daily ingestion of the additive so as to provide a total amount of iodine in excess of 225 µg for foods labeled without reference to age or physiological state; and when age or conditions of pregnancy or lactation are specified, in excess of 45 µg for infants, 105 µg for children under 4 years of age, 225 µg for adults and children 4 or more years of age, and 300 µg for pregnant and lactating women. The food additive kelp is the dehydrated, ground product prepared from *Macrocystis pyrifera*, *Laminaria digitata*, *Laminaria saccharina* and *Laminaria cloustoni*.

\*\*See above text for other limitations.

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Table 7. FEMA reported uses of algin.

Food Category	Use Level (ppm)		Food Category	Use Level (ppm)	
	Usual	Max		Usual	Max
Fats, oils	10	10	Gelatin, pudding	4000	4000
Frozen dairy	1100	2400	Nonalcoholic beverage	50	240

### 1.3.2. Other uses of kelp

*L. japonica* is a major species of marine algae and has been utilized as a foodstuff for millennia. It is one of the most popular seaweed foods in Japan and is regarded as a "healthy" ingredient in Japan because of its low fat content and low caloric value and high fiber value (Teas, 1983; Ohkawa and Suzuki, 1992; Jurkovic *et al.*, 1995). Traditionally, *L. japonica* fronds are cut into small pieces and dried over fire until they become crisp, yielding *kombu*. *Kombu* is considered as an important food and has a long history of use, particularly in Eastern Asia. In food, *L. japonica* extract is used for its characteristic flavor. It is especially important in making stocks for savory dishes. *L. japonica* is also used as green *kombu* and is consumed like other vegetables or used pulverized for addition to soup or as a spice. It is also used for wrapping dried fish. Tea may also be prepared from *kombu*. The active ingredient responsible for the flavor of *L. japonica* is thought to be sodium salt of the amino acid glutamic acid, or monosodium glutamate.

Nutritionally, seaweed (including *Laminaria* spp.) are low caloric foods with a high concentration of minerals (Mg, Ca, P, K and I), vitamins, proteins and indigestible carbohydrates, and a low content of lipids (Jimenez-Escrig and Goni Cambrodon, 1999). Rauma *et al.* (1995) suggested use of seaweed, including *Laminaria*, for vitamin B12 deficiency, but others questioned the bioavailability and bioactivity of vitamin B12 from plant foods (Dagnelie, 1997; Davis, 1997). Jurkovic *et al.* (1995) recommended use of algae (*L. japonica*) as food additives to improve the nutritive value of traditional diets and for health benefits. These investigators studied the chemical composition of *L. japonica* and determined the energy value and energy share from *L. japonica* diet. These results are summarized in Table 8 and 9.

Table 8. Chemical and mineral compositions of *L. japonica*. Adapted from Jurkovic *et al.* (1995).

Constituents	Amount (g/100 g dry weight)
Crude protein	13.00
Fats	2.01
Cellulose	16.20
Ashes	31.00
Carbohydrates	37.10
Nucleic acid	0.67
<b>Minerals</b>	<b>(mg/100 g)</b>
Lead	0.087
Cadmium	0.017
Copper	0.247
Iron	1.190
Zinc	0.886
Manganese	0.294
Magnesium	484.00
Calcium	805.00
Phosphorus	444.00

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**Table 9. Nutritive value of *L. japonica*. Adapted from Jurkovic *et al.* (1995)**

<b>Component</b>	<b>Energy value/Energy share</b>
Total	95.6 Kcal (401 Kj)
Protein	54.5 %
Fats	24.6 %
Carbohydrates	20.9 %

*Laminaria japonica* is approved for use as an obstetrical and gynecological prosthetic device. A hygroscopic laminaria cervical dilator is a device designed to dilate (stretch open) the cervix by cervical insertion of a conical and expansible material (tent) made from the root of seaweed (*Laminaria digitata* or *Laminaria japonica*).

#### **1.4. Proposed uses for *L. japonica* broth and extract**

*Laminaria japonica* liquid broth is intended for use as part of marinade flavoring system for meat products, poultry and fish products. *L. japonica* extract powder is proposed for use as part of a soup mix or liquid soup base and in gravies. Additionally, the extract will be used as a seasoning and flavor component of foods. The purpose of these additions is to enhance the flavor of the food. The liquid broth concentration in the marinade flavoring liquid will be used at levels up to 0.8%. The USDA allows 8% marinade flavoring liquid in meat and poultry products. In the 8% marinade flavoring, a maximum of 1% of kelp broth will be used. This would result in 0.08% of the broth in the final 100 g soaked product. For other uses such as soups, gravies and seasonings & flavors a maximum of 800 ppm of the extract will be used in the final product. The proposed use levels of the broth are presented in Table 10.

##### **1.4.1. Estimated daily intake from the proposed use**

Daily estimated intake of *L. japonica* was calculated, using the proposed maximum use level values of the broth or extract and the published information on the mean consumption of the foods (USDA, 1998) to which the broth or extract is added. Mean consumption of these foods is determined using the USDA 1996 Continuing Survey of Food Intakes by Individuals for users only data. Mean consumption per person is obtained by multiplying mean consumption values for users only by the percent of individuals reported consuming the food item. Proposed use levels and the resulting possible daily intake of *L. japonica* broth and extract are presented in Table 10. While all of the extract in a soup and gravies would be consumed, only a portion of marinade flavoring actually adheres to the meat. Hence, instead of the entire 800 ppm adhering to the meat, it is likely that only 25% of the marinade actually remains on the meat, poultry and fish products and the rest is discarded. In order to estimate 90<sup>th</sup> percentile consumption of broth and extract, corresponding mean values were multiplied by three on the grounds that 90<sup>th</sup> percentile consumption rarely exceeds the mean by more than a factor of three. As *L. japonica* broth or extract is used at a maximum level of 800 ppm, the estimated mean and 90<sup>th</sup> percentile consumption of *L. japonica* broth and extract in the United States is determined to be 50 and 150 mg/person/day, respectively.

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Table 10. Proposed use levels and Possible Daily Intake of *L. japonica* broth and extract

Food Category (number)	Mean Consumption <sup>‡</sup> (g/person/day)	Maximum Use Level (ppm)	Daily Intake of broth/extract (mg/person)	Corrected Daily Intake* (mg/person)
Meat products	47.35	800	37.88	9.47
Poultry	27.43	800	21.94	5.48
Fish products	10.5	800	8.40	2.48
Soups	31.7	800	25.36	25.36
Gravies	8.3	800	6.64	6.64
Seasonings & flavors	0.01	800	0.008	0.008
<b>Total daily intake (mg/person)</b>			<b>100.23</b>	<b>49.44</b>

\*It is estimated that only 25% of the marinade actually remains on the meat, poultry and fish products.

<sup>‡</sup>CSFII 1994-96 (1998) database was used for the analysis. As several different kinds of soups, gravies and seasonings were reported in USDA data, for these calculations, available MRCA mean frequency of eating and USDA mean portion size data were utilized.

## 1.5. Estimated intake of Kelp and Brown Algae Extract

### 1.5.1. Theoretical Added Maximum Daily Intake (TAMDI)

As discussed above the proposed use of *L. japonica* broth or extract will result in the estimated mean and 90<sup>th</sup> percentile consumption of 50 and 150 mg/person/day, respectively. In order to compare these values with other applications, daily usual and maximum intake of algin was calculated. The TAMDI is calculated on the basis of upper use levels and the estimated daily intakes of foods. For example, FEMA GRAS is for two levels of use, the “average usual” and “average maximum” (Burdock, 2002b). The TAMDI would be determined using the “average maximum” level times the estimated daily intake of the food to which the substance is added. The estimated daily intake would presumably be maximized as well, using the 90<sup>th</sup> or 95<sup>th</sup> percentile consumption.

The FEMA PADI (Possible Average Daily Intake) is similar to the TAMDI concept, using “usual” use level values and mean consumption values (based on Market Research Corporation of America mean frequency of eating and USDA mean portion size of 34 general food categories) (MRCA, 1965). FEMA has provided maximum and usual daily intake of algin Table 7) (Burdock, 2002a). Therefore, the FEMA PADI (115.13 mg/person/day or 1.92 mg/kg/day of algin) is the *mean* consumption of foods containing the usual amount. The conservatism of the PADI method assumes that the usual amount of substance is added to the entire food category, not just the substance within that category.

A possible maximum daily intake (PMDI) can be calculated using the mean consumption of food and the maximum levels proposed by FEMA (Table 7). The PMDI calculated theoretical value for algin is 168.19 mg/day or 2.80 mg/kg/day for an average individual weighing 60 kg.

### 1.5.2. Other Consumption Reports

*Laminaria japonica* is a major species of marine algae that has been consumed as a foodstuff (Ohkawa and Suzuki, 1992; Jurkovic *et al.*, 1995). Because *L. japonica* is a widely

used food source in Far and Middle East countries, Jurkovic *et al.* (1995) studied the chemical composition of *L. japonica* and determined the energy value and the energy share from a *L. japonica* diet. These investigators recommended a maximum daily intake of approximately 300 g dry weight of *L. japonica*.

In Japan, seaweed is a popular food and estimates of seaweed consumption in Japan range from 4.3 to 7.3 g/person/day (Toyokawa, 1978; Teas, 1981; Fujiwara-Arasaki *et al.*, 1984) to 25% of the diet (SCOGS, 1973). Some form of seaweed is used with almost every meal: as a garnish, in soup, as a vegetable, in sweet cakes and jellies, in sauces, as a tea and in salads. It is also incorporated into flour, which is used to make noodles, a common dietary item in Japan. Among the seaweeds, *Laminaria* is most often used to make stock for miso soup, which is normally eaten as a part at least two meals each day. The ubiquity of *Laminaria* in the Japanese diet makes actual seaweed consumption difficult to measure (Teas, 1983).

Consumption of seaweed was determined in a study of 3,609 households from three districts in Japan. The reported daily range for the amount of seaweed consumed per person varied between 0 to 5 g per person to 65 to 70 g per person. The average daily per capita consumption was 7.3 g (with a standard deviation of 11 g) (Toyokawa, 1978; Teas, 1981). As *L. japonica* is the primary species of seaweed consumed in Japan, it is estimated that approximately 50% of all consumption of seaweed will be from *L. japonica*. Hence, the daily consumption of *L. japonica* in Japan is estimated to be approximately 3.65 g/day.

In a recent report by FAO, the state of world fisheries and aquaculture, trends in production, utilization and trade, is summarized. According to this report, *L. japonica* (kelp), ranked number one by volume in world's cultured aquatic production. In 1996, the production of kelp (*L. japonica*), totaled 4.17 million tonnes (9193 million lb). FAO states that in terms of volume, production of *L. japonica* made it the most important aquaculture product for the year 1996 (FAO, 1999). Therefore, if the entire world's population of 5.8 billion (in 1996) consumed the 4.17 million tonnes, the consumption of *L. japonica* will be approximately 1 g/person/day and will be much greater in areas where it is regularly consumed as a foodstuff. For the year 1997, FAO reported that the highest global production among cultured aquatic organism was the kelp (*L. japonica*); totaling over 4.4 million mt. The farming of *L. japonica* is rapidly growing and the annual production rate of this seaweed during 1990 and 1995 has increased by 20% over that during 1984-1990 (Pedini and Shehadeh, 1997). These reports document that *L. japonica* is highly produced and commonly consumed food.

#### 1.6. Consumption summary

The proposed mean (50 mg/day) and 90<sup>th</sup> percentile (150 mg/day) consumption of *L. japonica* is approximately 100 and 30-fold less compared to the estimated daily current intake of kelp (4900 to 7300 mg/day) in Japan. Because *L. japonica* is the primary species of seaweed consumed in Japan, it is assumed that about 50% of all consumption of seaweed will be from *L. japonica*. Based on these assumptions, the daily consumption of *L. japonica* in Japan is estimated to be 3.65 g/day. The proposed estimated consumption of 50 mg/person/day of *L. japonica* is approximately 70 fold less than the current consumption of *L. japonica* in Japan. As *L. japonica* broth/extract contains approximately 1% aspartate and 2% glutamate, the proposed

consumption of broth/extract will result in approximately 0.5 mg and 1 mg of these amino acids, respectively, which is very small and meets the current approved levels.

### 1.7. Iodine Exposure from Kelp, Algin and *Laminaria japonica*

The primary source of data for *per capita* estimates are the surveys conducted by the National Academy of Sciences under contract to FDA which were used by Clydesdale (1997). According to the available *per capita* consumption data, the amount of kelp consumed per day is 0.5109 mg/person/day. As kelp contains approximately 1607 ppm iodine, the amount of iodine consumed from kelp is 0.82 micrograms/day. Three other possible sources of kelp (algae) that may contain iodine are Algae red, extract (*Porphyra* spp., *Gloiopel tiszurcata* and *Rhodymeniapalmata*); Algae brown, extract (*Macrocystis* and *Laminaria* spp.); and Algae, red (*Porphyra* spp., *Gloiopel tiszurcata* and *Rhodymeniapalmata*). While these three sources might contribute to iodine consumption, FDA notes there were no reported uses of these ingredients as late as 1987. (A fourth possible source, *Dried algae meal*, is approved for animal food use only). Lucas *et al.* (1999) conducted the *FEMA 1995 Poundage and Technical Effects Update Survey*. Based on the Lucas *et al.* (1999) reported consumption of 0.0568 mg algin/day (applying FDA assumption), the amount of iodine consumed from algin is 0.09 microgram/day. FEMA approved PADI and PMDI of 115.13 and 168.19 mg, respectively (see section 1.5.1), would result in daily iodine intakes of 185 and 270 microgram/day, respectively.

The proposed maximum use level (800 ppm) of *Laminaria japonica* extract results in daily intake of 50 mg/day of the broth and extract as a flavoring agent. This will result in daily iodine intake of 83 microgram/day. The proposed consumption of the broth is less than the FEMA approved intake of 115.135 mg/day of algin. The other sources of kelp may contribute to the iodine intake, but the total intake from all sources, including that from *L. japonica* as a flavoring agent, will not be above the FDA approved intake of 225 microgram/day.

Although FDA has proposed a maximum daily intake of 225 µg iodine from kelp, the Japanese have a comparatively very high average urinary iodine concentration (3400 µg/day) compared to Americans (209 µg/day). The high excretion of iodine in Japanese is attributed to dietary use of seaweed in soups, salad and sushi and as a powdered condiment (Abascal and Yarnell, 2001). The daily iodine intake of the Japanese varied between 200 µg to 20 mg. The average daily intake was 500-1000 µg (Teas, 1981).

A recent study comparing the results of the National Health and Nutrition Examination Survey I (NHANES) and NHANES III shows urinary iodine concentrations have dropped dramatically (>50%) among US residents during the last 20 years. Hollowell *et al.* (2002) found the urinary iodine concentration decreased from 32 µg/dL in NHANES I (1971-1974) to 14.5 µg/dL in NHANES III (1988-1994). These investigators also noted low urinary iodine concentrations (<5 µg/dL) were 4.5 times more common in 1988-1994 population than in the 1971-1974 group (11.7% vs 2.6%). Urinary concentration of less than 5 µg/dL in 20% or more population is considered as a sign of iodine deficiency and a public health concern.

## 2. Toxicological Studies

As *L. japonica* is considered foodstuff, standard toxicity studies were not found in the literature. Several investigators have studied the beneficial effects of *L. japonica*. These studies on beneficial effects are included here to demonstrate that consumption of *L. japonica* does not result in any adverse effects. Totality of these studies provides evidence against any toxicity from consumption of *L. japonica* broth and extract.

Lamela *et al.* (1989) studied the effects of several seaweed extracts, including *Laminaria ochroleuca*, on glycemia and triglyceridemia in male New Zealand rabbits. Oral administration of ethanol extracts of *Laminaria* did not affect the blood glucose levels, while administration of 20 g/kg *Laminaria* extract produced a statistically significant 20% reduction in serum triglyceride at 4 hours. At 6 hours after the administration, triglyceride levels were 18% below the control value, but were no longer significant compared to the control value.

Maruyama *et al.* (1991) studied the effects of dietary kelp (*L. religiosa*) on lipid peroxidation and glutathione peroxidase activity in the liver of rats. Female Sprague Dawley rats were given DMBA (20 mg/kg) on day 27 of feeding with a diet containing 2% kelp. The experiment was terminated on Day 210. In the same report, a short-term exposure experiment was conducted using female Sprague Dawley rats, where DMBA was given on Day 7 from the start of feeding of a kelp diet and the experiment was terminated on Day 14. At the end of the studies, livers were processed for quantitative determinations and histological observations. Lipoperoxide in animals receiving kelp and DMBA was significantly lower than in animals treated with DMBA alone. A marked fatty change in livers of rats given DMBA alone compared to kelp + DMBA was noticed in the long-term experiment, but not in the short-term study. The amounts of glutathione peroxidase and selenium in livers of rats fed kelp (210 days) and treated with DMBA were higher compared to animals given only DMBA. These results suggest that kelp mitigates the DMBA toxicity.

SCOGS (1973) report summarized a study by Tsujimuro *et al.* (1953) describing effects of *L. japonica* on growth in rats. The details of the study, such as sex and species of the animals used and duration of feeding were not available. Tsujimuro *et al.* (1953) fed rats with either flavin-deficient or flavin-deficient supplemented with powdered *L. japonica* at levels of 1 g/day. Animals receiving flavin-deficient diet showed poor growth and roughing of the fur; some animals died. However, animals treated with flavin or receiving *L. japonica* diet both showed normal growth and smooth fur. Furthermore, the animals maintained on *L. japonica* diet grew more rapidly than the flavin group indicating that *L. japonica* contained nutritional factors in addition to flavin.

### 2.1. Anti-carcinogenic studies

Several animal studies show that seaweeds and seaweed extracts, including *L. japonica*, inhibit carcinogen-induced tumorigenesis or growth of tumorigenic cell implants in rodents. Although the exact mechanism of anti-tumorigenic effects of seaweed remains to be investigated, the lack of cytotoxic action of seaweed suggest that it is not related to cytotoxicity. Yamamoto *et al.* (1987) evaluated the effects of six different seaweeds, including *L. japonica* (fed 2% of diet), on 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis in rats. Female Sprague Dawley rats (20/group) were fed diets containing 2% powdered *L.*

*japonica* for 152 days and a basic diet for 60 successive days. DMBA (20 mg/kg) was administered to all rats on Day 27 after the start of the experiment. *L. japonica* had a strong inhibitory effect on tumor initiation, with the incidence of cancer in animals fed *L. japonica* 50% compared to 69% in the control group. Feeding of diet containing 2% *L. japonica* powder for 152 days did not affect mean body weight, body weight gain or food intake.

In another study, 21-day-old female Sprague Dawley rats were fed sun-dried seaweed (*Laminaria angustana*) at a level of 5% in semipurified diet. The controls were given the same amount of cellulose. At 55 days of age, both groups were given DMBA (5 mg by gavage). The median time of appearance of palpable tumors was 77 days in control rats, whereas it was 139 days in seaweed fed rats. The control animals had a higher number of adenocarcinomas initially, but at the end of experiment, both groups of rats developed similar numbers of adenocarcinomas (Teas *et al.*, 1984). Yamamoto and Muruyama (1990) reported inhibition of intestinal absorption of DMBA by dietary kelp (*L. religiosa*). Maruyama and Yamamoto (1993) reported that algal dietary fiber such as *L. religiosa* minimizes the retention of orally ingested carcinogen N-[methyl-<sup>14</sup>C]-nitrosodimethylamine (DMNA) in the liver, possibly as a result of reduced DMNA absorption from the intestinal tract. These studies indicate that oral ingestion of seaweed inhibits absorption of carcinogen and also minimizes retention of carcinogen in liver.

Chida and Yamamoto (1987) investigated the antitumor activity of a crude fucoidan (a complex polysaccharide, one among many polysaccharides found in *kombu*) fraction prepared from the commercial root of kelp, including *Laminaria* spp. Sarcoma-180 ascites cells, Ehrlich ascites tumor cells, L1210 leukemia cells or P-388 leukemia cells were inoculated intraperitoneally in to ICR, ddY or CDF1 mice (n = 7/group). Intraperitoneal injection of the crude fucoidan in 0.1 ml of distilled water at a dose of 100 mg/kg was started 24 hours after cell inoculation and was continued for a total of 6, 8 or 10 successive days. The control animals received a daily intraperitoneal injection of distilled water. A marked antitumor activity against Sarcoma-180 and Ehrlich ascites tumors with an increase in life span of over 99% and over 55%, respectively, was noted in mice implanted with these tumor cells. However, no activity of fucoidan extract was found when tested against L-1210 and P-388 leukemias (Chida and Yamamoto, 1987). In another study, Jolles *et al.* (1963) reported a tumor growth inhibitory effect of sulphated degraded laminarin, a polysaccharide obtained from *Laminaria* spp. injected at the transplant site of Sarcoma-180 cells and into already established and growing tumors.

Yamamoto *et al.* (1982) studied the antitumor activity of *L. japonica* extract in CDF1 mice inoculated with L-1210 leukemia cells. The brown algae was dried, extracted in boiling water for 4 hours, concentrated by freeze-drying and dialyzed. The concentrated non-dialyzable fraction was injected intraperitoneally to CDF1 male mice inoculated 24 hours previously with a suspension of L-1210 leukemia cells. The experimental animals received 400 mg/kg/day of extract for six successive days. The control animals received water instead of the extract. The life span of *L. japonica* extract treated mice was 39% longer than control animals. Similar results were obtained with extracts from other *Laminaria* spp. (*L. angustana* and *L. religiosa*). These results support anti-tumor activity of *L. japonica*.

In another study, feeding of a diet containing powdered seaweed or hot water extract from *L. japonica* to male ddY mice inhibited the growth of Sarcoma-180 tumors (Yamamoto *et*

*al.*, 1986). Different preparations of *L. japonica* including powdered seaweed, hot water extract, non-dialyzable fraction and the residue of hot water extraction were fed to male ddY mice (7 animals/group) starting 24 hours after Sarcoma cell implantation at a level of 0.7, 0.2, 0.1 and 0.4%, respectively, in the diet for 35 days. Control animals received basic diet. At the end of the experiment, animals were necropsied and tumor growth was determined. No changes in body weight and food intake were noted except a decrease in body weight in animals fed 0.7% powdered *L. japonica*, which appeared to be because of the difference between tumor weight in the two groups. Feeding of the powdered weed, hot water extract and residue of hot water were effective in inhibiting the growth of Sarcoma-180 cells with inhibition ratio ranging from 56 to 81%. Similarly, intraperitoneal injection of hot water extract (200 mg/kg/day for 9 days) and non-dialyzable fraction (100 mg/kg/day for 10 days) prepared in distilled water also inhibited the growth of Sarcoma-180 cells by 52 and 68%, respectively. This study shows antitumor activity for *L. japonica* extract.

Yamamoto and Maruyama (1985) also studied the effect of dietary *L. japonica* preparations on 1,2-dimethylhydrazine (DMH) induced intestinal carcinogenesis in rats. Male Sprague Dawley rats were injected subcutaneously with DMH at a dose of 20 mg/kg/week for 12 weeks. Rats were fed diets containing, either powder (2%), hot water extract (0.5%) or residue of hot water extract (1.5%) of *L. japonica* for 12 weeks. Animals receiving basal diet and DMH served as controls. The experiments were terminated at 20 weeks (8 weeks after the cessation of both experimental diet and DMH administration). At the end of the experiments, animals were autopsied and the intestinal tumors were confirmed histologically. A statistically significant decrease in the number of tumors (approximately 50%) per rat was noted in animals fed powdered and hot water extract of *L. japonica*. Feeding of the powder, extract or residue did not affect the food intake or body weight compared to respective controls. In another study, Yoo *et al.* (2001) reported a decreased incidence of DMH initiated aberrant crypt foci in the colon of mice given a traditional Chinese medicine composed of eight crude drugs including *Laminaria*.

Reddy *et al.* (1985) studied effect of dietary *L. angustata* (brown seaweed) on azoxymethane induced intestinal carcinogenesis in male F344 rats. Five-week-old rats were fed semipurified diet containing 0 and 10% seaweed. Two weeks after the initiation of the seaweed feeding, animals (n = 30/group) received weekly subcutaneous injections of azoxymethane (20 mg/kg/body weight/week) in normal saline for two weeks. Vehicle treated animals in each group (12/group) received an equal volume of saline. All animals were fed the experimental diet for 28 weeks after the last injection of azoxymethane. The incidence (percent of animals with tumor) and multiplicity (tumors/animal) of small intestinal tumors did not differ between the seaweed fed animals and controls. However, in contrast to most studies suggesting an anti-tumorigenic activity for seaweed diets, the incidence and multiplicity of colon adenomas and the size of colon tumors were significantly increased in rats fed the seaweed diet compared to rats fed control diet.

Ohigashi *et al.* (1992) studied the *in vitro* anti-tumor promoting activity of several marine algae, including *L. japonica*. Fresh marine algae were extracted with methanol and each ethyl acetate soluble part of the methanol extract was tested for the inhibition of Epstein-Barr virus (EBV) activation induced by a tumor promoter, teleocidin B-4. In the case of commercially obtained dried algae, dichloromethane extracts were used directly for the assay. 3-Oxoursolic acid, a potent inhibitor of EBV activation, was used as a positive control. The inhibitory action

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of the algae extract (4 µg/ml medium) on EBV-early antigen induction by teleocidin B-4 (20 ng/ml medium) were expressed by the relative inhibitory rate. Extracts of *L. japonica* and one of its var. *ochotensis* showed a "strong antitumor" activity in this assay.

Noda *et al.* (1989) studied the antitumor activity of 56 species of marine algae, including *L. japonica* in mice. Male mice were orally administered 1600 mg/kg/day powdered *L. japonica*. On Day 14 of administration, mice were inoculated with Ehrlich carcinoma and the feeding was continued further for 14 days. The antitumor activity was evaluated by comparing the tumor weight of the test group with that of control. *L. japonica* feeding resulted in a statistically significant inhibition (68%) of the growth of Ehrlich carcinoma.

A study reported in Russian with an English abstract investigated the long-term dietary effects of *L. japonica* on radiation injury. Rats were irradiated by <sup>131</sup>I (10 Gy) incorporated in the thyroid and by <sup>137</sup>Cs external source (6 Gy). Part of the animals were fed a *L. japonica* containing diet. Feeding of the *Laminaria* diet "reduced" the frequency of leukemia and other malignant tumors and increased the latent period of tumor formation (Knizhnikov *et al.*, 1993). In another study, Maruyama and Yamamoto (1992) reported that dietary seaweed (*L. religiosa*) rich in iodine and in dietary fiber suppresses uptake of radioactive iodine by the thyroid and may prevent internal radiation injury of the thyroid by radioactive iodine.

## 2.2. Allergenicity and Sensitivity

*Laminaria* tents used as medical devices for cervical dilation have been involved in six cases of anaphylaxis (Nguyen and Hoffman, 1995; Chanda *et al.*, 2000; Cole and Bruck, 2000). The allergenicity or sensitivity noted in all these reports is a result of use of intra-cervical tent and is not expected from proposed oral consumption of *L. japonica*. Secondly, no report of anaphylaxis from ingestion of *L. japonica* has been found in the literature, in spite of high consumption of *L. japonica* in Far East countries.

## 2.3. Genotoxicity

Okawa and Suzuki (1992; 1993) studied mutagenic and antimutagenic activity of *L. japonica* by Ames assay. Dried leaves were pulverized and both boiling water extract and insoluble fractions were prepared. Additions of both the fractions to the assay plates in the presence or absence of S9 fraction from rat liver did not cause an increase in the number of revertant colonies of *S. typhimurium* strains TA98 and TA100. The insoluble fraction reduced the numbers of revertant colonies induced by known mutagens such as dinitropyreneTrp-P-1, Trp-P-2, 2-aminoanthracene, benzo[a]pyrene and crude coffee extract.

Okai *et al.* (1993) studied antimutagenic activity of hot water soluble extract of *L. japonica* against typical genotoxic substances by the *umu* gene expression assay in *S. typhimurium* (TA1535/pSK1002). The extract showed a highly significant antimutagenic activity against 2-acetylaminofluorene (2-AAF) or 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) induced mutagenesis in the presence of S-9 liver fraction. A weak but significant inhibitory effect was noted against N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or furylfuramide (AF-2) induced mutagenesis in the absence of S9 fraction. The polysaccharide fraction of the extract showed a minor, but roughly equal activity against all four mutagens. The nonpolysaccharide

fraction exhibited a relatively strong activity against 2-AAF or Trp-P-1 induced mutagenesis and a weak activity against MNNG or AF-2 induced mutagenesis. Further separation of non-polysaccharide fraction into high and low-molecular weight fractions and antimutagenicity studies showed strong activity from the low weight fraction. The results of this study suggest that hot water soluble extract of *L. japonica* contains antimutagenic activity against typical genotoxic substances.

In another study, Okai *et al.* (1994) investigated the antimutagenic and anti-tumor promoting activities of methanol-soluble extracts of Japanese edible seaweeds, including *L. japonica*, on Trp-P-1-induced *umu* C gene expression in SOS response of *S. typhimurium* (TA 1535/pSK 1002) and TPA-dependent ornithine decarboxylase (ODC) induction in BALB/c 3T3 fibroblast cells. *L. japonica* extract showed a significant inhibitory activity against TRP-P-1-induced *umu* C gene expression in *S. typhimurium* in the presence of liver metabolizing enzymes. In the TAP-dependent ODC activity assay in 3T3 fibroblast cells, *L. japonica* extract showed a strong inhibitory activity towards ODC.

Reddy *et al.* (1984) investigated antimutagenic effects of acetone, ether, chloroform, chloroform + methanol, hot water and cold water extracts of Japanese seaweed extract (*L. angustana*) on the mutagenicity induced by DMBA, a breast carcinogen and 3,2'-dimethyl-4-aminophenyl (DMAB), a colon and breast carcinogen, using *Salmonella typhimurium* strains TA98 and TA100. The extracts were not mutagenic in either tester strains. The addition of 10-100 mg solvent extracts of seaweed/plate greatly inhibited DMAB-induced mutagenicity in both the tester strains (80-96% inhibition) and DMBA-induced mutagenicity in TA100 (~82%). Cold and hot water extracts of *Laminaria* produced a moderate inhibition in a dose-related-manner in both strains. In another study, Lau *et al.* (1992) reported antimutagenic effects of *kyo-green*, a mixture of edible plant extracts containing *Laminaria* spp. in the Ames *Salmonella* assay.

#### 2.4. Other studies

Tang and Shen (1989) studied changes in lipid profiles in rabbits fed *Laminaria* (*L. digitata*). Rabbits (10/group) with "experimental hyperlipoproteinemia" (details not available) were given either *Laminaria* powder (1 g daily) or "routine menu" for 14 days. Rabbits given *Laminaria* powder showed a significant decrease in total cholesterol, total lipoprotein, triglyceride and an increase in HDL-c and HDL<sub>2</sub>-c (Article in Chinese with English abstract).

#### 2.5. Observations in humans

Kaneko and Koike (1984) studied the effect of protein intake level from various sources including *L. japonica* on urinary energy/nitrogen ratio (the ratio of heat of combustion of urine to nitrogen) in Japanese. A total of 179 female and 14 male college subjects were divided in to twelve groups and the subjects were given different test diets. Five female subjects were given a diet composed of cornstarch, sucrose, shortening, mineral mixture, vitamin mixture, agar and *ma-konbu* (*L. japonica*) at 20 or 40 g dry weight/day (0.7-1.2 g/kg body weight) as a source of protein. Subjects were given the diet "for more than seven days." Urine was collected "for the last three days" of each experimental period. Urinary nitrogen was determined by the Kjeldahl method and gross energy of lyophilized urine was measured with a bomb calorimeter. Urinary energy/nitrogen ratio for subjects given *L. japonica* was 14.4 kcal/g nitrogen. For the control

group receiving conventional diet (protein intake 1 g/kg), the ratio was 9.2 kcal/g nitrogen. The urinary urea excretion was almost the same in both groups. The high ratios of urinary energy/nitrogen in *L. japonica* consuming subjects suggest that urinary energy originates not only from nitrogen-containing compounds, but also from other organic compounds containing no nitrogen.

In an early study cited in SCOGS report, Iino *et al.* (1958) investigated the effects of *L. japonica* intake on thyroidal uptake of iodine in human subjects. Ten normal subjects ingested 7 to 16 g of *L. japonica* (0.31% iodine) for 1 to 14 days. A marked decrease was noted in the 24-hour thyroid uptake of <sup>131</sup>iodine. Preingestion values returned within two weeks after termination of the intake of *L. japonica*. These investigators also reported that ingestion of 10 g of *L. japonica* per day by four patients with exophthalmic goiter resulted in a marked suppression of thyroid uptake of <sup>131</sup>iodine. This response returned to preingestion values within two weeks of termination of the intake. Other details of this study were not available (summary given in the SCOGS report).

Ishizuki *et al.* (1988) reported 8 patients (1 male, 7 female) with transient "thyrotoxicosis" in Japan with increased serum levels of inorganic iodine, T<sub>4</sub>, T<sub>3</sub> and r-T<sub>3</sub> with normal T<sub>3</sub>/T<sub>4</sub> ratio. These patients had taken 8.3 mg or more iodine in *kombu* every day. These cases were diagnosed as T<sub>4</sub>-predominant toxicosis with negative thyroid stimulating binding inhibitor immunoglobulin. Prohibition of consumption of *kombu*-rich diet resulted in normal serum levels of thyroid related parameters. Okamura *et al.* (1978) reported a case of Hashimoto's thyroiditis with thyroid immunological abnormalities manifested after habitual ingestion of seaweed. The details of the amount and specifics of the seaweed were not reported by the authors. However, iodine restriction resulted in normal levels of T<sub>4</sub> and TSH in three months. The authors suggested that congenital or acquired predisposition for abnormal immune response may play an important role together with excess iodide in this particular case of Hashimoto's thyroiditis.

Teas (1981; 1983) reviewed the biological properties of seaweed, including *Laminaria*, and its possible role in prevention of breast cancer. Teas (1981) proposed several mechanisms of action of seaweed protection such as reduction of plasma cholesterol, binding of biliary steroids, inhibition of carcinogenic fecal flora, binding of pollutants, stimulation of the immune system and the protective effects of β-sitosterols responsible in the prevention of breast cancer. The author suggested that low breast cancer incidence in Japan may be related to a high intake of seaweed.

Abascal and Yarnell (2001) also suggested that low incidence of breast cancer in some countries is related to the high intake of seaweed. In a review article on prevention of cancer by vegetables and plants, Hocman (1989) reported a correlation between the consumption of seaweed (*Laminaria*) and decreased incidence of breast cancer in Japanese women compared to US women. Based on the results of major dietary findings derived from a quantitative food frequency technique in a case-control study in Kyoto, Japan, Ohno *et al.* (1988) reported that β-carotene as well as vitamin A consumption from seaweed and kelp were "suggestively" protective against prostate cancer.

### 3. DISCUSSION

*Laminaria japonica* is one of the major species of seaweed and has been consumed both as a food ingredient and foodstuff for millennia as a result of its nutritive value and technological effects as a flavor-enhancer and as a thickening agent. It is one of the most popular edible seaweeds in Japan. The source of kelp and brown algae for use in food may include *L. japonica* as well as other species. FDA has approved brown algae as GRAS for use in food as a flavoring agent and adjuvant in spices, seasonings and flavorings. Kelp is also permitted as food additive for direct addition to food for human consumption. Similarly, kelp as well as brown algae is recognized as GRAS by FEMA.

Per FDA regulations, use of kelp is allowed in food as a source of the essential mineral iodine, provided the maximum intake of the food consumed during a period of one day, or as directed for use in the case of a dietary supplement, should not result in daily ingestion of the additive so as to provide a total amount of iodine in excess of 225  $\mu\text{g}$  for foods labeled without reference to age or physiological state. Using conservative estimates, the proposed consumption of *L. japonica* as a flavor ingredient in the form of broth and extract in the foods included in this GRAS document will result in a maximum daily intake of 50 mg. The proposed consumption of *L. japonica* (50 mg/day) is 100 fold less compared to the estimated daily current intake of kelp (4900 to 7300 mg/day) in Japan. The proposed use level will result in iodine intake of 88  $\mu\text{g}$ /day and is also well below FDA guidelines for iodine intake. While the use of *L. japonica* may add to the other consumption sources of iodine, a recent epidemiological study clearly shows considerable decline in urinary iodine levels in US. As the trends of urinary iodine declining the proposed use of *L. japonica* may be helpful. It is noteworthy that Japanese have very high average urinary iodine concentration (3400  $\mu\text{g}$ /day) compared to Americans (209  $\mu\text{g}$ /day).

Toxicological and other studies described here on brown algae are relevant to safety evaluation of *L. japonica* broth and extract as the extract and broth does not contain any component other than those found in brown algae. As 1 kg of *L. japonica* produces 0.876 kg of extract or broth, the possibility of concentrating a particular ingredient is minimal. Secondly, the broth and extract contains several ingredients. The extent of concentrating is minimal. In mutagenicity studies, extracts of *L. japonica* were negative. In several *in vitro* and *in vivo* studies, *L. japonica* and other seaweeds showed anti-mutagenic effects against a number of known carcinogens. *In vitro* immunological studies show immuno-stimulatory activity of *L. japonica*. Several animal studies demonstrate that *L. japonica* inhibits experimentally induced tumorigenesis. In these tumorigenesis studies, feeding of *L. japonica* did not affect food intake or animal weight. Epidemiological studies also indicate an association between the reduced incidence of breast cancer and consumption of kelp (*L. japonica*). A few cases of reversible thyrotoxicosis are reported in the literature, but these patients consumed 8.3 mg or more iodine from kombu (*Laminaria*) every day. The iodine consumption from the proposed use of *L. japonica* would not result in an exposure producing this type of effect.

The consumption of *L. japonica* in Japan is relevant to establish its safety in US. There may be some minor differences between populations in Japan and US, but given the differences in consumption of 100-fold for kelp and 70-fold for *L. japonica*, the proposed consumption of 50 mg/day/person in US is considered safe. A long history of safe consumption and limited epidemiological and clinical studies also support the safety of *L. japonica*.

In 1973, Select Committee on GRAS evaluated health aspects of certain red and brown algae as food ingredients (SCOGS, 1973). Since the evaluation in 1973 by the Select Committee, additional and relevant information on safety and consumption of kelp, including *L. japonica* has appeared in the scientific literature (including the study by Kaneko and Kaike in 1984).

In summary, on the basis of the data presented above and a substantive history of consumption and use, consumption of *Laminaria japonica* broth and extract as an added food ingredient/flavoring agent is considered safe at levels up to 0.8% in marinade flavoring liquid or at level of 800 ppm in final products in meat products, poultry, fish products, soups, gravies and seasonings & flavors. The proposed uses are compatible with current regulations *i.e.*, the extract is used as a seasoning [170.3(n)(26)], functionality is as a flavor enhancer [170.3(0)(11)] and the maximum use level does not exceed current good manufacturing practice.

#### 4. CONCLUSION

Based on critical, independent and collective evaluation of the available data and information, the Expert Panel has determined that, based on common knowledge throughout the scientific community knowledgeable about the safety of substances added to food, *Laminaria japonica* broth and extract, meeting appropriate food grade specifications and produced in accordance with current Good Manufacturing Practice (cGMP), is Generally Recognized As Safe (GRAS), by scientific procedures, when used as a flavoring at levels not to exceed 800 ppm in the following foods: meat products, poultry, fish products, soups, gravies and seasonings & flavors, resulting in a total mean and 90<sup>th</sup> percentile consumption of 50 and 150 mg/person/day, respectively.

#### Signatures

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06 January 2003  
Date

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## 2. REFERENCES

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Food and Drug Administration  
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 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

World Health Organization  
 Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

**Industrial**

Chemical Companies; Trade Associations

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**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 (1960)  
 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

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

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

International Society for Regulatory Toxicology and Pharmacology's International Achievement Award for 2001- December 2001

Society of Toxicology- Education Award- March 2002

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**Contributing authorship on the following publications of the Life Sciences Research Office,  
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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 caprylic acid as a food ingredient. 1974.

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.

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.
- 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.
- 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.

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.

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.

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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.

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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, dialauryl 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.

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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.

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

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 cornmint 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.

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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**

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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

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## PROFESSIONAL EXPERIENCE

**Burdock Group**  
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 Founder and President

**1988 - Present**

Dr. Burdock is an internationally recognized authority on the safety of food ingredients, personal care products and dietary supplements. He has more than twenty years experience dealing with regulatory issues related to product safety and risk assessment. He provides safety and toxicity information on foods, food additives, drug excipients and contaminants to a varied client list, including corporations, law firms and individuals. This information may be in the form of regulatory petitions, Generally Recognized As Safe (GRAS) self-determinations, GRAS notifications and litigation support. He has extensive experience searching and evaluating the scientific literature in a number of subject areas. He provides reviews of the literature on substances and advises clients on safety and regulatory matters concerning their products and procedures. He is also engaged, on an on-going basis, by a publisher to provide reference books on food additives, flavor ingredients and regulatory matters. He is experienced in the generation and submission of Food Additive Petitions and has experience in negotiating with the regulatory authorities.

**Flavor and Extract Manufacturers' Association (FEMA)**  
**Washington, D.C.**  
 Director of Scientific Affairs

**1986 - 1992**

Dr. Burdock assisted member companies in the preparation of materials for submission to the FEMA Expert Panel for GRAS review, maintained awareness for the Expert Panel and Association of scientific developments in the food and flavor arena and changes in regulatory policy as a result of these developments. He authored and edited comprehensive reviews of the literature on flavor additives. Dr. Burdock also managed the FEMA scientific program, coordinated activities of testing laboratories, consultants and allied industry committees and organizations.

**Shulton Research Division, American Cyanamid Corporation**  
**Clifton, New Jersey**  
 Manager of Biological Services

**1984 - 1986**

As senior toxicologist, Dr. Burdock represented the Consumer Products Division on toxicology matters within the corporation with other divisions, outside vendors, government agencies and trade associations. Dr. Burdock was a member of the Pharmacology/Toxicology Committee and the Cosmetic Ingredient Review Subcommittee of the Cosmetic, Toiletries and Fragrance Association. In-house, Dr. Burdock managed Product Safety section, Microbiological Research Services, the Clinical Evaluation Laboratory and the Product Evaluation Center. Dr. Burdock was responsible for the toxicologic and microbiologic safety of products applied to the test groups in the clinical evaluation laboratories and those products released for public use.

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**Hazleton Laboratories America, Inc.**  
**Vienna, Virginia**  
 Senior Staff Scientist

1979 - 1984

As a Study Director, Dr. Burdock designed and managed toxicological studies, reproduction and teratology studies in a variety of species. Dr. Burdock was also concerned with regulatory requirements, quality assurance, budgetary monitoring, and monitoring the performance of subcontractors. He negotiated program design and individual toxicity study requirements for registration of substances with regulatory agencies (FDA and EPA). Dr. Burdock also supervised two laboratory sections, Teratology/Reproduction and Subchronic Rodent Toxicology.

## EDUCATION

Ph.D., Toxicology, School of Pharmacy, University of Mississippi, 1980  
 Master of Combined Sciences, Physiology and Biochemistry, University of Mississippi, 1973  
 Bachelor of Science, Biology, University of Mississippi, 1969

## CERTIFICATION

Diplomate, American Board of Toxicology, 1983; Recertified, 1988, 1993, 1998

## PROFESSIONAL MEMBERSHIPS

American Chemical Society  
 American College of Toxicology  
 American Oil Chemists Society  
 Institute of Food Technologists  
 National Capital Area Chapter of the Society of Toxicology  
 International Society for Regulatory Toxicology and Pharmacology (Treasurer & Councilor)  
 Society of Toxicology (Associate Member)  
 Food and Drug Law Institute

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**G.A. Burdock** (2002). Status and safety assessment of foods and food ingredients produced by genetically modified microorganisms Chapter 3 in: Biotechnology and Safety Assessment, 3<sup>rd</sup> ed. Thomas, J.A. and Fuchs, R. (eds.). Elsevier Science (USA), (2002) pp 39-83

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- G.A. Burdock (1983). Diethanolamine-Induced Changes in Liver and Kidney of the Neonatal Rat. *The Toxicologist* 4(1):491.
- G.A. Burdock, R. B. Hackett and L.W. Masten (1980). A Comparison of Hepatic Microsomal Enzyme Induction by Methadone, Phenobarbital and 3-Methylcholanthrene in the Mouse. *Biochemical Pharmacology* 28:3476-3482.
- J.C. Kapeghian, G.A. Burdock and L.W. Masten(1980). The Effect of the Route of Administration of Microsomal Enzyme Induction Following Repeated Methadone Administration in the Mouse. *Biochemical Pharmacology* 28:3021-

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3025.

**G.A. Burdock** (1980). Some Toxic Effects of Diethanolamine in the Neonatal Rat. Doctoral Dissertation, 1980.

**G.A. Burdock** and L.W. Masten (1979). Diethanolamine Induced Changes in the Neonatal Rat. *Toxicology and Applied Pharmacology* 48:A30.

J.C. Kapeghian, **G.A. Burdock** and L.W. Masten (1977). Effect of the Route of Administration on Microsomal Enzyme Induction Following Repeated Administration of Methadone in the Mouse. *Toxicology and Applied Pharmacology* 41:159.

**G.A. Burdock**, R. B. Hackett and L.W. Masten (1976). Dose-Response Relationship of Oral Methadone Administration and Liver Microsomal Enzyme Activity. *Federation Proceedings* 35:469.

J.D. Catravas, I.W. Waters, **G.A. Burdock** and W.M. Davis (1975). Haloperidol and Propanolol in the Treatment of Acute Amphetamine Intoxication in the Dog. *Toxicology and Applied Pharmacology* 33:185.

## REPORTS

Dr. Burdock has been responsible for the generation of a number of technical reports as a consultant and as a scientist at the Flavor and Extract Manufacturers' Association, Hazleton Laboratories and American Cyanamid. The substance of these reports is proprietary to the clients sponsoring the research and to American Cyanamid and FEMA and is thus confidential and not available for publication.

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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.

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,

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.

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"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.

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.

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.

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End Submission

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