

GRAS Notice (GRN) No. 565 with amendment

<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm>

GR



ORIGINAL SUBMISSION

000001

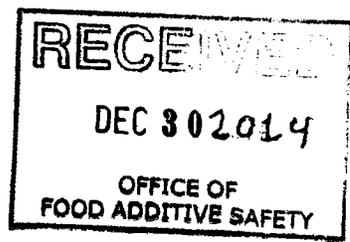
1 565

Soni & Associates Inc.

749 46th Square
Vero Beach, FL 32968, USA
Telephone: 772-299-0746
Facsimile: 772-299-5381
E-mail: msoni@soniassociates.net
GRN 000565

December 19, 2014

Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835



Subject: GRAS Notification for Fucoidan Concentrate from *Undaria pinnatifida*

Dear Sir/Madam:

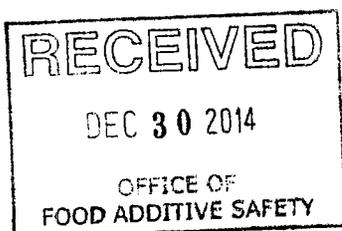
Pursuant to proposed 21 CFR 170.36 (62 FR 18960; April 17, 1997), Marinova Pty. Ltd. (Marinova), Australia, through Soni & Associates Inc. as its agent, hereby provides notice of a claim that the food ingredient Fucoidan concentrate derived from *Undaria pinnatifida* described in the enclosed notification document is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be Generally Recognized As Safe (GRAS), based on scientific procedures.

As required, please find enclosed three copies of the notification. If you have any questions or require additional information, please feel free to contact me by phone at 772-299-0746 or by emails at msoni@soniassociates.net or sonim@bellsouth.net.

Sincerely,
(b) (6)

Madhu G. Soni, Ph.D., FATS

Enclosure: Three copies of the GRAS notice



Soni & Associates Inc.

749 46th Square
Vero Beach, FL 32968, USA
Telephone: 772-299-0746
E-mail: msoni@soniassociates.net
www.soniassociates.net

I. Claim of GRAS Status

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

Marinova Pty. Ltd. (Marinova), Australia, has determined that fucoidan concentrate derived from *Undaria pinnatifida* is Generally Recognized As Safe, and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use. This determination is based on scientific procedures as described in the following sections, under the conditions of fucoidan concentrate's intended use in food, among experts qualified by scientific training and expertise.

Signed,

(b) (6)



Date: December 19, 2014

Madhu G. Soni, Ph.D., FACN, FATS

Agent for:

Marinova Pty. Ltd.
Cambridge, Tasmania
AUSTRALIA

000003

B. Name and Address:

Damien Stringer, Ph.D.
Marinova
249 Kennedy Drive
Cambridge, Tasmania 7170
AUSTRALIA

Phone: +61 3 6248 5800
Fax: +61 3 6248 4062
Email: damien.stringer@marinova.com.au

C. Common or usual name of the GRAS substance:

The common name of the substance of this GRAS assessment is fucoidan. Fucoidan for food uses will be marketed as standardized powder (Maritech®).

D. Conditions of use:

Maritech® fucoidan is intended for use in food categories such as Baked goods (bread, cake, noodles); Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors at use levels up to 30 mg/serving (reference amounts customarily consumed; 21 CFR 101.12). The intended uses of fucoidan in the above mentioned food categories is estimated to result in the mean and 90th percentile intake for the total population of 135.45 and 249.66 mg/person/day, respectively.

Foods that are intended for infants and toddlers, such as infant formulas or foods formulated for babies or toddlers, and meat and poultry products that come under USDA jurisdiction are excluded from the list of intended food uses of the subject fucoidan.

E. Basis for GRAS Determination:

In accordance with 21 CFR 170.30, Maritech® fucoidan concentrate has been determined to be Generally Recognized As Safe (GRAS) based on scientific procedures. The determination is supported by the opinion of the Expert Panel. A comprehensive search of the scientific literature was utilized for this determination. There exists sufficient qualitative and quantitative scientific evidence, including human and animal data to determine safety-in-use for fucoidan concentrate. The source material of fucoidan concentrate, brown algae *Undaria pinnatifida* also known as wakame is an important part of the human diet in several countries and has been consumed since ancient times. The brown algae (seaweed), including *U. pinnatifida*, is generally recognized as safe (GRAS) as per 21 CFR §184.1120 for use in food. The safety determination of fucoidan concentrate for the present GRAS assessment is based on the totality of the available scientific evidence that includes human observations and a variety of preclinical and clinical studies. On the basis of scientific procedures¹, Marinova

¹ 21 CFR §170.3 Definitions. (h) Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

000004

considers the consumption of fucoidan concentrate (Maritech®), as a food ingredient to be safe at levels up to 250 mg/person/day. Based on the available safety-related information, the Expert Panel concluded that the intended uses of Maritech® fucoidan concentrate as described herein are safe at the estimated daily intake, if ingested daily over a lifetime.

F. Availability of Information:

The data and information that forms the basis of Marinova's fucoidan GRAS determination will be available for the Food and Drug Administration's review and copying at the following address or will be provided to the agency upon request:

Madhu G. Soni, Ph.D., FATS
Soni & Associates Inc.,
749 46th Square,
Vero Beach FL, 32968
Phone: (772) 299-0746; E-mail: sonim@bellsouth.net

II. Detailed Information About the Identity of the GRAS Substance:

A. Synonyms:

Sulfated L-Fucose algal polysaccharide; Galacto-fucoidan; Galactofucan sulfate (GFS), Fucoidin; Fucan, Fucosan, or Sulfated fucan.

B. Trade Name:

The subject of this GRAS assessment will be marketed under the name Maritech®.

C. Physical Characteristics

Off-white to brown powder

D. Chemical Abstract Registry (CAS) Number

9072-19-9 and 223751-81/3

E. Chemical Formula and Molecular Weight

(C₆H₁₀O₇S)_n. The molecular weight of fucoidan derived from *U. pinnatifida* ranges from 100 to 700 kDaltons.

F. Structure

The general chemical structure of Maritech® *Undaria pinnatifida* fucoidan is presented in Figure II.F.1.

000005

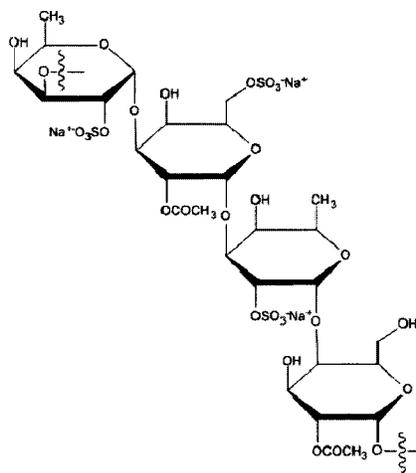


Figure II.F.1. General Chemical Structure of Maritech® *Undaria pinnatifida* fucoidan

G. Typical Specifications

Food grade specifications of fucoidan concentrate derived from *U. pinnatifida* have been established by Marinova and are presented in Table II.G.1. To demonstrate conformance with the food-grade specifications, Marinova analyzed several batches of fucoidan derived from *U. pinnatifida*. Analytical results from five non-consecutive lots (Appendix I) for fucoidan derived from *U. pinnatifida* confirm that it is consistently manufactured to meet the standard specifications. The product is standardized to the content of fucoidan according to Marinova method 'C05', which determines fucoidan content based on the carbohydrate, sulfate, counterion, and acetyl content of the fucoidan polymers. The sulfate content of the concentrate typically comprises 20-30% by weight. The fucoidan content of the product ranges from 75 to 95%. The iodine content of fucoidan (Maritech®) derived from *U. pinnatifida* is typically less than 50 ppm, which is much less than the average iodine content of kelp, which is reported to range from 1500 to 2500 ppm (Mussig et al., 2006). Typical compositional analysis of fucoidan derived from *U. pinnatifida* is summarized in Table II.G.2.

000006

Table II.G.1. Food Grade Specifications of Fucoidan (Marinova, 2013)*

Parameters	Specification	Assay method
Description	Off-white to brown powder	Visual
Moisture	<10% (105°C for 2 hours)	USP
pH value	4.0 - 7.0 (1% suspension at 25°C)	pH Meter
Solubility	Dissolves readily in water	In-House
Particle size	Minimum 80% less than 300 microns	USP
Fucoidan	≥ 75% (<i>U. pinnatifida</i>)	Marinova Method C05
Pesticide residues	Complies with USP	USP
Heavy metals		
Arsenic (inorganic)	2 ppm Max	ICP
Lead	2 ppm Max	ICP
Cadmium	3 ppm Max	ICP
Mercury	1 ppm Max	ICP
Microbiological parameters		
Total Aerobic microbial count	10000 cfu/g (max)	AOAC
Yeasts and molds	100 cfu/g (max)	AOAC
Total enterobacteria count	Absent / g	AOAC
<i>Eschericia coli</i>	Absent / g	AOAC
<i>Salmonella</i> species	Absent / 10 g	USP
<i>Staphylococcus aureus</i>	Absent / g	USP
*Based on information provided by Marinova. ppm = parts per million; cfu = colony forming units		

Table II.G.2. Typical Compositional Analysis of Fucoidan*

Component name	Amount
Fucoidan	75.0-95.0%
Alginate	2.0-6.5%
Polyphloroglucinol	0.5-3.0%
Mannitol	1-15%
Natural salts	0.5-1.0%
Other carbohydrates	0.5-2.0%

*Based on information provided by Marinova; values are expressed as w/w

000007

H. Manufacturing process

Fucoidan is extracted according to current good manufacturing practices (cGMP), as outlined in Figure II.H.2, at Marinova Pty Ltd, 249 Kennedy Drive, Cambridge TAS 7170, Australia. The unique Maritech® extraction process has been specifically designed to extract fucoidan from brown seaweed without the use of organic solvents. For the extraction of fucoidan, wild-grown seaweed, hand-harvested from the cleanest ocean waters is collected. The seaweed thus obtained is dried, milled and suspended in pure water. The acidification of water is carried out with food-grade, organic certified acid to mildly acidic pH and the suspension is subjected to agitation. The suspension is filtered to remove seaweed residue (fucoidan-rich filtrate retained) with organic certified, food grade filtration aid. The filtrate thus obtained is neutralized with food-grade, organic certified base and subjected to secondary filtration to remove salts (mechanical only). This extraction process ensures the chemical constituent of the fucoidan molecule remains unaltered and equivalent to their natural state. The secondary filtrate is concentrated, dried and milled to produce the powdered fucoidan extract.

The final product is free of allergens (milk, egg, fish, shellfish, tree nut, wheat, peanuts and soybean) and arthropod and mollusk infestations and other quarantine risk material. The purification step in the Maritech® process eliminates contaminants such as salts and remaining alginate impurities from the product. This process eliminates the numerous purification steps in the commonly used extraction methods in the industry, such as disinfection (hypochlorite and irradiation). In an extensive review article, Ale et al. (2011) reported that preservation of the structural integrity of the fucoidan molecules essentially depends on the extraction methodology which has a crucial, but partly overlooked, significance for retaining the relevant structural features required for specific biological activities and for elucidating structure-function relations.

The quality assurance method for analyzing fucoidan sugars to determine purity has been developed and validated for Marinova by the Complex Carbohydrate Research Centre at the University of Georgia (US). The Maritech® extraction process is controlled using an ISO9001 and HACCP accredited quality-management system. Marinova rigorously tests its final production batches to verify adherence to quality control specifications. Maritech® complies with Organic, Kosher and Halal quality requirements. All raw materials and processing aids used in the manufacture of fucoidan are suitable food-grade materials and/or are used in accordance with applicable U.S. federal regulations for such uses. The manufacturing facility is registered with the FDA under the number: 1065 1320 208.

000008

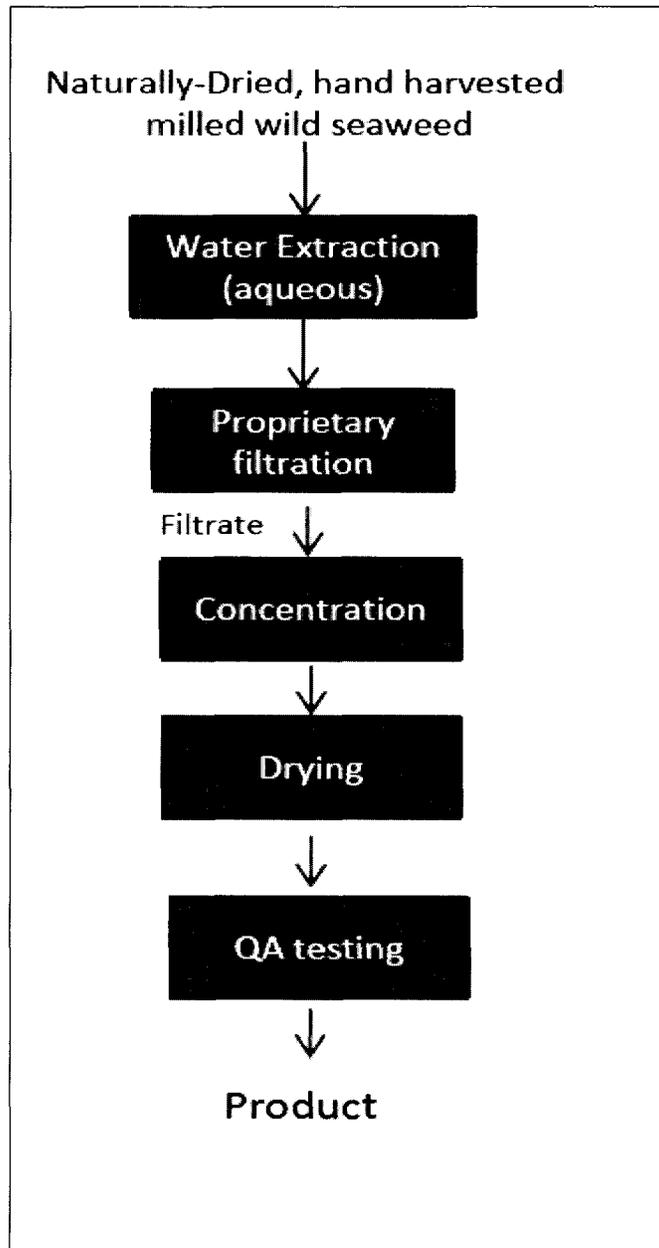


Figure II.H.2. Manufacturing Process of Maritech® Fucoidan

III. Summary of the Basis for the Determination that Fucoidan concentrate is GRAS

An independent panel of recognized experts, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Marinova to determine the Generally Recognized As Safe (GRAS) status of fucoidan derived from *U. pinnatifida*. The Expert Panel consisted of the following individuals: Professor John Thomas, Ph.D., FATS (Indiana University School of Medicine); Robert L. Martin, Ph.D. (Retired FDA Deputy Director); and Madhusudan G. Soni, PhD, FACN, FATS (Food Ingredient Safety Consultant).

000009

A comprehensive search of the scientific databases for safety and toxicity information on fucoidan was conducted through September 2014. Additionally, safety and regulatory evaluations by national and international agencies were also searched and considered for the present assessment.

Based on a critical evaluation of the pertinent data and information summarized herein, and employing scientific procedures, the Expert Panel members have individually and collectively determined that the addition of fucoidan derived from *U. pinnatifida* to the foods [Baked goods (bread, cake, noodles); Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors at use levels up to 30 mg/serving (reference amounts customarily consumed; 21 CFR 101.12)], when not otherwise precluded by a Standard of Identity, meeting the specification cited above and manufactured in accordance with current Good Manufacturing Practice, is Generally Recognized As Safe (GRAS) under the conditions of intended use, as specified herein.

In arriving at this decision that fucoidan is GRAS, the Expert Panelists relied upon the conclusions that neither fucoidan nor any of its constituents pose any toxicological hazards or safety concerns at the intended use levels, as well as on published toxicology studies and other articles relating to the safety of the product. It is also the opinion of the Expert Panelists that other qualified and competent scientists, reviewing the same publicly available toxicological and safety information, would reach the same conclusion. The GRAS Panel did not prepare a separate report or statement, but reviewed the entire GRAS dossier.

000010

IV. Basis for a Conclusion that Fucoidan from *Undaria pinnatifida* is GRAS for its Intended Use

EXPERT PANEL STATEMENT

**DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE
(GRAS) STATUS OF
FUCOIDAN FROM *UNDARIA PINNATIFIDA*
AS A FOOD INGREDIENT**

Marinova Pty. Ltd.
249 Kennedy Drive
Cambridge, Tasmania 7170
AUSTRALIA

Panel Members

Robert L. Martin, Ph.D.
John A. Thomas, Ph.D., FATS, DATS
Madhusudan G. Soni, PhD, FACN, FATS

000011

**DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS)
STATUS OF**

**Maritech® FUCOIDAN FROM *UNDARIA PINNATIFIDA*
AS A FOOD INGREDIENT**

TABLE OF CONTENT

1. INTRODUCTION.....	12
1.1. Background	12
1.2. Description.....	13
1.3. Typical Specifications and Composition.....	13
1.4. Manufacturing/Extraction Process	15
1.5. Chemical Structure.....	16
1.6. Regulatory History.....	17
1.7. Uses and Consumption	18
1.8. Intended Use Levels and Food Categories.....	20
1.8.1. Estimated Daily Intake from the Intended Uses	20
1.8.1.1. Use of MRCA exposure data.....	20
1.8.1.2. Use of USDA Data.....	21
1.8.2. Consumption Summary.....	22
1.9. Common Knowledge of Safe Use of Source Material.....	22
2. SAFETY RELATED DATA	23
2.1. Safety of <i>U. pinnatifida</i> Fucoidan	24
2.1.1. Human Studies	24
2.1.2. Animal Toxicity Studies	26
2.1.3. Genotoxicity Studies	27
2.2. Safety of Fucoidan from Other Sources.....	29
2.2.1. Human Studies	29
2.2.2. Animal Studies	32
2.2.3. Genotoxicity Studies	33
2.3. Absorption, Distribution, Metabolism and Excretion (ADME)	33
2.4. Allergenicity	34
2.5. Anticoagulant Activity.....	34

000012

2.6. Structure and Biological Activity 38
2.7. Safety of Other Components..... 38
3. Common Knowledge Elements for a GRAS Determination..... 39
4. RISK ASSESSMENT 40
5. SUMMARY 41
6. CONCLUSION 42
7. REFERENCES..... 43
8. APPENDIX I 49

000013

DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF Maritech® FUCOIDAN FROM UNDARIA PINNATIFIDA AS A FOOD INGREDIENT

1. INTRODUCTION

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Expert Panel)², qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was convened at the request of Marinova Pty. Ltd. (Marinova), to determine the Generally Recognized As Safe (GRAS) status of the use of Maritech® fucoidan derived from brown seaweeds, *Undaria pinnatifida* (wakame). The panel assessed the safety of Maritech® fucoidan as a food ingredient in conventional foods such as Baked goods (bread, cake, noodles); Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors at use levels up to 30 mg/serving (reference amounts customarily consumed, 21 CFR 101.12). A comprehensive search of the scientific literature for safety and toxicity information on fucoidan and its source material, *U. pinnatifida* (wakame) was conducted through September 2014 and made available to the Expert Panel. The Expert Panel independently and critically evaluated materials submitted by Marinova and other information deemed appropriate or necessary. Following an independent, critical evaluation, the Expert Panel conferred on December 15, 2014 and unanimously agreed to the decision described herein.

1.1. Background

Seaweeds, including various brown seaweeds, such as *Undaria* spp., are part of the food culture in Asia, notably in Japan, Philippines, and Korea, and seaweed extracts have also been used as a remedy in traditional healthcare (Ale et al., 2011). The brown color of these algae results from the dominance of the xanthophyll pigment fucoxanthin, which masks the other pigments. In recent years, much attention has been focused on functional polysaccharides isolated from natural sources. Fucoidan is a class of sulfated, fucose-rich, polysaccharides found in the fibrillar cell walls and intercellular spaces of brown seaweeds of the class Phaeophyceae (Senthilkumar et al., 2013). Fucoidan-containing sulfated polysaccharides (FCSP) may also contain galactose, mannose, xylose, glucose and/or glucuronic acid, usually in minor amounts. Fucoidan was first isolated in 1913 from marine brown algae and was named “fucoidin” (Kylín, 1913). As per IUPAC nomenclature it is named “fucoidan” but is also called fucan, fucosan or sulfated fucan (Berteau and Mulloy, 2003). In several recent scientific studies, fucoidans from seaweed have been investigated for potential biological functions such as antioxidant activity, antitumor, immunomodulatory, antiviral, antithrombotic, anticoagulant, anti-inflammatory and antilipidemic activity (Fitton, 2011; Senthilkumar et al., 2013). The production of well characterized reproducible fucoidan fractions on a commercial scale has become possible in recent years, thus making specific uses of fucoidan possible. Marinova intends to use standardized fucoidan derived from a species of brown seaweed (*Undaria pinnatifida*) as a food ingredient in selected food products.

²Modeled 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.

000014

1.2. Description

The subject of this GRAS determination, Maritech® *Undaria pinnatifida* fucoidan, is a standardized spray dried polysaccharide derived from the brown seaweed *U. pinnatifida* (wakame). It is an off-white to brown colored powder without any characteristic taste and odor. It will be marketed under the trade name Maritech® with product identifiers *U. pinnatifida* Extract, ‘GFS’ and Fucorich®. General descriptive parameters and properties of fucoidan manufactured by Marinova are summarized in Table 1.

Table 1. General Descriptive Characteristics of Fucoidan

Parameter	Description (Marinova, 2014)*
Botanical source	<i>Undaria pinnatifida</i>
Synonym of source	Wakame; Mekabu Brown seaweed; Japanese kelp
CAS No.	9072-19-9 and 223751-81/3
Appearance	Powder
Color	Off-white to brown
Odor	Bland
Taste	Bland
Storage	Store in well sealed containers in a cool position. Protect from light, moisture and heat
Shelf life	Five years in the original pack

*Based on information provided by Marinova

The hierarchical classification of *U. pinnatifida* is presented in Table 2. *U. pinnatifida*, commonly known as wakame, is a brown seaweed that can reach an overall length of 1-3 meters. It is considered as a sea vegetable, or edible seaweed. It has a subtly sweet flavor and is most often served in soups and salads. In Japan, sea-farmers have grown wakame since the Nara period (AD 710 - 794).

Table 2. Classification of *Undaria pinnatifida*

	<i>Undaria pinnatifida</i>
Kingdom	Chromista
Phylum	Heterokontophyta or Ochrophta
Class	Phaeophyceae
Order	Laminariales
Family	Alariaceae
Genus	<i>Undaria</i>
Species	<i>Undaria pinnatifida</i>

1.3. Typical Specifications and Composition

Food grade specifications of fucoidan have been established by Marinova and are presented in Table 3. To demonstrate conformance with the food-grade specifications, Marinova analyzed several batches of fucoidan derived from *U. pinnatifida*. Analytical results from five non-consecutive lots (Appendix I) of fucoidan derived from *U. pinnatifida* suggest that it is consistently manufactured to meet the standard specifications. The product is standardized to the contents of fucoidan according to Marinova method ‘C05’ which determines fucoidan content based on the carbohydrate, sulfate, counterion, and acetyl content of the fucoidan polymers. The

000015

peak molecular weight of Maritech® *U. pinnatifida* fucoidan concentrate is of the order of 100 - 700 kDa. Sulfate contents of the product typically comprise 20-30% of the extract by weight. The fucoidan content of the product ranges from 75-95%. The iodine content of fucoidan (Maritech®) derived from *U. pinnatifida* is typically less than 50 ppm. The average iodine content of kelp is reported to range from 1500 to 2500 ppm (Mussig et al., 2006). Typical compositional analysis of fucoidan derived from *U. pinnatifida* is summarized in Table 4.

Table 3. Typical Food Grade Specifications of Fucoidan (Marinova, 2014)*

Parameters	Specification	Assay method
Description	Off-white to brown powder	Visual
Moisture	<10% (105°C for 2 hours)	USP
pH value	4.0 - 7.0 (1% suspension at 25°C)	pH Meter
Solubility	Dissolves readily in water	In House
Particle size	Minimum 80% less than 300 microns	USP
Fucoidan	≥75% (<i>U. pinnatifida</i>)	Marinova Method
Pesticide residues	Complies with USP	USP
Heavy metals		
Arsenic (inorganic)	2 ppm Max	ICP
Lead	2 ppm Max	ICP
Cadmium	3 ppm Max	ICP
Mercury	1 ppm Max	ICP
Microbiological parameters		
Total Aerobic microbial count	10000 cfu/g (max)	AOAC
Yeasts and molds	100 cfu/g (max)	AOAC
Total enterobacteria count	Absent / g	AOAC
<i>Eschericia coli</i>	Absent / g	AOAC
<i>Salmonella</i> species	Absent / 10 g	USP
<i>Staphylococcus aureus</i>	Absent / g	USP

*Based on information provided by Marinova. ppm = parts per million; cfu = colony forming units

Table 4. Typical Compositional Analysis of U. Pinnatifida Fucoidan

Component name	Typical Values
Fucoidan	75.0-95.0%
Alginate	2.0-6.5%
Polyphloroglucinol	0.5-3.0%
Mannitol	1-15%
Natural salts	0.5-1.0%
Other carbohydrates	0.5-2.0%

*Based on information provided by Marinova; values are expressed as w/w

000016

1.4. Manufacturing/Extraction Process

Fucoidan is extracted according to current good manufacturing practices (cGMP), as outlined in Figure II.H.2, at Marinova Pty Ltd, 249 Kennedy Drive, Cambridge TAS 7170, Australia. The unique Maritech® extraction process has been specifically designed to extract fucoidan from brown seaweed without the use of organic solvents. For the extraction of fucoidan, wild-grown seaweed, hand-harvested from the cleanest ocean waters is collected. The seaweed thus obtained is dried, milled and suspended in pure water. The acidification of water is carried out with food-grade, organic certified acid to mildly acidic pH and the suspension is subjected to agitation. The suspension is filtered to remove seaweed residue (fucoidan-rich filtrate retained) with organic certified, food grade filtration aid. The filtrate thus obtained is neutralized with food-grade, organic certified base and subjected to secondary filtration to remove salts (mechanical only). This extraction process ensures the chemical constituent of the fucoidan molecule remains unaltered and equivalent to their natural state. The secondary filtrate is concentrated, dried and milled to produce the powdered fucoidan extract.

The final product is free of allergens (milk, egg, fish, shellfish, tree nut, wheat, peanuts and soybean) and arthropod and mollusk infestations and other quarantine risk material. The purification step in the Maritech® process eliminates contaminants such as salts and remaining alginate impurities from the product. This process eliminates the numerous purification steps in the commonly used extraction methods in the industry, such as disinfection (hypochlorite and irradiation). In an extensive review article, Ale et al. (2011) reported that preservation of the structural integrity of the fucoidan molecules essentially depends on the extraction methodology which has a crucial, but partly overlooked, significance for retaining the relevant structural features required for specific biological activities and for elucidating structure-function relations.

The quality assurance method for analyzing fucoidan sugars to determine purity has been developed and validated for Marinova by the Complex Carbohydrate Research Centre at the University of Georgia (US). The Maritech® extraction process is controlled using an ISO9001 and HACCP accredited quality-management system. Marinova rigorously tests its final production batches to verify adherence to quality control specifications. Maritech® complies with Organic, Kosher and Halal quality requirements. All raw materials and processing aids used in the manufacture of fucoidan are suitable food-grade materials and/or are used in accordance with applicable U.S. federal regulations for such uses. The manufacturing facility is registered with the FDA under the number: 1065 1320 208.

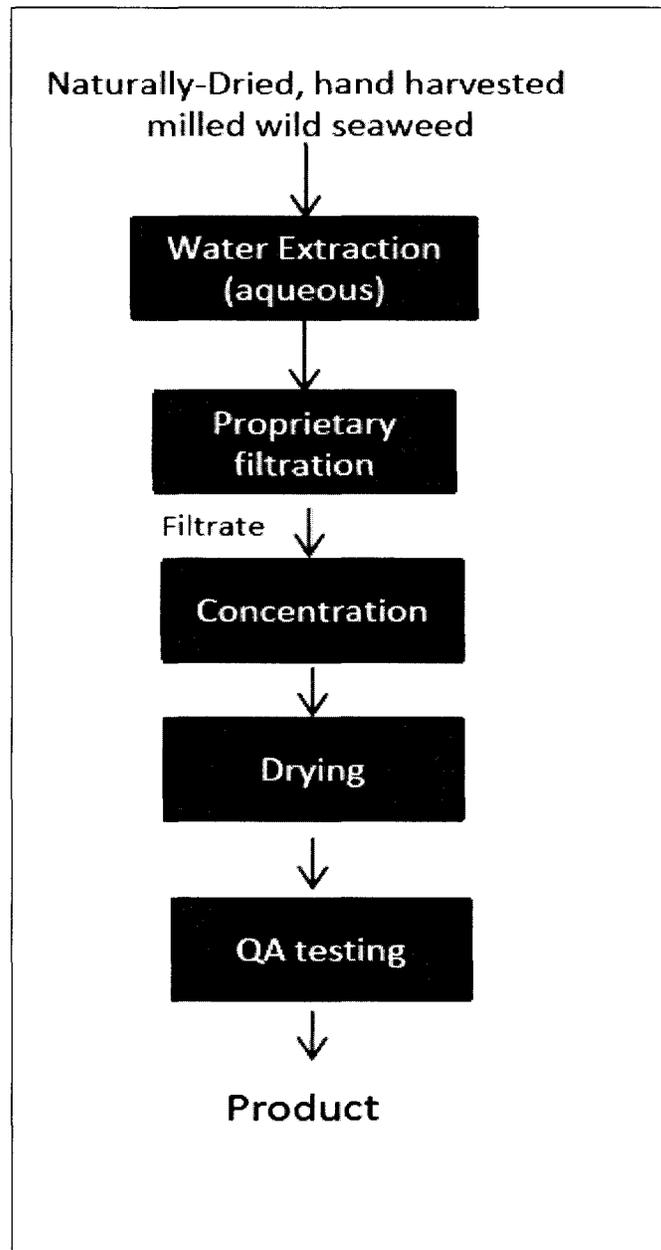


Figure 1. Manufacturing Process of Fucooidan

1.5. Chemical Structure

As mentioned earlier, fucooidan is a type of polysaccharide that contains substantial percentages of L-fucose and sulfate ester groups, mainly derived from brown seaweed (Li et al., 2008a). In recent years, fucooidan has been extensively studied for its chemical structure and biological activities. The available data thus show that the term “fucooidan” has been used for several different chemical structures and, *vice versa*, that fucooidan is a term that covers a diverse family of fucose-containing sulfated polysaccharides. Ale et al. (2011) suggested to use the term fucose-containing sulfated polysaccharides (FCSPs) rather than fucooidan as a collective term for these polysaccharides. In the case of sulfated polysaccharides, the position of the sulfate groups

000018

has been postulated to be important to any biological activity. The representative chemical structure of fucoidan derived from *U. pinnatifida* is presented in Figure 2.

The most studied fucoidans have a backbone built of (1→3)-linked α -L-fucopyranosyl residues or of alternating (1→3)- and (1→4)-linked α -L-fucopyranosyl residues. It also includes sulfated galactofucans with backbones built of (1→6)- β -D-galacto- and/or (1→2)- β -D-mannopyranosyl units with fucose or fuco-oligosaccharide branching, and/or glucuronic acid, xylose or glucose substitutions (Ale et al., 2011). These fucopyranosyl residues may be substituted with short fucoside side chains or sulfate groups at C-2 or C-4 (Senthilkumar et al., 2013). In addition to fucose and sulfate, fucoidan also contains other monosaccharides (mannose, galactose, glucose, xylose, etc.) and uronic acids, even acetyl groups and protein. For example, *F. vesiculosus* fucoidan is a high fucose sulfated fucoidan. Based on the published literature, the most common source of fucoidan used for experimental studies is derived from *F. vesiculosus*. Other common fucoidans are sourced from edible species such as *Cladosiphon okamuranus*, *Laminaria japonica* and *U. pinnatifida*. Fucoidan from *U. pinnatifida* has been reported to contain a fucose/galactose ratio of 1/1.1 (Li et al., 2008a).

U. pinnatifida fucoidans are heterodisperse, polymeric compounds that consist of sulfated fucose and galactose units with acetyl substituents and counterions to balance the sulfate anions. Maritech® *Undaria pinnatifida* fucoidan, the subject of the present GRAS assessment is typically over 75% pure.

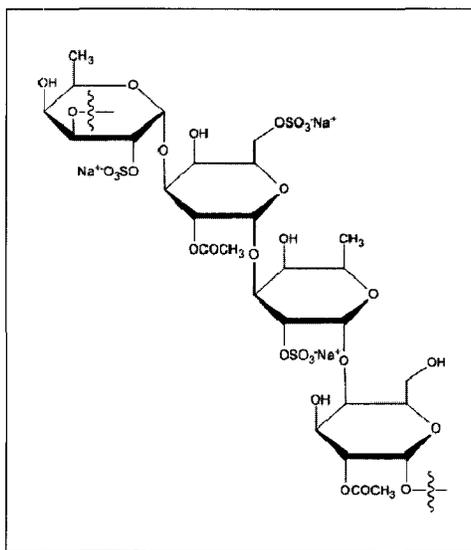


Figure 2. Chemical structure of fucoidan derived from *U. pinnatifida*

1.6. Regulatory History

In 1973, the Select Committee on GRAS evaluated health aspects of certain red and brown algae as food ingredients (SCOGS, 1973), at the request of the US FDA (Report No. 38). The brown algae reviewed by the Select Committee included *U. pinnatifida* and other species. Following its review, the Committee concluded that, “There is no evidence in the available information on the brown algae [species listed] that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that now seem to be

000019

current or that might reasonably be expected in the future if their use is confined to ingredients of spices, seasonings, and flavorings.” This report has been the basis for the US Code of Federal Regulation (CFR) regulation §184.1120.

Fucoidan, as such, is not regulated by the US FDA. However, one of the brown algae (*U. pinnatifida*) a source material for fucoidan, the subject of this GRAS assessment, is described in the CFR. As per US FDA regulation, brown algae (seaweed), including *U. pinnatifida*, is generally recognized as safe (GRAS) as per 21 CFR §184.1120 for use in food under the following specific limitations: added at a level not to exceed current good manufacturing practice (cGMP) to spices, seasonings, and flavorings as a flavor enhancer or adjuvant. The “specific limitations” under this regulation invokes §184.1(b)(2) according to which any use of these algae other than that mentioned in the regulation will require a food additive petition. The regulation is for brown algae specifically and not for the constituents derived or purified from it. The available evidence suggests the source material is commonly consumed as food in Asian countries and the product of this GRAS determination is a water extract; no organic solvents are used in its extraction.

Fucoidans derived from different brown seaweeds are commonly marketed in the United States as dietary supplements under different names³. These products are regulated under the Dietary Supplement Health and Education Act (DSHEA, 1994) in the US. Recently, on January 23, 2013, FDA has accepted and filed a New Dietary Ingredient Notification (NDIN) on *Laminaria hyperborean* extract. The recommended daily dose in the notification states “a daily dose of 200 to 300 mg ProtaSea fuciodan [*sic*] per day, equivalent to 3.3 to 5 mg/kg/day for a 60 kg individual” (FDA, 2013)

1.7. Uses and Consumption

Seaweed as a staple item of the diet has been used in Japan, Korea and China since ancient times. Seaweed remains a popular food in Japan and estimates of seaweed consumption in this country range from 4.3 to 7.3 g/person/day (Toyokawa, 1978; Teas, 1981; Fujiwara-Arasaki et al., 1984; Teas et al., 2009) to 25% of the diet (SCOGS, 1973). The National Nutrition Survey in Japan reported the daily intake of seaweeds to be about 14.3 g per adult person, with women eating more than men (Fukuda et al., 2007). In Japan and other East Asian countries, 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. A major source of dietary seaweed among Japanese populations is the edible brown kelp, wakame (*U. pinnatifida*) and kombu (*Laminaria japonica*) (Skibola, 2004). It can be stored, dried, and used to make a nutritious tea, and/or added to soups and stews in flakes or powder form for flavor. The consumption of another brown seaweed, *F. vesiculosus* has been documented as early as 1937 (Kiple and Ornelas, 2000).

In Japan and East-Asian countries, *U. pinnatifida*, commonly known as wakame, is considered as an economically important food crop, next to nori. It is consumed both dried and fresh as an additive to soups (wakame soup is served with virtually every meal in Japan); toasted (Yaki-wakame); used half resoaked, with boiled rice; and coated in sugar and tinned (Ito-wakame). In Korea, *U. pinnatifida* is used in salads or soup such as miyeokguk. Many women consume *U. pinnatifida* during pregnancy, and ‘miyeokguk’ is popularly consumed by women

³ Several products can be found under name fucoidan at Ebay website: <http://www.ebay.com/bhp/fucoidan>

after giving birth. Wakame is more popular in the Republic of Korea than in Japan, although the market in Japan has expanded. Wakame is traditionally regarded as a luxury food in both countries (FAO, 2003). There are several forms of edible *U. pinnatifida*, or wakame that include: dried, chips, flakes, and strips; as an ingredient in sea vegetable salads, in condiments and chutneys; with soup and salad and pasta and oatmeal mixes, etc. (Seaweed Industry Association, 2013).

The typical carbohydrates in brown algae varieties include fucoidan, laminaran, cellulose, alginates, and mannitol. Fucoidans are considered as an important component of brown algae and constitute up to 25-30% of the algae dry weight, depending on the specific seaweed species (Myers et al., 2011). The three most popular seaweed products in Japan are nori (*Porphyra*), wakame (*Undaria*) and kombu (*Laminaria*). The available information also indicates that the seaweed consumed can be red, green, and brown. The daily intake of seaweed has been reported to range from 4.3 to 14.3 g/person/day. Assuming that half of the seaweed consumed is brown algae that contains approximately 25% fucoidan, the daily likely intake of fucoidan from intake of seaweed can range from 0.54 to 1.79 g/person/day. The available information indicates that humans, particularly in Japan, regularly consume fucoidan from the dietary intake of seaweed. The available evidence suggests that *U. pinnatifida* that is used as the source material of the Maritech® *U. pinnatifida* fucoidan, the subject of current GRAS assessment, is commonly consumed as food in Asian countries. Additionally, Maritech® fucoidan is obtained by water-based extraction process, without the use of any organic solvents.

Globally, fucoidan extracts are consumed extensively throughout Asia, particularly in Japan, Korea and Taiwan. In addition, *U. pinnatifida* fucoidan extracts have received approval as listable ingredients by the Australian Therapeutic Goods Agency and by Health Canada. The Health Canada approval for NPN 80032473 (Stemenhance-2) is of particular relevance to the current GRAS assessment, as the approval details a capsule containing fucoidan (*Undaria pinnatifida*), at a total daily dose of up to 172.5 mg (3 x 57.5 mg). There are a number of food products, including beverages, currently available that include fucoidan in applications similar to those envisaged in this assessment. These products are summarized in Table 5.

000021

Table 5. Products Containing Fucoidan Marketed Around the World

Country	Product	Fucoidan Dosage	Fucoidan species	Reference
South Korea	Natural Choice Seaweed Beverage	400 – 1200 mg/day	<i>Undaria pinnatifida</i>	http://www.alibaba.com/product-detail/-Natural-Choice-Seaweed-Beverage-Fucoidan_145110293.html
South Korea	Wellfine Co Herbal Health Drink			http://wellfine.en.ec21.com/Health_Food_Herbal_Health_Drink--8087272_8741583.html
South Korea	Haerimfucoidan Eco			http://www.alibaba.com/product-detail/Haerimfucoidan-Eco_124455274.html
Taiwan	Original Okinawa Fucoidan	600 mg/day	<i>Cladosiphon okamuranus</i>	http://www.nutrimaxorganic.com/fucoidan/fucoidan.html
Japan	Yakult Fucoidancha		<i>Cladosiphon okamuranus</i>	http://www.yakult.co.jp/english/ir/management/pdf/ar2005.pdf
New Zealand	Matakana Superfoods Fucoidan Powder	270 mg/day	<i>Undaria pinnatifida</i>	http://begoodorganics.com/products/fucoidan-powder
USA	FusionCreatine	100 mg/day	<i>Undaria pinnatifida</i>	http://fucoidanfusion.com/products/fusioncreatine?source_app=facebook&sfb_refer=true
USA	FusionWhey	500 mg/day	<i>Undaria pinnatifida</i>	http://fucoidanfusion.com/products/fusionwhey?source_app=facebook&sfb_refer=true
USA	LIMU Original	90 mg/day	<i>Sphaerotrichia divaricata</i>	http://win-edge.com/Limu.shtml
USA	ZRadical	200 mg/day	<i>Undaria pinnatifida</i>	http://www.youngevity.net/product/3026.html

1.8. Intended Use Levels and Food Categories

Marinova intends to use fucoidan as a food ingredient at use levels up to 30 mg/serving in Baked goods; Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors (Table 6). Although some foods with standards of identity are included in the list of foods, at present, the use of fucoidan is intended for foods without a standard of identity. Additionally, foods that are intended for infants and toddlers, such as infant formulas or foods formulated for babies or toddlers, as well as meat and poultry products that come under USDA jurisdictions are excluded from the list of intended food uses of the subject fucoidan preparation.

1.8.1. Estimated Daily Intake from the Intended Uses

1.8.1.1. Use of MRCA exposure data

Estimates of possible daily intake of fucoidan from the "maximum" intended use levels of the final product preparation have been determined using the mean consumption estimates of designated food categories based on Market Research Corporation of America (MRCA) mean frequency of eating and USDA mean portion size of 34 general food categories data (MRCA, 1965). In addition to intake surveys by USDA, marketing research groups such as MRCA and the National Purchase Diary (NPD) have also surveyed the food consumption patterns of individuals and households. The primary purpose of these surveys is to determine the nutritional

000022

adequacy of diets rather than the safety of food with respect to additives or contaminants. However, these surveys are frequently used to assess exposure to additives and contaminants. Under an FDA contract, the Federation of American Societies for Experimental Biology (FASEB, 1988) reviewed the theory behind the calculation of exposure estimates from different surveys including the MRCA. The FDA's Office of Premarket Approval (OPA) has historically relied on the MRCA survey to determine consumption estimates.

Although the MRCA method was developed in 1965, it is still accepted by the FDA in determining the possible average daily intake of food ingredients (DiNovi and Kuznesof, 1995). The conservatism of this determination method assumes that the maximum amount of a substance is added to the entire food category, not just the food product within that category. Using MRCA estimated mean intakes of the food categories (Baked goods; Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors) for which fucoidan is proposed to be added, the possible maximum daily intake of fucoidan from each of the categories is summarized in Table 6.

Analysis of the results of projected maximum consumption and thus exposure revealed that the intended uses of fucoidan in the specified food categories will result in a mean estimated daily intake of 79.67 mg of fucoidan/person. In order to estimate the 90th percentile consumption of fucoidan, the corresponding mean total intake value from all food categories was multiplied by two on the grounds that the 90th percentile consumption rarely exceeds the mean by more than a factor of two (FDA, 2006). These assumptions and the analysis above indicate that the mean and 90th percentile estimated daily intake of the fucoidan from its intended food uses is 79.67 and 159.34 mg/person/day, respectively.

Table 6. Proposed Use Levels and Possible Daily Intake of Fucoidan Based on MRCA Data¹

Food category	Mean consumption of food product (g/day)	Use levels/ serving (mg)	Approximate serving size ² (g)	Mean Daily intake (mg/person)	High (90 th %) Daily intake (mg/person)
Baked Goods	137.2	30	55	74.84	149.68
Snack Foods	1.30	30	30	1.30	2.60
Soups	31.7	25	245	3.23	6.46
Imitation Dairy Products	0.9	25	225	0.10	0.20
Seasonings & Flavors	0.01	10	0.5	0.20	0.40
Total (mg/person/day)				79.67	159.34

¹The daily intake calculations are based on MRCA (1965) data on mean frequency of eating and USDA report on mean portion size. ²Serving size is based on Reference Amounts Customarily Consumed per Eating Occasion (21 CFR 101.12) and other related information.

1.8.1.2. Use of USDA Data

In addition to the above described MRCA data, the USDA survey data were used to estimate mean and high (90th percentile) per capita levels of consumption of fucoidan from the chosen food categories. Based on USDA CSFII surveys (Smiciklas-Wright et al., 2002) for quantities of foods consumed daily, the mean and 90th percentile consumption of fucoidan from the proposed uses in Baked goods; Soups; Snack Foods; Imitation Dairy Products; and

000023

Seasonings & Flavors were determined (Table 7). The CSFII data provides the intake levels of several different types of baked goods. In Table 7, values for biscuits are included. Similarly, for imitation dairy products, yogurt is used as a representative category. The intended use of fucoidan at levels up to 30 mg *per* serving will result in mean and 90th percentile intake of 135.45 and 249.66 mg/person/day, respectively.

Table 7. Intended Use Levels and Possible Daily Intake of Fucoidan Based on USDA Data¹

Food category	Consumption of food product (g/day)		Use levels/ serving (mg)	Serving size; RACC (g)	Daily intake by adult (mg/person)	
	Mean	90 th %			Mean	90 th %
Baked Goods ²	64	118	30	55	34.91	64.36
Soups	398	697	30	245	48.73	85.35
Snack Foods	41	84	25	30	34.17	70.00
Imitation Dairy Products ³	157	266	25	225	17.44	29.55
Seasonings & Flavors	0.01*	0.02*	10	0.5	0.20	0.40
Total (mg/person/day)					135.45	249.66

¹The daily intake calculations are based on USDA data (CSFII) and mean portion size; ²Biscuits intake is used to represent baked good. ³Includes yogurt as representative for this category. *As CSFII did not report consumption, MRCA data was used. Serving size is based on Reference Amounts Customarily Consumed per Eating Occasion (21 CFR 101.12) and other related information.

1.8.2. Consumption Summary

The estimated intake of fucoidan from its natural presence in seaweed appears to range from 540 to 1790 mg/person/day. The high intake of fucoidan is likely to be in countries like Japan where seaweed is commonly consumed. Based on MRCA data, the intended use of fucoidan at levels up to 30 mg/serving in food categories such as in Baked goods; Soups; Snack Foods; Imitation Dairy Products; and Seasonings & Flavors will result in mean and 90th percentile estimated daily intake of 79.67 and 159.34 mg/person/day, respectively. Based on the USDA CSFII database, the intended use of fucoidan in the selected food categories will result in mean and 90th percentile intakes of 135.45 and 249.66 mg/person/day, respectively. For safety assessment purposes, the high intake of 250 mg fucoidan/person/day (4.17 mg/kg bw/day) is considered.

1.9. Common Knowledge of Safe Use of Source Material

There is common knowledge of a long history of human consumption of seaweeds. For centuries seaweeds have been traditionally collected by man for its use as food, therapeutic and fertilizer. The available information indicates that since ancient times, seaweed as a staple item of diet has been used in Japan, Korea and China. About 21 species of seaweed are used in everyday cookery in Japan, six of them since the 8th century (Guiry, 2013). Until recently, seaweed accounted for over 10% of the Japanese diet. Seaweeds still play a wide and varied role in modern life and are used as a food resource and a source of industrial and other chemicals. Among different seaweeds in Japan, the most important food species are nori (*Porphyra* species), kombu (*Laminaria* species), and wakame (*U. pinnatifida*).

000024

In Japan, *U. pinnatifida* is a more important crop than *Laminaria* both in value and production. Approximately 20,000 wet tons of *U. pinnatifida* were collected from wild sources, whereas 127,000 wet tons were cultivated in Japan. The harvested algae are dried after washing in freshwater (Guiry, 2013). After resoaking, the plant material is used as an additive to soups (wakame soup is served with most meals in Japan); toasted (Yaki-wakame); used half resoaked, with boiled rice; and coated in sugar and tinned (*Ito-wakame*). Besides Japan, it is also commonly harvested and used as a foodstuff in China and Korea. Seaweeds containing fucoidans have been used as foods such as sea vegetables, for centuries (Udani and Hesslink, 2012). As discussed earlier, fucoidan is an important component of brown algae and may constitute up to 25-30% by weight. The available information demonstrates that there is common knowledge of consumption of seaweed, including *U. pinnatifida* that is the source of the subject Maritech® fucoidan.

2. SAFETY RELATED DATA

The safety of fucoidan is supported by several lines of evidence including multiple human clinical trials, as well as by a variety of animal and *in vitro* experimental studies that further corroborate the human observations. There has been considerable effort to elucidate the biological role of fucoidan, one of the active constituent of brown seaweed. As a result, the literature is abundant with information on seaweed and fucoidan. Relevant biological and toxicological studies on fucoidan, derived from *U. pinnatifida* as well as from other brown seaweed sources, are included in the following section. The safety data from animal studies is extensive. Efforts have been made to present both the data supporting the safety as well as any data on the toxicity of fucoidan. As the present GRAS assessment is for fucoidan derived from *U. pinnatifida*, an attempt has been made in the following sections to first present safety related information of fucoidan derived from *U. pinnatifida* followed by safety data of fucoidan derived from other sources. The safety related animal and human studies of fucoidan derived from *U. pinnatifida* as well as from some other sources are summarized in Table 8. These studies are further discussed in the individual safety section of the particular source organism.

Table 8. Summary of Toxicity studies of Fucoidan from Various Sources

Fucoidan Characteristics	Details of Studies	Dose	Species	Results	Reference
Fucoidan derived from <i>U. pinnatifida</i>					
53% total sugar, 7.4% sulfate, 27% Uronic acid, 54% fucose, 35% galactose	Short-term <i>in vivo</i> toxicity; Ames test; Bone marrow micronucleus	1000 mg/kg body weight per day for 28 days	Sprague Dawley rats	Not toxic at 1000 mg/kg bw/day; Increase in ALT at 2000 mg/kg; No genotoxicity	Chung et al., 2010
64.4 ± 6.0% fucose, 31.9 ± 4.7% galactose, 3.6 ± 1.3% mannose, and 31.7 ± 2.2% sulfate	Genotoxicity: Bacterial mutation; Bone marrow Micronucleus formation	Up to 2000 mg/kg/bw orally	Sprague Dawley rats	Fucoidan presents no significant genotoxic concern.	Kim et al., 2010a
64.4 ± 6.0% fucose, 31.9 ± 4.7% galactose, 3.6 ± 1.3% mannose, and 31.7 ±	Toxicity measures- body weight, ophthalmoscopy urinalysis,	Up to 1350 mg/kg bw/day for 4 weeks orally	Sprague Dawley rats	No change to prothrombin time or activated partial	Kim et al., 2010b

000025

2.2% sulfate	hematology, and histopathology; Clotting parameters-Prothrombin time or activated partial thromboplastin time			thromboplastin time	
75% fucoidan	Full blood count, clinical biochemistry	3 g per day for 12 days	Human	No toxicity noted	Irhimeh et al., 2005, 2007, 2009
Fucoidan derived from <i>F. vesiculosus</i>					
75% Fucoidan	115 participants with osteoarthritis (96 moderate, 17 mild and 2 severe); 96 with moderate osteoarthritis analyzed	300 mg/person/day for 12 weeks	Human	No treatment related adverse effects; No significant changes in liver, renal, hemopoietic function	Myers et al., 2014
Fucoidan derived from <i>F. vesiculosus</i> (also includes <i>Macrocystis pyrifera</i>, <i>L. japonica</i>)					
75% total fucoidan	Full blood count, clinical biochemistry	0.1 and 1 g for 84 days	Human	No toxicity	Myers et al., 2010
75% total fucoidan	Full blood count, clinical biochemistry	0.1 and 1 g for 28 days	Human	No toxicity	Myers et al., 2011
Fucoidan derived from <i>L. japonica</i>					
Fucoidan Fraction MW average "10–300 kD"	Oral dosing in experimental model; Toxicity by clinical observation	Escalation doses up to 20 mg/kg	Dogs with hemophilia A; Rats	No clinical toxicity	Prasad et al., 2008
Fluorescent labeled fucoidan	Subcutaneous	5 mg/kg	Rat	Half life 83 min	Prasad et al., 2008
MW average 189 kDa Fucose 28% sulfate 29% total sugars 48%	Acute and sub-chronic toxicity	300, 900 and 2500 mg/kg bw/day for 6 months	Wistar Rats	Not toxic at 300 mg/kg bw/day Prolonged clotting at 900 and 1200 mg/kg bw	Li et al., 2005
Fucoidan derived from <i>Cladisiphon</i> sp.					
85% fucoidan	Patients with HTLV1 were treated clinically	6 g per day up to 13 months	Human	Four patients diarrhea; No other toxicity noted; Reduction in viral load	Araya et al., 2011

2.1. Safety of *U. pinnatifida* Fucoidan

2.1.1. Human Studies

In a randomized double-blinded placebo-controlled trial in a non-seaweed consuming population, Teas et al. (2009) investigated the effects of seaweed (*U. pinnatifida*) consumption in 13 men (age 47.4 ± 9.9 years) and 14 women (age 45.6 ± 12.2 years) with at least one symptom of the metabolic syndrome. Subjects were assigned to either Group 1 (1 month placebo, followed by 1 month of 4 g/day seaweed) or Group 2 (1 month of 4 g/day seaweed, followed by 1 month

000026

of 6 g/day of seaweed). Blood pressure, weight, waist circumference, inflammation biomarkers, and lipids were measured monthly. In Group 2, systolic blood pressure decreased after a month of 6 g/day seaweed, primarily in subjects with high-normal baseline blood pressure. Waist circumference changed only for women participants, with a 2.4 cm decrease in Group 1 after treatment with placebo. In Group 2, women had a mean decrease of 2.1 cm after 4 g/day and a further 1.8 cm decrease after 1 month 6 g/day seaweed. No other changes were observed. Serum markers of inflammation (nitric oxide and C-reactive protein) and all other serum parameters did not change significantly. Only minor adverse side effects were noted. As *U. pinnatifida* has been reported to contain 8-12% fucoidan, the subjects in this study received approximately 400 and 600 mg fucoidan per day. The investigators suggested that consumption of 4 to 6 g/day seaweed, typical for most people in Japan, may be associated with low metabolic syndrome prevalence.

In a series of extensive investigations, Irhimeh and colleagues studied the effects of fucoidan derived from *U. pinnatifida* on blood coagulation related parameters. In a pilot study in human subjects, Irhimeh et al. (2009) investigated the safety and clinical effects of fucoidan (provided by Marinova) ingestion on hemostasis as well as its *in vitro* anticoagulant activity. In this single-blinded clinical trial, 20 human volunteers (age 23 to 58 years; average 40 years) were allocated to both the placebo group (n=10) or to the active treatment group (n=10) who ingested 3 g of 75% fucoidan, daily, for 12 days. Venous blood samples were collected using citrate and EDTA anticoagulant-containing tubes. Platelet indices, activated partial thromboplastin time, antithrombin-III, thrombin time, prothrombin time, and antifactor-Xa were analyzed. The plasma fucoidan concentration for the placebo group was 0.17 mg/l, whereas it was 13.06 mg/l for the fucoidan-treated group. The activated partial thromboplastin time (aPTT) increased from 28.41 to 34.01 seconds (P=0.01) at the end of 12 days. Other parameters measured after 4 days of treatment such as thrombin time decreased from 18.62 to 17.55 seconds (P=0.04), and antithrombin-III increased from 113.5 to 117% (P=0.03). In comparison with the placebo group, there were no significant changes in any of platelet indices. The global clotting time (aPTT) change was not considered to be clinically significant. The investigators also suggested that the effect of fucoidan on hemostasis was not obvious; probably due to low intestinal absorption. Thus, fucoidan in the form used in this study does not appear to have an oral anticoagulant activity. However, as described below it has a strong *in vitro* anticoagulant activity.

In the *in vitro* study, fucoidan prolonged the aPTT time from 30.8 seconds for control to 172.5 seconds at 63 mg/l (Irhimeh et al., 2009). No detectable clot formation for concentrations higher than 100 mg/l was noted. The thrombin time was also prolonged but at a higher rate in which it was 15.2 seconds at baseline and went up to 240.1 seconds at 15.6 mg/l and then no clot was detected at higher concentrations. Low concentrations (ranging from 7.8 to 63 mg/l) of the 75% fucoidan had no effect on PT, but at 125 mg/l, the PT began to increase. The prothrombin ratio [international normalized ratio (INR)] was also affected and it increased but not constantly reflecting the changes in the PT. The AT-III decreased with the fucoidan treatment from 108% for control to 89% at 10,000 mg/l. Interestingly, at high levels (10,000– 50,000 mg/l) fucoidan had a strong effect on anti-Xa assay, whereas at low levels the effect was not obvious. Fucoidan increased activated partial thromboplastin time, thrombin time, and prothrombin time, whereas antithrombin-III decreased. These observations show a prominent anticoagulant activity of fucoidan. The investigators concluded that fucoidan has anti-coagulant activity *in vitro*, but that the *in vivo* activity is weak, probably due to poor absorption (Irhimeh et al., 2009).

000027

In another study, Irhimeh et al. (2007) examined the effects of orally ingested *U. pinnatifida* fucoidan on the peripheral blood stem cells, the expression of cell surface receptor CXCR4, and plasma levels of stromal derived factor-1 (SDF-1), interleukin IL-12, and interferon IFN-g. For these investigations, six volunteers took 3 g of guar gum (placebo), another six volunteers took 3 g of whole *Undaria* containing 10% w/w fucoidan, and another 25 volunteers took 3 g of 75% w/w fucoidan daily for 12 days. No adverse effects were reported, and none of the volunteers exhibited toxicity when 3 g of the placebo, guar gum, or 10% fucoidan, or 75% Maritech® fucoidan extracts were taken orally per day for 12 days. Fucoidan ingestion caused mild leukopenia and lymphopenia but had no effect on neutrophils. A nonsignificant decrease in the total number of leukocytes in the peripheral blood was noted when 10% fucoidan was ingested, but when 75% fucoidan was ingested the decrease was significant after 12 days. Following ingestion of fucoidan, CD34+ cells increased significantly from 1.64 to 1.84 cells/mL after 4 days. The proportion of CD34+ cells that expressed CXCR4 increased from 45 to 90% after 12 days, the plasma level of SDF-1 increased from 1978 to 2010 pg/mL, and IFN-g level increased from 9.04 to 9.89 pg/mL. Oral administration of fucoidan significantly amplified the CXCR4+ progenitor stem cell population.

In yet another study, Irhimeh et al. (2005) investigated the bioavailability of fucoidan using a monoclonal antibody methodology. For this study, healthy volunteers (age 20-46 years; average 29) were divided into three groups. The first group (placebo) of volunteers (n = 6) took 3 g of guar gum as placebo. The second group (n = 6) took 3 g of Galactofucan sulfate (GFS®) containing 10% fucoidan. The third group (n = 40) took 3 g of GFS containing 75% fucoidan (provided by Marinova Pty. Ltd.) daily for 12 days. Citrated venous blood was collected. Plasma samples were quantified for the presence of fucoidan using the described competitive ELISA method. The plasma concentration of fucoidan in the placebo group was 0 mg/l, while in volunteers who received 10% or 75% fucoidan, it was 4.00 and 12.99 mg/l, respectively. The investigators concluded that small quantities of orally administered fucoidan may cross the intestinal wall as whole molecules probably by the process of endocytosis.

2.1.2. Animal Toxicity Studies

In addition to the above described genotoxicity studies, Chung et al. (2010) also performed a 28-day repeat dose oral toxicity study. In this study, Sprague-Dawley (SD) rats (5/sex/group) were administered (via gavage) fucoidan from *Undaria pinnatifida* at a dose level of 0 (vehicle), 250, 500, 1000, 2000 mg/kg bw/day for 28 days. The health condition, clinical symptoms and mortality of the animals were checked twice daily, and body weights, feed consumption and water consumption were recorded once a week. At termination, blood samples were collected for hematological and biochemical parameter measurements. At necropsy, the animals were euthanized and tissues were collected, weighed and detailed pathological and morphological observation was performed. No specific clinical symptom was observed in any animal. There was no significant difference or trend in body weight, or water or feed consumption among the groups. At doses up to 1000 mg/kg bw/day, no significant differences in hematological or biochemical parameters were noted. However, at 2000 mg/kg bw/day, ALT and triglyceride levels in male groups were significantly higher, and the total and HDL cholesterol levels in the 2000 mg/kg bw/day female groups were significantly higher (data not presented in the publication). Additionally, MCHC in the 2000 mg/kg bw/day female groups was significantly lower. Fucoidan administration at levels up to 1000 mg/kg bw/day did not cause any significant difference in organ weight or pathology. However, thyroid weights at 2000

000028

mg/kg bw/ day were significantly increased in both sexes. No liver histopathological finding was observed in any of the fucoidan-treated groups, compared with those of the control. Although the liver morphology was normal, based on the increase in liver enzyme (ALT) in male rats at the highest dose levels, the investigators indicated that fucoidan is safe at doses up to 1000 mg/kg bw/day. The no-effect-level for clotting time was 1000 mg/kg for 28 days (Chung et al., 2010).

Kim et al. (2010b) also tested the toxicity of fucoidan extracted from the sporophyll of *U. pinnatifida* in a 4-week oral trial in SD rats. The study was conducted in compliance with the test guidelines from the Korea Food and Drug Administration (KFDA) under Good Laboratory Practice regulations for Nonclinical Laboratory Studies. The chemical composition of fucoidan was reported as 64.4±6.0% fucose, 31.9±4.7% galactose, 3.6±1.3% mannose, and 31.7±2.2% sulfate. Fucoidan (0, 150, 450, and 1350 mg/kg bw/day) was administered daily by oral gavage to age-matched male and female rats (10/sex/group) for 28 days. No animals died during the experimental period, and fucoidan did not produce toxic signs in any animals. Fucoidan treatment did not alter weight gain or feed and water intake. Ophthalmologic examinations were normal. Fucoidan did not consistently change hematology or serum biochemistry values. No increase in the activity of serum toxicity marker enzymes (ALT, AST) was noted. However, BUN levels in the female groups (11.9±1.2) treated with fucoidan decreased compared with the control group (13.9±1.3). Blood urea nitrogen (BUN) levels in the male groups treated with fucoidan did not change. Fucoidan administration did not significantly affect any other hematology or biochemical parameters, including prothrombin or Activated Partial Thromboplastin Time values in any treatment groups. Gross examination revealed no abnormalities. Significantly lower values in the relative weights of the liver were observed in male (2.85±0.11) and female (2.83±0.1) rats treated with a high dose of fucoidan (1350 mg/kg) compared to control males (3.02±0.08) and females (2.87±0.1), but absolute liver weights were not different. High-dose fucoidan decreased the absolute and relative right adrenal weights. However, these changes showed no dose-dependent responses and no histopathological findings, and were therefore judged to be unrelated to fucoidan administration. Histological examinations did not reveal any pathological signs. Fucoidan administration did not affect the liver tissue or produce morphological variation in its lining. Fucoidan did not change other vital organs (lung, heart, spleen, and liver). The results of this study show that *Undaria pinnatifida* fucoidan is not toxic when orally administered at 150, 450, and 1350 mg/kg bw/day for 4 weeks, and do not have anticoagulant activity, reducing concern about adverse effects in this regard.

2.1.3. Genotoxicity Studies

Chung et al. (2010) investigated potential adverse effects of fucoidan derived from *U. pinnatifida*. These investigators studied genotoxicity by an *in vitro* Salmonella Ames test and an *in vivo* micronucleus test with ICR mice, while short-term toxicity was evaluated following 28-day oral repeated administration tests in rats. Fucoidan used in these studies was isolated by hydrolyzing *U. pinnatifida* in 0.05 M or 0.5 M HCl at 80 °C for 30 min and then neutralizing it with 1 M NaOH. After desalting by gel filtration, the hydrolysate was lyophilized. The chemical composition of the prepared fucoidan was reported as 27% uronic acid, 53% monosaccharides and 7.4% sulfate.

The Ames test was performed with *Salmonella typhimurium* strains TA100 (base pair mutation) and TA98 (frame shift mutation). Fucoidan was tested at levels of 0, 125, 250, 375, 500 µg/plate (Chung et al., 2010). Additionally, *Salmonella* antimutagenicity test (Ames test) was also conducted with 4-Nitroquinoline-1-oxide (4NQO, 0.15 µg/plate). As compared with the

000029

spontaneous revertant colonies formed in the control group, fucoidan treatment did not induce significant dose dependent revertant colonies at any of the doses tested, in either *S. typhimurium* TA 98 or TA 100 strains. Additionally, fucoidan treatments exhibited dose-dependent antimutagenic effects in both TA98 and TA100 against 4NQO as a mutagen. The maximum inhibition of mutagenicity ratio with fucoidan treatment was 76%.

For the *in vivo* bone marrow micronucleus assay, fucoidan was administered orally (0, 250, 500, 1000, 2000 mg/kg) to 5 week-old ICR male mice (Chung et al., 2010). Mitomycin C was administered (2 mg/kg) as a positive control. After 36 hours of treatment, the animals were euthanized and bone marrow cells were processed for measurement of micronucleated polychromatic erythrocyte percentage ratio (MNPCEs) per polychromatic erythrocytes (PCEs). In total, 500 polychromatic erythrocytes and/or normochromatic erythrocytes (NCEs) were scored for %PCEs/(PCEs + NCEs). During the course of experiment, no lethality or significant clinical symptoms were noted. As compared with the negative control groups, fucoidan administration at the doses tested caused no significant change in %MNPCE or %PCE (PCE + NCE), while as expected mitomycin C administration, the positive control, caused significant changes in %MNPCE and %PCE (PCE + NCE). The findings from the Ames test and micronucleus assay suggest that fucoidan is not genotoxic.

Kim et al. (2010a) investigated the potential genotoxic effects of fucoidan extracted from the sporophyll of *U. pinnatifida* using a test battery of three different methods. In a reverse mutation assay using four *S. typhimurium* strains (TA98, TA100, TA1535, and TA1537) and *Escherichia coli* (WP2uvrA), fucoidan (312.5, 625, 1250, 2500 and 5000 µg fucoidan/plate) did not increase the number of revertant colonies in any tester strain regardless of metabolic activation by S9 mix. Fucoidan did not cause more than a twofold increase in the mean number of revertants per plate compared to the negative control. The positive controls for each strain resulted in the expected increase in the number of revertant colonies. These data indicate no evidence of gene mutagenic potential under the conditions used in this test for fucoidan.

The chromosomal aberration assay was conducted using a Chinese hamster lung cell line (CHL/IU), both in the presence and absence of S9 metabolic activation (Kim et al., 2010a). The chromosome aberration was assessed via two different procedures; a 6-hour exposure followed by an 18-hour recovery (with or without metabolic activation), and a 24-hour continuous exposure. Fucoidan (313-5000 µg/mL) produced dose-related changes in cytotoxicity but did not change the number of cells with numerical aberrations. Fucoidan did not cause chromosomal aberration in short tests with S9 mix or in the continuous (24 hour) test.

For the *in vivo* micronucleus assay, mice received a gavage dose of fucoidan at dose levels of 0, 500, 1000, and 2000 mg/kg bw/day, or positive control cyclophosphamide at dose level of 70 mg/kg bw/day (Kim et al., 2010a). No signs of toxicity or gross behavioral changes, significant weight changes or death were noted. At 24 hours after the final dose, mice were euthanized and their femurs removed. Bone marrow cells were collected by washing the femur cavity with FBS to prepare a slide for MN test. There were no statistically significant treatment-related differences in incidences of MNPCEs or the PCE/NCE ratio, whereas the positive control induced significant increased incidence of MNPCEs. The results of this assay demonstrate that fucoidan did not induce chromosome aberrations in rat bone marrow cells.

Song et al. (2012) investigated the potential genotoxicity of low molecular weight fucoidan (LMF) using a standard battery of tests (bacterial reverse mutation assay, chromosomal

000030

aberrations assay, and mouse micronucleus assay). LMF was prepared by acid hydrolysis of high molecular weight fucoidan (HMF) extracted from sporophylls of *U. pinnatifida*. In a reverse mutation assay using four *S. typhimurium* strains and *E. coli*, LMF did not increase the number of revertant colonies in any tester strain regardless of metabolic activation by S9 mix, and did not cause chromosomal aberration in short tests with the S9 mix or in the continuous (24 hour) test. In the bone marrow micronucleus test in ICR mice that were administered via oral gavage at doses up to 2000 mg/kg bw/day, no significant or dose-dependent increases in the frequency of micronucleated polychromatic erythrocytes was noted. Based on the results of these studies, the investigators concluded that the LMF was not genotoxic under the conditions of the reverse mutation assay, chromosomal aberrations assay, or mouse micronucleus assay.

2.2. Safety of Fucoidan from Other Sources

2.2.1. Human Studies

Clinical studies of fucoidan derived from other seaweeds, such as *Fucus*, *Laminaria* and *Cladosiphon*, are summarized in Table 9. In a double-blind randomized placebo-controlled trial, Myers et al. (2014) investigated the effects of Maritech® fucoidan derived from *F. vesiculosus* in individuals with osteoarthritis (study completed by Myers et al., 2012 and report provided by Marinova). In this study, 144 healthy volunteers aged between 18 and 85 years with a diagnosis of osteoarthritis of the knees (n=122 with moderate arthritis- main study, n=18 with mild arthritis- mild sub-study and n=4 with severe arthritis- severe sub-study) were enrolled. The study was completed by 115 participants (96 moderate, 17 mild and 2 severe). The main analysis was undertaken in 96 participants with moderate osteoarthritis who completed the study. For this study, aqueous Maritech® extract of *F. vesiculosus*, prepared using the same process as for the Maritech *U. pinnatifida* fucoidan in this monograph, were delivered as a dried powder (150 mg) in capsule form. Participants randomized to the active group took two capsules (300 mg) per day (morning and night) for 12 weeks. The placebo group received an identical capsule containing microcellulose. In addition to the Comprehensive Osteoarthritis Test, weight, blood pressure, pulse, and clinical laboratory measures (full blood count, liver function tests as well as urea, creatinine and electrolytes) were measured at baseline and week 12. Adverse events and any changes to treatment were recorded at each clinic visit. Safety was assessed by measuring cholesterol, liver function, renal function and hemopoietic function over the course of the study and closely monitoring adverse events (Myers et al., 2012; 2014).

In total 29 participants withdrew from the study (Myers et al., 2012; 2014). The withdrawal rate from the main study was 21% (26 out of 122 initially enrolled); 5% in the mild sub-study (1 out of 18 initially enrolled); and 50% in the severe sub-study (2 out of 4 initially enrolled). One participant was withdrawn due to a serious adverse event. The major reason for withdrawal was pain affecting 15 participants (14 from the main study and 1 in the severe sub-study). Ten of the 15 individuals withdrawing due to pain were on the placebo (this included 9/14 in the main study). Non-compliance with study protocols led to the withdrawal of 7 participants; and, inability to attend due to work commitments to the withdrawal of 3 participants. Diarrhea led to the withdrawal of 2 participants (one active and one placebo group); and nausea to the withdrawal of 1 participant (active group). Overall, there were three serious adverse events which were unlikely to be associated with the study treatment as all three participants were receiving placebo. All other adverse events recorded were mild and self-limiting. There were no changes in the blood parameters that were of any clinical significance during the course of the study. The results of this study suggest that intake of fucoidan derived

000031

from *F. vesiculosus* is safe at levels of 300 mg/day for 12 weeks (Myers et al., 2012; 2014). The Primary Investigator for the trial reported that the drop-out rate for this study was typical for a study of its type, with an elderly cohort suffering chronic pain.

Table 9. Human Clinical Studies of Fucoidan Derived from Other Sources

Source	Dose	Duration	Subjects	Findings	Reference
<i>Fucus vesiculosus</i>	300 mg	Daily for 12 weeks	Osteoarthritis of the knees (115); 96 with moderate osteoarthritis analyzed	No adverse effects, including changes in liver, renal, hemopoietic function	Myers et al., 2014
<i>F. vesiculosus</i>	0.1 and 1 g	Daily for 28 days	Healthy adults (10)	No adverse effects. No changes in blood hemopoietic, hepatic, or renal function	Myers et al., 2011
<i>F. vesiculosus</i>	0.1 and 1 g	Daily for 84 days	Healthy adults (12)	No adverse effects. No changes in liver, renal, hemopoietic function	Myers et al., 2010
<i>Laminaria japonica</i>	400 mg	Daily for 5 weeks	Healthy adults (13)	Antithrombotic effect	Ren et al., 2013.
<i>Cladosiphon</i>	100 mg	Daily for 3 weeks	Adults with Gastric ulcer	Improved rate of healing	Juffrie et al., 2006.
<i>Cladosiphon</i>	4 g	Daily	Colorectal cancer patients. 20 (10 on fucoidan)	Reduced fatigue Increased chemo cycles.	Ikeguchi et al., 2011.
<i>Cladosiphon</i>	6 g	Daily for 6-13 months	Adults with HTLV1 associated myelopathy	Lowered proviral load in patients. No disease progression	Araya et al., 2011.
<i>Cladosiphon</i>	0.83 g	Daily for 12 months	Adults with Hepatitis		Mori et al. 2012
<i>Cladosiphon</i>	4.05 g	Daily for 2 weeks	Healthy normal adults	Normal lab values except favorable change in cholesterol.	Abe et al. 2013

In an earlier published study, Myers et al. (2010) investigated the effects of a seaweed extract nutrient complex on osteoarthritis. In this open label combined phase I and II pilot trial, Maritech® extract formulation, containing extracts from three different species of brown algae, plus nutrients, was investigated for acute safety and efficacy. Twelve volunteers (5 females- 62±11 years and seven males- 57±9 years) with knee osteoarthritis were randomized to receive either 100 mg (n = 5) or 1000 mg (n = 7) of the formulation per day for 12 weeks. The formulation contained *F. vesiculosus* (85% w/w), *Macrocystis pyrifera* (10% w/w) and *Laminaria japonica* (5% w/w) plus vitamin B6, zinc and manganese. The formulation was standardized to a fucoidan content of 75%. In addition to efficacy parameters, safety measures included full blood count, serum lipids, liver function tests, urea, creatinine and electrolytes determined at baseline and week 12. Additionally, all adverse events were recorded. Eleven participants completed 12 weeks and one completed 10 weeks of the study. The preparation was

000032

well tolerated and the six adverse events noted were unlikely to be related to the treatment. The first event, influenza occurred prior to the commencement of the trial and the participant withdrew. Two participants had hypertension, one baseline and one at week 4. Both participants had a history of hypertension. One participant had a chest infection at week 12, one had root canal work at week 12, and one participant had hyperacidity at week 12 with a history of gastric acidity at baseline. There were no changes in blood parameters measured over the course of the study with the exception of an increase in serum albumin which was not clinically significant. There were no changes in the cholesterol, liver function, renal function, and hemopoietic function that were of any clinical significance during the course of the study. The results of this study suggest that intake of the formulation at a dose level of up to 1000 mg/day for 12 weeks did not cause any adverse effects.

In yet another published study, Myers et al. (2011) attempted to determine whether a seaweed nutrient complex containing extracts from three different species of brown algae plus nutrients is safe to administer and has biological potential as an immune modulator. The formulation used in this study was similar to that described in the above study (Myers et al., 2010). In this open label study, volunteers (n = 10) were randomized to receive the study formulation at either a 100 mg (n = 5) or 1000 mg (n = 5) dose over 4 weeks. The participants comprised nine females (mean age 33.4 years) and one male (age 45 years). The reports of adverse events were mild and self-limiting. Two participants who experienced an adverse event (hay fever n = 1; head cold n = 1) occurred in the last 2 days of the study and were not considered to be related to the treatment. The descriptive statistics for blood safety measures (full blood count, liver function tests, and determination of urea, creatinine, electrolytes, cholesterol, and triglycerides) on days 1 and 28 did not reveal any significant changes except for potassium. However, the change in potassium was small and well within the clinical reference range so was assessed to not be of clinical significance. The preparation was found to be safe over the 4 weeks, at both tested doses.

In a clinical trial in healthy human volunteers, Abe et al. (2013) investigated the effects of excessive intake of fucoidan extracted from Okinawa Mozuku (*Cladosiphon okamuranus*) on the changes in blood and urine parameters and also the alteration in abdominal and fecal states. The test foods composed of 4.05 g fucoidan in 150 mL (5 times the typical fucoidan usage). Twenty healthy adults (4 men and 16 women with a mean age of 22.9 ± 1.4 years) participated in this study. The subjects ingested the test food for 2 weeks. The subjects were instructed to record test food ingestion, stool frequency, and the presence and severity of specific abdominal or any other symptoms every week on a questionnaire sheet. Blood and urine samples were collected before (baseline) and after 2 weeks of ingestion, for measurements of all common parameters for such tests. Blood biochemical examinations revealed a statistically significant reduction in total-cholesterol and LDL-cholesterol, while chloride showed significant increase. Although significant, the blood chloride levels were within the normal range and were not considered biologically significant. Kidney and liver related parameters did not show any significant differences. There were some changes from baseline among laboratory analysis (blood cells, hepatic and urine tests) but no statistically significant changes were noted for subjects. No adverse events or laboratory abnormalities were observed. In addition, no adverse effect attributable to the ingestion of the fucoidan was reported in the subject interviews about the abdominal and fecal states. The results of this study show that daily administration of fucoidan at levels of 4.05 g for two weeks is safe for human consumption.

000033

Mori et al. (2012) examined the effects of fucoidan extracted from the marine alga, *Cladosiphon okamuranus* Tokida on hepatitis C virus (HCV) activity in humans. In this open-label uncontrolled study, 15 patients (7 men and 8 women; age, 66.1 ± 11.1 years; range, 42-86) with chronic hepatitis C, and HCV-related cirrhosis and hepatocellular carcinoma were treated with fucoidan (0.83 g/day) for 12 months. The clinical symptoms, biochemical tests, and HCV RNA levels were assessed before, during, and after treatment. Fucoidan was found to be effective in lowering HCV RNA level in this study, although its effect was temporary. No adverse events were observed in any patients, suggesting that daily oral administration of fucoidan for 12 months is safe and tolerable. In another similar open label study, 13 patients with HAM/TSP⁴ were treated with 6 g fucoidan (source not clear but base on supplier appears to be derived from *C. okamuranus*) daily for 6-13 months (Araya et al., 2011). Fucoidan therapy resulted in a 42.4% decrease in the HTLV-1 proviral load without affecting the host immune cells. During the treatment, no exacerbation was observed. Four patients with HAM/TSP developed diarrhea, which improved immediately after stopping fucoidan administration. No other adverse effects of fucoidan were noted.

2.2.2. Animal Studies

Based on the results of a study in rats, Choi et al. (2010) suggested that anti-ulcer properties of fucoidan might contribute in protecting the inflammatory cytokine-mediated oxidative damage to gastric mucosa. In this study, the effects of fucoidan (obtained from Sigma Chemical Co., St. Louis, MO; most probably derived from *F. vesiculosus*) on aspirin-induced ulcers in adult Wistar rats were evaluated. For these investigations, in addition to three other groups, one group of rats received only fucoidan via gavage at a dose level of 20 mg/kg bw/day for 14 days. As compared to control group, fucoidan treated rats did not show any adverse effects as evaluated by serum levels of aspartate (AST) and alanine (ALT) transaminases, BUN and total cholesterol. Additionally, histopathological evaluation of gastric tissue of fucoidan treated rats did not reveal any toxicity. The results of this study show that oral administration of fucoidan at dose level of 20 mg/kg/day for 14 days did not reveal any toxic effects.

Zaragoza et al. (2008) investigated the adverse effects of two extracts from *F. vesiculosus* containing 28.8% polyphenols or 18% polyphenols plus 0.0012% fucoxanthin. The LD₅₀ by the oral route in rats for extracts 1 and 2 ranged between 1000 and 2000 and >2000 mg/kg, respectively, while with female mice, they ranged between 1000 and 2000 and >750 mg/kg, respectively. In the 4 week toxicity study, five groups of seven males and seven females rats were daily administered either 1% carboxymethylcellulose (control group) or extract 1 or 2 at two doses via gavage. The doses used were 200 and 750 mg/kg bw/day as the low dose and the high dose, respectively. At the end of the treatment period, blood was collected and the most important organs were removed, weighed, and subjected to histological examination. The hematological and clinical chemistry parameters were evaluated. The overall results obtained from the 4 week toxicity study indicate that even at the daily dose of 750 mg/kg bw for 4 weeks, no relevant signs of toxicity occurred with the two *F. vesiculosus* extracts studied. The levels of fucoidan in the extracts were not mentioned.

⁴HAM/TSP = Human T-lymphotropic virus type-1 (HTLV-1), a human retrovirus that causes HTLV-1-associated myelopathy/tropical spastic paraparesis.

Li et al. (2005) investigated the acute and subchronic (6 months) toxicity of varying levels of fucoidan extracted from *L. japonica* in Wistar rats after oral administration. For the preliminary acute toxicity study, several doses of fucoidan (0, 100, 500, 1000, 2000 and 4000 mg/kg bw) were tested and in the main study dose of 4000 mg/kg bw was employed. No signs of toxicity or gross behavioral changes were noted at 4000 mg/kg dose. Gross and microscopic examinations also did not reveal any evidence of toxicity. The LD₅₀ appears to be greater than 4000 mg/kg bw.

For the repeat-dose long term toxicity study, rats (10/sex/group) were administered (via gavage) fucoidan at a dose level of 0 (vehicle), 300, 900, and 2000 mg/kg bw/day for 6 months (Li et al., 2005). Two additional groups of rats (10/sex/group), one control and another high dose recovery group, were also included. The results showed that no significant toxicological changes were noted at the dose level of 300 mg/kg bw/day fucoidan administered to rats. However, when the dose was increased to 900 and 2500 mg/kg bw/day, the clotting time was significantly prolonged. Except this observation, no other signs of toxicity were noted. Based on these results, the investigators concluded that the no adverse effect level (NOAEL) of fucoidan from *L. japonica* is 300 mg/kg bw/day.

In another study, Gideon and Rengasamy (2008) investigated the toxicity of fucoidan from *Cladosiphon okamuranus* in rats after oral administration for 3 months. In this study, fucoidan was administered to Wistar rats via oral gavage at dose levels of 0, 300, 600, 1200, 2400 and 4000 mg/kg bw, 6 days per week for 90 days. No significant toxicological effects were noted at dose levels of 300 or 600 mg/kg/day. At fucoidan doses of 1,200 mg/kg/day and above, prolonged clotting time was noted. Given these effects, 600 mg/kg/day was considered to be the NOAEL in this study.

2.2.3. Genotoxicity Studies

Leite-Silva et al. (2007) assessed the genotoxic and antigenotoxic potential of three different concentrations (0.25, 0.5 and 1.0 mg/mL) of *F. vesiculosus* aqueous extract in cultured human lymphocytes. Genotoxicity was measured by the frequencies of chromosome aberrations and the induction of DNA damage as detected by the Comet assay. Exposure of the lymphocyte cultures to 0.25, 0.5 and 1.0 mg/mL *F. vesiculosus* aqueous extract had no effect on the chromosome aberration frequency or on the extent of DNA damage. The antigenotoxic effects of the extract were tested in the lymphocyte cultures at levels of 15 µg/mL of doxorubicin, either alone or combined with the different concentrations of the extract that was added to the cultures before, simultaneously with or after the doxorubicin. A reduction in doxorubicin-induced chromosome aberrations and DNA damage was detected by the Comet assay only when lymphocytes were pre-treated with the extract. The results of these investigations demonstrate that *F. vesiculosus* aqueous extract is not genotoxic in cultured human lymphocytes and indicate that when added to lymphocyte cultures before doxorubicin it has antigenotoxic activity against doxorubicin-induced DNA damage. Although the amount of fucoidan in the extract was not reported, it is likely to be present. In another study, Ruperez et al. (2002) reported that the antioxidant activity of the *F. vesiculosus* aqueous extract was due to the sulfated-polysaccharide fucoidan.

2.3. Absorption, Distribution, Metabolism and Excretion (ADME)

The bioavailability of fucoidan extracts from a number of species has been investigated in both animal and human studies with reports indicating little to no systemic uptake of fucoidan

000035

following oral administration. In an *in vitro* investigation of the digestibility of fucoidan from *U. pinnatifida* by human fecal bacteria, Michel et al. (1996) demonstrated a lack of degradation, suggesting that the ingested fucoidan remains unaltered within the gut. In a rat model, (Tokita et al., 2010) serum analysis indicated the presence of trace amounts of fucoidan, originating from *Cladosiphon okamuranus*. In this study, analysis of the serum and plasma fucoidan demonstrated that the fucoidan itself had remained unchanged. The highest reported uptake of fucoidan in human studies was reported by Irhimeh et al. (2005), who suggested that up to 1% of the oral dose had been absorbed, through analysis of serum with a non-specific antibody-based assay. Thus, literature reports of fucoidan pharmacokinetics suggest that only small amounts (up to 1% of the oral dose) of fucoidan are absorbed.

2.4. Allergenicity

A search of published information did not reveal any evidence of allergies following consumption of fucoidan. No allergic reactions have been reported in the clinical studies performed by Marinova with fucoidan. In addition, no allergy complaints have been received by Marinova in the 10+ years that Marinova's Maritech® extracts have been produced and consumed in the marketplace. Marinova has also performed specific topical allergen testing (HRIPT) on fucoidan derived from *U. pinnatifida*. Based on these unpublished studies, the extract was determined to be a non-primary sensitizer, and non-photo sensitizer when applied topically.

Ingesting fucoidan is unlikely to induce any changes in allergic response. There are no known reports of allergic responses to ingested fucoidan. However, there are reports of reduced allergic responses in animal models for topically applied fucoidan (Yang, 2012). In addition, fucoidan suppressed IgE from *ex vivo* peripheral blood cells from patients with the allergic condition of atopic dermatitis. Whilst there is one additional report of reduced allergic response (Maruyama et al., 2005), this refers to intra-peritoneal (IP) delivered fucoidan rather than edible fucoidan. Thus the cumulative evidence from Marinova's clinical studies, combined with the lack of allergic responses to oral doses in the literature reinforces the low allergenicity of fucoidan extracts.

2.5. Anticoagulant Activity

The anticoagulant activity of fucoidan is by far the most extensively investigated. Although some of the coagulation-related (*in vitro*, animal and human) studies of fucoidan are described in earlier sections, an attempt has been made to understand implications of these effects as it relates to the safety-in-use at the proposed uses of fucoidan by Marinova. The *in vivo* animal safety studies in which effects of fucoidan on coagulation were investigated are summarized in Table 10. Additional details of these studies are summarized in Table 8.

Table 10. Summary of Hematological Findings from Animal Toxicity Studies

Reference	Species	Fucoidan source	Dose levels	Findings	Comments
Kim et al. (2010b)	SD rat	Fucoidan from <i>U. pinnatifida</i> with 64.4% fucose, 31.9% galactose, 3.6% mannose, 31.7% sulfate	0, 150, 450, 1350 mg/kg for 28 days via oral gavage (10/sex/group), 7 days/week	There was no change in prothrombin time or activated partial thromboplastin time	NOAEL for clotting: 1350 mg/kg/day for 28 days
Chung et al. (2010)	SD rat	Fucoidan from <i>U. pinnatifida</i> , 27%	0, 250, 500, 1000, 2000 mg/kg/day	No evaluation of clotting time, limited	NOAEL for hematology:

000036

		uronic acid, 28.6% fucose, 18.9% galactose and 8% other monosaccharides, 7.4% sulfate	once/day for 28 days (5/sex/group). Hematology, clinical chemistry conducted	number of hematological and clinical chemistry parameters	1000 mg/kg/day for 28 days
Li e et al. (2005)	Wistar rat	<i>L. japonica</i> , 48% total sugar, 28% fucose, 29% sulfate, MW 189 k	0, 300, 900, 2500 mg/kg/day for 180 days; oral gavage (10 or 20/sex/group)	Increased clotting time at two high doses in both sexes; recovery in high dose males, but not high dose females after one month	NOAEL for clotting: 300 mg/kg/day for 180 days
Gideon and Rengasamy (2008)	Wistar rat	Extract of <i>Cladosiphon okamuranus</i> with 40.2% fucose, 3.7% uronic acid, 24.7% monosaccharides, 18.6% sulfate, MW 380 k	0, 30, 600, 1200, 2400, 4000 mg/kg for 90 days via oral gavage in water (6/sex/group), 6 days/week	Increased clotting time at ≥ 1200 mg/kg in both sexes with greater severity in males. No effects at 600 mg/kg	NOAEL for clotting: 600 mg/kg/day for 90 days

The available information from multiple *in vitro* and *in vivo* studies suggest that the sulfate content, molecular weight, and sugar composition may be related to the anticoagulant activity of fucoidan (Collic et al., 1991; Kim et al., 2007; Li et al., 2008a; Li et al., 2008b). In general, the higher content of sulfate has been reported to be associated with the higher anticoagulant activity. Conversely, the anticoagulant activity gradually decreased up to a point where the sulfate content was too high. This was confirmed with the use of oversulfated fucoidans prepared by chemical sulfation of natural fucoidan where highly sulfated fucoidan showed an increase in anticoagulant activity up to a certain degree of sulfation that then gradually decreased anticoagulant activity (Li et al., 2008a).

In addition to sulfate content, the molecular weight of fucoidan was also found to be closely related to its anticoagulant action. The available information indicates that fucoidan requires a sugar-chain long enough to bind the thrombin, so a certain minimum molecular weight is required to attain anticoagulant activity. Fucoidan extracted from *Lessonia vadosa*, which had high anticoagulant activity, possessed a molecular weight of 320,000 Da (Chandia and Matsuhira, 2008). A smaller fucoidan fraction with a molecular weight of 32,000 Da showed weak anticoagulant activity. Some studies have also shown that the anticoagulant activity may be related to the sugar composition of fucoidan (Nishino et al., 1989). Li et al. (2008a) suggested that the sugars did not affect the anticoagulant activity but that the sulfate groups attached to those sugars were responsible for the altered anticoagulant activity. In another study, Li et al. (2008b) reported that uronic acid composition, although not necessary for anticoagulant activity, could improve the anticoagulant action by enhancing the sugar chain's flexibility.

In an attempt to understand any association between anticoagulant activity and the differences between fucoidan compositions, several parameters such as carbohydrate composition, sulfate, acetyl groups and cations were compared for fucoidan derived from *Undaria*, *Fucus* and *Laminaria* (Table 11). The available information indicate that the molecular weights and sulfate contents of fucoidan derived from these three species are similar. *Fucus* and *Laminaria* are most similar in their neutral carbohydrate profile, which is primarily fucose,

000037

however *Fucus* and *Undaria* have the most similar total neutral carbohydrate content – *Laminaria* differs in its high uronic acid content. These observations indicate that coagulation-related effects of fucoidan derived from *Undaria*, *Fucus* and *Laminaria* are expected to be similar between these species.

Table 11. Typical Compositional Analysis of Fucoidan from *Undaria*, *Fucus* and *Laminaria**

Parameters	<i>Undaria pinnatifida</i>	<i>Fucus vesiculosus</i>	<i>Laminaria japonica</i>
Carbohydrates			
Fucose (%w/w)	29.3	49.7	26.5
Galactose (%w/w)	21.2	2.9	3.3
Xylose (%w/w)	0.0	3.0	0.8
Mannose (%w/w)	0.9	0.3	3.5
Glucose (%w/w)	0.9	0.0	0.6
Arabinose (%w/w)	0.0	0.0	0.2
Rhamnose (%w/w)	0.0	0.0	0.7
Uronic acid (%w/w)	4.3	6.8	17.0
Others			
SO ₄ (%w/w)	25.2	27.0	24.0
Acetyl (%w/w)	2.5	0.0	0.5
Cations (%w/w)	7.0	6.8	10.0

*Based on information provided by Marinova

As discussed earlier (see section 2.1.1.), Irhimeh et al. (2009) reported that fucoidan derived from *U. pinnatifida*, given orally, had a modest but significant effect on some of the coagulation assays, in particular, the intrinsic pathway. However, the coagulation tests were still within reference ranges and unlikely in themselves to be ‘clinically valuable’. It should be noted that in this study, fucoidan was administered at a dose level of 3 g/person/day. As compared to the intended use levels of this submission, the dose level in this study was much (12 times) higher.

In order to identify the structural features important for increasing fucoidan's procoagulant activity and minimizing anticoagulant activity, Zhang et al. (2014) investigated thrombin generation (CAT), anticoagulant effect (aPTT) and TFPI- inhibition as a function of fucoidan's molecular size and charge density. In this study, *F. vesiculosus* fucoidan was fractionated by charge and size and was also over- and desulfated to different degrees to yield preparations with various structural properties. Each fraction's pro- and anticoagulant activities were assessed by calibrated automated thrombography (CAT) and activated partial thromboplastin time (aPTT assay). Binding to the inhibition of the anticoagulant protein tissue factor pathway inhibitor (TFPI) and the ability to activate coagulation via the contact pathway were also investigated. The results of this study show that a chain length (DP) of at least 70 sugar units (MW ~ 15 kDa) and a charge density (OS) of at least 0.5 sulfates/unit maintain procoagulant activity, but lose most of the anticoagulant activity and cannot activate the contact pathway.

Prasad et al. (2008) investigated potential efficacy and safety of fucoidan derived from *F. vesiculosus* and *L. japonica* in dogs with hemophilia A (hemophilia A dogs) with minimally increased hemostasis and in treatment-naïve severe hemophilia A dogs. Subcutaneous

000038

administration of fucoidan to low-FVIII dogs improved hemostasis as exhibited in thromboelastography (TEG) and cuticle bleeding time (CBT) tests. Moreover, oral administration of fucoidan to AAVFVIII dogs and treatment-naive severe hemophilia A dogs for a multi week dose escalating period yielded correction to normal ranges in both TEG and CBT end points at 5 to 15 mg/kg and 15 to 20 mg/kg dose levels, respectively. In all 3 separate studies, throughout their duration, fucoidan was well tolerated by the dogs without any adverse events. Additional pharmacologic characterization of fucoidan included intravenous pharmacokinetic analysis in rats. The findings from this study did not reveal any increase in aPTT clotting times for dogs at 15 mg/kg/day. These investigators reported that their observations along with the published findings suggest that fucoidans are well tolerated and that safe hemostasis can be achieved.

In summary, the available information related to anticoagulant activity, also described earlier in safety sections, indicates a low level of toxicity. Among the different *in vivo* safety-related studies, in five repeat dose oral studies in rats that lasted for 14 to 180 days, coagulation-related effects were investigated (Table 12). In the longer exposure period studies, the only significant and consistent effect noted was a prolongation of clotting time. Additionally, there were isolated, scattered other effects that were not observed consistently across studies. The effect on clotting time is consistent and has been widely reported in the literature. These data are summarized in Table 11. These studies indicate that the dose to induce prolonged clotting time is related to the length of administration, and also suggests that in order to induce clotting effect, fucoidan needs to accumulate in the blood to certain critical levels. In these studies, administration of fucoidan at dose levels of 900, 1200, or >1350 mg/kg/day was required to prolong coagulation after 180, 90 or 28 days of administration, respectively. These studies also suggest that the pattern of effect and no-effect levels depend on the choice of the high dose and next lower dose where effects are not observed and the length of time of dose administration. Compared to the intake of fucoidan (4.17 mg/kg bw/day) from the proposed uses of fucoidan, the lowest dose at which fucoidan (900 mg/kg bw/day) induced prolongation of clotting time is over 200-fold higher.

Table 12. Summary of Coagulation-Related *in vivo* Animal and Human Studies of Fucoidan

Reference	Species	Treatment Duration	Minimum anti-coagulation dose (mg/kg bw/day)	Anti-coagulation NOAEL (mg/kg bw/day)
Irhimeh et al. (2009)	Human	4 days	Not determined	96
Chung et al. (2010)	Rat	28 days	2000 ^a	1000 ^a
Kim et al. (2010b)	Rat	28 days	>1350	1350
Gideon and Rannasamy (2008)	Rat	90 days	1200	600
Li et al. (2005)	Rat	180 days	900	300

^aClotting time was not evaluated but mean corpuscular hemoglobin concentration was decreased at 2000 mg/kg bw/day

In regard to any possible interference with anticoagulant therapy, the available evidence indicates that fucoidan at dietary levels up to 250 mg/day would not interfere with anticoagulant therapy. Studies of fucoidan absorption indicate that a 250 mg/day dose would result in ≤ 2.5 mg

000039

uptake or a maximal serum fucoidan concentration of 0.5 mg/L for an average adult with 5 L of blood volume. Irhimeh et al. (2009) reported that concentrations greater than 15.6 mg/L of fucoidan from *Fucus vesiculosus* were required before significant effects on aPTT were observed, whilst PT remained unaffected until plasma concentrations of 125 mg/L were reached. Thus, at the dosages considered in this submission, resulting serum levels are expected to remain 30 times lower than that which would be required for a significant effect on coagulation pathways.

2.6. Structure and Biological Activity

Fucoidan is a complex polysaccharide composed primarily of fucose subunits, but also including galactose, xylose, mannose and other sugar monomers. Varying degrees of sulfation are present on the fucoidan backbone, which leads these molecules to possess a significant negative charge. Fucoidan can also vary in the sulfation position, linkages (between adjacent sugar monomers) and molecular weight (a large range of molecular weight fractions are typically present). A comparison of fucoidan extracts from *Fucus*, *Laminaria*, *Cladosiphon* and *Ascophyllum* genera demonstrated comparable anti-inflammatory activity irrespective of fucose and sulfate content in a rat model with IP delivery of the extracts. In the same study, *in vitro* P-selectin inhibitory activity, anticoagulant activity, tubulogenesis and carcinoma adhesion activities were found to vary between species (Cumashi et al., 2007).

The degree of sulfation (and thus the charge density) of fucoidan, was found to have an effect on the pro- and anticoagulant activities of fucoidan extracted from *Fucus vesiculosus*, with a higher degree of sulfation leading to higher activities in both properties. Molecular size was also found to affect the pro- and anticoagulant activities, with larger molecular weight fractions demonstrating greater activities akin to those of unfractionated fucoidan (Zhang and Till, 2014). Such variation in biological activity due to molecular weight has also been reported in liver fibrosis, anti-tumor and immune modulation models (Nakazo et al., 2010; Maruyama et al., 2005, 2003; Shimizu et al., 2005).

The biological activity of fucoidan extracts has been reported by numerous *in vitro* studies; however, as discussed in section 2.5 (above), the resulting low plasma concentration of fucoidan from the ingestion of the dose prescribed in this assessment is highly unlikely to result in any significant effects that preclude the safety of the extracts.

Fucoidan is a soluble fiber that is thought to be unchanged by fermentation with human gut microbiota (Michel et al., 1996). Fucoidan may have effects similar to other soluble fibers, such as oat glucans. These would not be expected to greatly alter gut microorganisms.

2.7. Safety of Other Components

The compositional analysis of fucoidan derived from *U. pinnatifida* (Table 4) suggest that in addition to fucoidan, the final product contains alginate (2.0-6.5%), polyphloroglucinol (0.5-3.0%), mannitol (1-15%), natural salts (0.5-1.0%) and other carbohydrates (0.5-2.0%). As described earlier, the unique extraction process (use of water as extraction solvent) employed by Marinova ensures that the chemical constituent of the fucoidan molecule remains unaltered and equivalent as in their natural state. This process also ensures that no other products are formed during the processing. The product constituents such as alginate, polyphloroglucinol, mannitol, and other carbohydrates are naturally present in kelp that has a safe history of human consumption.

000040

Alginates or salts of alginic acid are natural polyuronide constituents of certain brown algae. The FDA has affirmed alginates such as sodium alginate, potassium alginate, calcium alginate and ammonium alginate as GRAS. Sodium alginate is regulated by the FDA under 21 CFR 184.1724 as a texturizer, formulation aid, stabilizer, thickener, firming agent, flavor adjuvant, emulsifier, flavor enhancer, surface active agent. As compared to the permitted use levels of sodium alginate and other alginates, the resulting use (1.95 mg/serving) or intake of alginate (16.25 mg/person/day) from the proposed uses of fucoidan is very small and is considered as safe.

Another constituent of fucoidan, mannitol, is allowed as a food additive for use as food, or in contact with food on an interim basis pending additional study. The FDA has reviewed the safety of the uses of mannitol in food and concluded that certain uses of mannitol are safe as codified under 21 CFR 180.25. In recent actions, FDA has amended the regulation at 21 CFR 180.25 to provide for additional methods of manufacture of mannitol. While it is not clear if the FDA considered any additional uses of mannitol at that time, it appears that the FDA continued to accept the safety assessment that less than 20 g/person/day is safe. The resulting maximum intake of mannitol (0.037 g/person/day) from the proposed uses of fucoidan is very small and is considered as safe. Similarly, the intake of other constituents of fucoidan, such as polyphloroglucinol (phenolics, phlorotannins), natural slats and other carbohydrates, from the proposed use is very small and is considered as safe.

3. Common Knowledge Elements for a GRAS Determination

The first common knowledge element for a GRAS determination is that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing information that is present in public domain and studies published in scientific journals. Several of the studies, particularly animal and human clinical studies reviewed for this safety assessment have been published in peer reviewed scientific journals as reported in Table 8 and in Section 2.1 and 2.2. FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called “common knowledge element,” in terms of the two following elements:⁵ (A) Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and (B) There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as the National Academy of Sciences. To be sure, the Expert Panel of the present GRAS assessment recognizes that the safety of fucoidan derived from *Undaria pinnatifida* is supported by its presence in the human diet, particularly in Japan and other East Asian countries. Additionally, many scientific studies have been conducted and published.

⁵62 FR 18938 (17 April 1997) which is accessible at <http://www.gpo.gov/fdsys/pkg/FR-1997-04-17/html/97-97-9706.htm>.

000041

4. RISK ASSESSMENT

There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to determine safety-in-use of fucoidan derived from *Undaria pinnatifida* (wakame) as a food ingredient in conventional foods. The intended use of fucoidan by Marinova will result in an estimated daily 90th percentile intake of 250 mg fucoidan/person/day (4.17 mg/kg bw/day). The available scientific evidence suggests that fucoidan will be as safe as the seaweeds from which it is derived. There is common knowledge of a significant history of human consumption of seaweeds, including that from *U. pinnatifida*, as a staple item of diet. The available information suggest that daily intake of seaweed can range from 4.3 to 14.3 g/person/day, while that of fucoidan can range from 0.54 to 1.79 g/person/day. This background exposure information suggests that intake of fucoidan from its proposed uses is likely to be safe.

In addition to the background exposure, several scientific studies, particularly on fucoidan derived from *U. pinnatifida*, further supports the safety. Following oral consumption, small quantities of orally administered fucoidan may cross the intestinal wall as whole molecules probably by the process of endocytosis. In a dose-response 4 week toxicity study in rats, administration of fucoidan derived from *U. pinnatifida* at dose levels up to 1350 mg/kg bw/day did not reveal any adverse effects, including any anticoagulant activity, reducing concern about adverse effects related to excess bleeding. Additional safety related findings from animal, human and genotoxicity studies further support the safety of fucoidan derived from *U. pinnatifida*.

Fucoidan is known for its anticoagulant activity in *in vitro* studies. In the special case of haemophilic blood, fucoidan may act as a procoagulant, by promoting the extrinsic clotting pathway *in vitro* (Zhang et al., 2014). In a normal situation, oral intake of fucoidan does not lead to appreciable effects on global clotting in humans. In clinical studies using fucoidan, there have been no reports of adverse effects on clotting, even at high levels of intake. Animal toxicity studies also demonstrate very little effect of high dosage on clotting parameters. Clotting parameters were changed at 900 mg/kg oral *L. japonica* fucoidan in a rat model (Li et al., 2005) (but not at 300 mg/kg). In a short-term rat study, fucoidan derived from *U. pinnatifida*, at a dose level of 1350 mg/kg/day for 28 days did not cause any changes in clotting parameters (Kim et al., 2010b). In the NDIN (FMC, 2012) that has been accepted and filed by FDA (2013), anti-coagulation effects of fucoidans have been extensively described and assessed. The notifier concluded that at a dose of 200-300 mg/day, fucoidan dose would be anticipated to be safe.

The safety of Maritech® fucoidan derived from *U. pinnatifida* is supported by:

- The long history of safe dietary exposure to seaweeds, including wakame (*U. pinnatifida*), going back thousands of years.
- The absence of toxic effects in *in vitro* and *in vivo* toxicity studies at significant multiples of anticipated human exposure.
- Lack of adverse effects in human studies.

The safety assessment of Maritech® fucoidan derived from *U. pinnatifida* is based on the totality of available evidence, including background exposure and experimental studies (human, animal and genotoxicity). A variety of experimental studies with animals and human clinical trials and comparison with data from other studies in which fucoidan derived from other sources is used further corroborate the safety. In a 4-week rat study, fucoidan derived from *U. pinnatifida* had no adverse effects at dose levels up to 1350 mg/kg bw/day, the highest dose tested.

000042

Compared to the safe dose in the animal study, the estimated daily intake of fucoidan from the intended uses of the extract at the 90th percentile of 250 mg/person (4.17 mg/kg bw/day) is over 300-fold lower. The estimated daily intake, if ingested daily over a lifetime, is considered safe.

5. SUMMARY

Marinova has developed a process to manufacture standardized fucoidan derived from *U. pinnatifida*. It is produced without the use of solvents other than water and its production occurs in accordance with standard operating procedures, using starting materials and processing materials that meet appropriate food grade specifications. The final Maritech® product derived from *U. pinnatifida* contains $\geq 75\%$ fucoidan. Other components in this product include: alginates 2.0-6.5%, polyphloroglucinol 0.5-15.0%, and mannitol 1-10%. The iodine content of fucoidan is typically less than 50 ppm and is over 30-fold lower than that reported in kelp.

Marinova intends to use Maritech® fucoidan as a food ingredient in baked goods, soups, snack foods, imitation dairy products, and seasonings & flavors at use levels up to 30 mg fucoidan *per* serving. The intended use of fucoidan in these food categories will result in an estimated daily intake for “users only” at the 90th percentile of approximately 250 mg/person (4.17 mg/kg body weight/day). Such exposure is considered safe based on the following elements:

- Seaweeds such as wakame, the source material of fucoidan, has a very long history of safe use in humans and animals, and is recommended as part of a healthy human diet in Japan.
- In *in vitro* and *in vivo* studies show that fucoidan is not genotoxic.
- No adverse effects of fucoidan in rats were reported in a 4 week toxicity experiment at levels up to 1350 mg/kg bw/day.
- Fucoidan (derived from another species) was well tolerated by human volunteers at doses up to 300 mg/day.

On the basis of scientific procedures⁶ and history of exposure from natural sources, the consumption of Maritech® fucoidan, derived from *U. pinnatifida*, as an added food ingredient is considered safe at levels up to 250 mg/day. The intended uses are compatible with current regulations, *i.e.*, fucoidan will be used in baked goods, soups, snack foods, imitation dairy products, and seasonings & flavors at use levels up to 30 mg fucoidan *per* serving and it is produced according to current good manufacturing practices (cGMP).

⁶ 21 CFR §170.3 Definitions. (h) Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

6. CONCLUSION

Based on a critical evaluation of the publicly available data summarized herein, the Expert Panel members whose signatures appear below, have individually and collectively concluded that consumption of fucoidan, derived from *Undaria pinnatifida*, as a food ingredient in selected food products (baked goods, soups, snack foods; imitation dairy products; and seasonings & flavors) at levels of up to 30 mg/serving (reference amounts customarily consumed, 21 CFR 101.12) when not otherwise precluded by a Standard of Identity as described in this dossier and resulting in the 90th percentile estimated intake of up to 250 mg/person/day (4.17 mg/kg body weight/day for an individual weighing 60 kg) is safe and GRAS.

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that fucoidan derived from *U. pinnatifida*, when used as described, is GRAS based on scientific procedures.

Signatures

(b) (6)



Robert L. Martin, Ph.D.

Dec. 13, 2014
Date

(b) (6)



John A. Thomas, Ph.D., F.A.T.S., D.A.T.S.

Dec. 15, 2014
Date

(b) (6)



Madhusudan G. Soni, Ph.D., F.A.C.N., F.A.T.S.

Dec. 19, 2014
Date

000044

7. REFERENCES

- Abe, S., Hiramatsu, K., Ichikawa, O., Kawamoto, H., Kasagi, T., Miki, Y., Kimura, T., Ikeda, T., 2013. Safety evaluation of excessive ingestion of mozuku fucoidan in human. *J. Food Sci.* 78(4):T648-651.
- Ale, M.T., Mikkelsen, J.D., Meyer, A.S., 2011. Important determinants for fucoidan bioactivity: a critical review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. *Marine Drugs* 9(10):2106-2130.
- Araya, N., Takahashi, K., Sato, T., Nakamura, T., Sawa, C., Hasegawa, D., Ando, H., Aratani, S., Yagishita, N., Fujii, R., Oka, H., Nishioka, K., Nakajima, T., Mori, N., Yamano, Y., 2011. Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. *Antivir. Ther.* 16(1):89-98.
- Berteau, O., Mulloy, B., 2003. Sulfated fucans, fresh perspectives: Structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 13:29-40.
- Chandia, N. P., Matsuhiro, B., 2008. Characterization of a fucoidan from *Lessonia vadosa* (Phaeophyta) and its anticoagulant and elicitor properties. *Inter. J. Biol. Macromolecules* 42: 235-240.
- Choi, J.I., Raghavendran, H.R., Sung, N.Y., Kim, J.H., Chun, B.S., Ahn, D.H., Choi, H.S., Kang, K.W., Lee, J.W., 2010. Effect of fucoidan on aspirin-induced stomach ulceration in rats. *Chem Biol Interact.* 183(1):249-254.
- Chung, H.J., Jeun, J., Houg, S.J., Jun, H.J., Kweon, D.K., 2010. Toxicological evaluation of fucoidan from *Undaria pinnatifida* in vitro and in vivo. *Phytother. Res* 24:1078-1083.
- Colliec, S., Fischer, A. M., Tapon-Brethaudiere, J., Boisson, C., Durand, P., Jozefonvicz, J., 1991. Anticoagulant properties of a fucoidan fraction. *Thrombosis Research* 64:143-154.
- Cumashi, A., Ushakova, N.A., Preobrazhenskaya, M.E., D'Incecco, A., Piccoli, A., Totani, L., Tinari, N., Morozevich, G.E., Berman, A.E., Bilan, M.I., et al., 2007. A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. *Glycobiology* 17:541-552.
- DiNovi, M.J., Kuznesof, P.M., 1995. Estimating Exposure To Direct Food Additives And Chemical Contaminants in the Diet. Available at <http://www.cfsan.fda.gov/~dms/opa-cg8.html>
- DSHEA, 1994. Dietary Supplements Health and Education Act of 1994. US Food and Drug Administration, Center for Food Safety and Applied Nutrition, Washington, DC.

000045

FAO, 2003. A guide to the seaweed industry. FAO Fisheries Technical Paper, 441. Chapter 8. Seaweeds Used as Human Food. pp 73-89.

FDA, 2006. Food and Drug Administration. *Estimating Dietary Intake of Substances in Food*. Guidance document released August 2006. Document available at: <http://www.fda.gov/food/guidancecomplianceregulatoryinformation/guidancedocuments/foodingredientsandpackaging/ucm074725.htm>

FDA, 2013. Food and Drug Administration. 75-Day Premarket Notification of New Dietary Ingredients. *Laminaria hyperborea* extract. FMC BioPolymer Corporation. FDA docket number FDA-2013-S-0023.

Fitton, H.J., 2011. Therapies from Fucoidan; Multifunctional Marine Polymers. Mar. Drugs 9:1731-1760.

FMC, 2012. 75-Day Premarket Notification of New Dietary Ingredients. *Laminaria hyperborea* extract. FMC BioPolymer Corporation. pp 1-37.

Fujiwara-Arasaki, T., Mino, N., Kuroda, M., 1984. The protein value in human nutrition of edible marine algae in Japan. Hydrobiologia 116/117: 513-516.

Fukuda, S., Saito, H., Nakaji, S., Yamada, M., Ebine, N., Tsushima, E., Oka, E., Kumeta, K., Tsukamoto, T., Tokunaga, S., 2007. Pattern of dietary fiber intake among the Japanese general population. Eur. J. Clin. Nutr. 61(1):99-103.

Gideon, T.P., Rengasamy, R., 2008. Toxicological evaluation of fucoidan from *Cladosiphon okamuranus*. J. Med. Food 11:638-642.

Guiry, M.D., 2013. Seaweed as Human Food. The Seaweed Site: information on Marine Algae. Available at: http://www.seaweed.ie/uses_general/humanfood.php

Ikeguchi, M., Yamamoto, M., Arai, Y., Maeta, Y., Ashida, K., Katano, K., Miki, Y., Kimura, T., 2011. Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer. Oncol. Lett. 2(2):319-322.

Irhimeh, M.R., Fitton, J.H., Lowenthal, R.M., 2007. Fucoidan ingestion increases the expression of CXCR4 on human CD34+ cells. Exp. Hematol. 35(6):989-994.

Irhimeh, M.R., Fitton, J.H., Lowenthal, R.M., 2009. Pilot clinical study to evaluate the anticoagulant activity of fucoidan. Blood Coagul. Fibrinolysis 20(7):607-610.

Irhimeh, M.R., Fitton, J.H., Lowenthal, R.M., Kongtawelert, P., 2005. A quantitative method to detect fucoidan in human plasma using a novel antibody. Methods Find Exp. Clin. Pharmacol. 27:705-710.

000046

- Juffrie, M., Rosalina, I., Damayanti, W., Djumhana, A., Ahmad, A.H., 2006. The efficacy of fucoidan on gastric ulcer. *Indonesian J. Biotechnol.* 11(2):908-913.
- Kim, K.J., Lee, O.H., Lee, B.Y., 2010a. Genotoxicity studies on fucoidan from Sporophyll of *Undaria pinnatifida*. *Food Chem. Toxicol.* 48: 1101-1104.
- Kim, K.J., Lee, O.H., Lee, H.H., Lee, B.Y., 2010b. A 4-week repeated oral dose toxicity study of fucoidan from the Sporophyll of *Undaria pinnatifida* in Sprague-Dawley rats. *Toxicology* 267:154-158.
- Kim, W.J., Kim, S.M., Kim, H.G., Oh, H.R., Lee, K.B., Lee, Y.K., Park, H.I., 2007. Purification and anticoagulant activity of a fucoidan from Korean *Undaria pinnatifida* Sporophyll. *Algae*, 22:247-252.
- Kiple, K.F., Ornelas, K.C., 2000. *The Cambridge World History of Food*. Cambridge University Press. Chapter II. Important Vegetable Supplements. pp 232-249.
- Kylin, H., Biochemistry of sea algae. *H. Z. Physiol. Chem.* 83:171-197.
- Leite-Silva, C., Gusmao, C.L.S., Takahashi, C.S., 2007. Genotoxic and antigenotoxic effects of *Fucus vesiculosus* extract on cultured human lymphocytes using the chromosome aberration and Comet assays. *Genet. Mol. Biol.* 30(1): 105-111.
- Li, B., Lu, F., Wei, X., Zhao, R., 2008a. Fucoidan: Structure and Bioactivity. *Molecules* 13:1671-1695.
- Li, B., Rui, X. Z., Xin, J. W., 2008b. Anticoagulant activity of fucoidan from *Hizikia fusiforme*. *Agro Food Industry Hi-Tech* 19:22-24.
- Li, N., Zhang, Q., Song, J., 2005. Toxicological evaluation of fucoidan extracted from *Laminaria japonica* in Wistar rats. *Food Chem. Toxicol.* 43:421-426.
- Marinova, 2013. Information on general description, specifications, composition and manufacturing of fucoidan derived from *Undaria pinnatifida* and *Fucus vesiculosus* provided for this GRAS assessment.
- Maruyama, H., Tamauchi, H., Hashimoto, M., Nakano, T., 2003. Antitumor activity and immune response of Mekabu fucoidan extracted from sporophyll of *Undaria pinnatifida*. *In Vivo* 17:245-249.
- Maruyama, H., Tamauchi, H., Hashimoto, M., Nakano, T., 2005. Suppression of Th2 immune responses by mekabu fucoidan from *Undaria pinnatifida* sporophylls. *Int. Arch. Allergy Immunol.* 137(4):289-294.

000047

Michel, C., Lahaye, M., Bonnet, C., Mabeau, S., Barry, J.-L., 1996. *In vitro* fermentation by human faecal bacteria of total and purified dietary fibres from brown seaweeds. *Br. J. Nutr.* 75:263-280

Mori, N., Nakasone, K., Tomimori, K., Ishikawa, C., 2012. Beneficial effects of fucoidan in patients with chronic hepatitis C virus infection. *World J. Gastroenterol.* 18(18):2225-2230.

MRCA, 1965. Market Research Corporation of America (MRCA), in conjunction with the "Food intake and nutritive value of the diets of men, women and children in United States, Spring 1965". A Preliminary Report by the Consumer and Food Economics Research Division, Agricultural Research Division. United States Department of Agriculture, Washington, DC.

Mussig, K., Thamer, C., Bares, R., Lipp, H.P., Haring, H.U., Gallwitz, B., 2006. Iodine-induced thyrotoxicosis after ingestion of kelp-containing tea. *J. Gen. Intern. Med.* 21(6):C11-14.

Myers, S.P., Brooks, L., Rolfe, M., 2012. A randomized placebo-controlled clinical trial on a Marinova seaweed extract on osteoarthritis. Final report. Southern Cross University. pp 1-56 (complete study report provided by Marinova; the study is also accepted for publication; see Myers et al., 2014).

Myers, S.P., Mulder, A.M., Baker, D., Robinson, S., Brooks, L., Fitton, J.H., 2014. A randomized placebo controlled trial using *Fucus vesiculosus* extract. *Nutrients* 5: xxx-xxx (In Press).

Myers, S.P., O'Connor, J., Fitton, J.H., Brooks, L.O., Rolfe, M.I., Connellan, P.A., Wohlmuth, H., Cheras, P.A., Morris, C.A., 2010. A combined phase I and II open label study on the effects of a seaweed extract nutrient complex on osteoarthritis. *Biologics: Targets and Therapy* 4:33-44.

Myers, S.P., O'Connor, J., Fitton, J.H., Brooks, L.O., Rolfe, M.I., Connellan, P.A., Wohlmuth, H., Cheras, P.A., Morris, C.A., 2011. A combined Phase I and II open-label study on the immunomodulatory effects of seaweed extract nutrient complex. *Biologics* 5:45-60.

Nakazato, K., Takada, H., Iha, M., Nagamine, T., 2010. Attenuation of N-nitrosodiethylamine-induced liver fibrosis by high-molecular-weight fucoidan derived from *Cladosiphon okamuranus*. *J. Gastroenterol. Hepatol.* 25:1692-1701.

Nishino, T., Yokohama, G., Dobahi, K., 1989. Isolation, purification and characterization of fucose-containing sulfated polysaccharides from the brown seaweed *Ecklonia kurome* and their blood-anticoagulant activities. *Carb. Res.* 186:119-129.

Prasad, S., Lillicrap, D., Labelle, A., Knappe, S., Keller, T., Burnett, E., Powell, S., Johnson, K.W., 2008. Efficacy and safety of a new-class hemostatic drug candidate, AV513, in dogs with hemophilia A. *Blood* 111:672-679.

Ren, R., Yoshida, M., Mizuno, M., Nishitani, Y., Ojima, T., Azuma, T., Azuma, Y., Hashimoto, T., Kanazawa, K., 2013. Modulation of platelet aggregation-related eicosanoid production by

000048

dietary F-fucoidan from brown alga *Laminaria japonica* in human subjects. *Br. J. Nutr.* 110(5):880-980.

Ruperez, P., Ahrazem, O., Leal, J.A., 2002. Potential antioxidant capacity of sulfated polysaccharides from the edible marine brown seaweed *Fucus vesiculosus*. *J. Agric. Food Chem.* 50:840-845.

SCOGS, 1973. Evaluation of the health aspects of certain red and brown algae as food ingredients. Federation of American Societies for Experimental Biology, Bethesda, MD, pp. 1 - 13. NTIS PB265505.

Seaweed Industry Association, 2013. Information on *Undaria pinnatifida*; *Fucus vesiculosus*. Available at: <https://seaweedindustry.com/about>

Senthilkumar, K., Manivasagan, P., Venkatesan, J., Kim, S.K., 2013. Brown seaweed fucoidan: biological activity and apoptosis, growth signaling mechanism in cancer. *Int. J. Biol. Macromol.* 60:366-374.

Shimizu, J., Wada-Funada, U., Mano, H., Matahira, Y., Kawaguchi, M., Wada, M., 2005. Proportion of murine cytotoxic T-cell is increased by high-molecular weight fucoidan extracted from Okinawa Mozuku (*Cladosiphon okamuranus*). *J. Health Sci.* 51:394-397.

Skibola, C.F., 2004. The effect of *Fucus vesiculosus*, an edible brown seaweed, upon menstrual cycle length and hormonal status in three pre-menopausal women: a case report. *BMC Complement. Altern. Med.* 4:10 (1-8).

Smiciklas-Wright, H., Mitchell, D.C., Mickle, S.J., Cook, A.J., Goldman, J.D., 2002. Foods Commonly Eaten in the United States: Quantities Consumed Per Eating Occasion and in a Day, 1994-1996. U.S. Department of Agriculture NFS Report No. 96-5, 252 pp. Available at: www.barc.usda.gov/bhnrc/foodsurvey/Products9496.html

Song, M.Y., Ku, S.K., Han, J.S., 2012. Genotoxicity testing of low molecular weight fucoidan from brown seaweeds. *Food Chem. Toxicol.* 50(3-4):790-796.

Teas, J., 1981. The consumption of seaweed as a protective factor in the etiology of breast cancer. *Med. Hypotheses* 7:601-613.

Teas, J., Baldeon, M.E., Chiriboga, D.E., Davis, J.R., Sarries, A.J., Braverman, L.E., 2009. Could dietary seaweed reverse the metabolic syndrome? *Asia Pac. J. Clin. Nutr.* 18(2):145-54.

Tokita, Y., Nakajima, K., Mochida, H., Iha, M., Nagamine, T., 2010. Development of a fucoidan-specific antibody and measurement of fucoidan in serum and urine by sandwich ELISA. *Biosci. Biotechnol. Biochem.* 74:350-357.

Toyokawa, H., 1978. Nutritional status in Japan from view point of numerical ecology. *Social Science Medicine* 12:517-524.

000049

Udani, J., Hesslink, R., 2012. The potential use of fucoidans from brown seaweed as a dietary supplement. *J. Nutr. Food Sci.* 2:171 (pp 1-6).

Zaragoza, M.C., Lopez, D. P., Saiz, M., Poquet, M., Perez, J., Puig-Parellada, P., Marmol, F., Simonetti, P., Gardana, C., Lerat, Y., Burtin, P., Inisan, C., Rousseau, I., Besnard, M., Mitjavila, M.T., 2008. Toxicity and antioxidant activity *in vitro* and *in vivo* of two *Fucus vesiculosus* extracts. *J. Agric. Food Chem.* 56(17):7773-7780.

Zhang, Z., Till, S., Jiang, C., Knappe, S., Reutterer, S., Scheiflinger, F., Szabo, C.M., Dockal, M., 2014. Structure-activity relationship of the pro- and anticoagulant effects of *Fucus vesiculosus* fucoidan. *Thromb. Haemost.* 111(3):429-437.

Zhang, Z., Till, S., 2014. Structure-activity relationship of the pro- and anticoagulant effects of *Fucus vesiculosus* fucoidan. *Thrombosis Haemostasis* 111(3):429-437.

000050

8. APPENDIX I

Analytical data from five non-consecutive lots of fucoïdan derived from *Undaria pinnatifida*

000051

Certificate of Analysis

75% GFS *Undaria* Fucoidan

Batch number: GFS2013521
Botanical name: *Undaria pinnatifida*
Fresh/dry: Dry
Manufactured: Australia

Common name: Mekabu
Extract solvent: 100% water
Extraction Date: June 2013
Expiry Date: June 2018

Storage conditions: Store in well sealed containers in a cool position. Protect from light, moisture and heat.

Test	Specification	Method	Result
Appearance:	Off white to brown powder	Visual	Off-white powder
Odour and taste:	Bland odour and taste	Organoleptic	Complies
Moisture:	<10%	USP	6.81%
pH:	4.0 - 7.0 (1% suspension at 25°C)	pH meter	5.38
Particle size:	≥80% less than 300 microns	USP	95%
Heavy metals:			
Lead	<3 ppm	ICP	0.5 ppm
Cadmium	<3 ppm	ICP	2.2 ppm
Mercury	<0.1 ppm	ICP	0.057 ppm
Arsenic (inorganic)	<2 ppm	ICP	0.2 ppm
Microbiology:			
Total aerobic microbial count	<1,000 CFU/g	AOAC	Complies
Yeast and mould count	<100 CFU/g	AOAC	Complies
Total enterobacteria count	Absent /g	AOAC	Complies
<i>Eschericia coli</i>	Absent /g	AOAC	Complies
<i>Salmonella species</i> ¹	Absent /10g	USP	Complies
<i>Staphylococcus aureus</i>	Absent /g	AOAC	Complies
Pesticide residues ¹ :	Complies with USP	USP	Complies
Phytonutrients ² :			
Fucoidan	≥ 75%	Marinova C05	83.5%

Notes:

1. Tested annually
2. Methods available for review

Quality Approval:

Date:

Dr Sam Karpiniec MRACI CChem
Senior Chemist

Release Approval:

Date:

Dr Damien Stringer MRACI CChem
Operations Manager

Issued: 23 Aug. 2013



249 Kennedy Drive • Cambridge • Tasmania 7170 • Australia
phone +61 3 6248 5800 • fax +61 3 6248 4062 • info@marinova.com.au • www.marinova.com.au

000052

Certificate of Analysis

75% GFS *Undaria fucoidan*

Batch number: GFS2013508
Botanical name: *Undaria pinnatifida*
Fresh/dry: Dry
Manufactured: Australia

Common name: Mekabu
Extract solvent: 100% water
Extraction Date: March 2013
Expiry Date: March 2018

Storage conditions: Store in well sealed containers in a cool position. Protect from light, moisture and heat.

Test	Specification	Method	Result
Appearance:	Off white to brown powder	Visual	Off white powder
Odour and taste:	Bland odour and taste	Organoleptic	Complies
Moisture:	<10%	USP	6.22
pH:	4.0 - 7.0 (1% suspension at 25°C)	pH meter	5.48
Particle size:	≥80% less than 300 microns	USP	85%
Heavy metals:			
Lead	<3 ppm	ICP	0.2 ppm
Cadmium	<3 ppm	ICP	2.6 ppm
Mercury	<0.1 ppm	ICP	< 0.01 ppm
Arsenic (inorganic)	<2 ppm	ICP	0.69 ppm
Microbiology:			
Total aerobic microbial count	<1,000 CFU/g	AOAC	Complies
Yeast and mould count	<100 CFU/g	AOAC	Complies
Total enterobacteria count	Absent /g	AOAC	Complies
<i>Eschericia coli</i>	Absent /g	AOAC	Complies
<i>Salmonella species</i> ¹	Absent /10g	USP	Complies
<i>Staphylococcus aureus</i>	Absent /g	AOAC	Complies
Pesticide residues ¹ :	Complies with USP	USP	Complies
Phytonutrients ² :			
Fucoidan	≥ 75%	Marinova C05	75.0

Notes:

1. Tested annually
2. Methods available for review

Quality Approval:

Date:

Dr Sam Karpiniec MRACI
R&D Chemist

Release Approval:

Date:

Dr Damien Stringer MRACI CChem
Product Development Manager

Issued: 11 Apr. 2013



249 Kennedy Drive • Cambridge • Tasmania 7170 • Australia
phone +61 3 6248 5800 • fax +61 3 6248 4062 • info@marinova.com.au • www.marinova.com.au

000053

Certificate of Analysis

75% GFS *Undaria fucoidan*

Batch number: GFS2013510
Botanical name: *Undaria pinnatifida*
Fresh/dry: Dry
Manufactured: Australia

Common name: Mekabu
Extract solvent: 100% water
Extraction Date: March 2013
Expiry Date: March 2018

Storage conditions: Store in well sealed containers in a cool position. Protect from light, moisture and heat.

Test	Specification	Method	Result
Appearance:	Off white to brown powder	Visual	Off white powder
Odour and taste:	Bland odour and taste	Organoleptic	Complies
Moisture:	<10%	USP	6.62
pH:	4.0 - 7.0 (1% suspension at 25°C)	pH meter	5.62
Particle size:	≥80% less than 300 microns	USP	96%
Heavy metals:			
Lead	<3 ppm	ICP	0.21 ppm
Cadmium	<3 ppm	ICP	2.3 ppm
Mercury	<0.1 ppm	ICP	< 0.01 ppm
Arsenic (inorganic)	<2 ppm	ICP	0.26 ppm
Microbiology:			
Total aerobic microbial count	<1,000 CFU/g	AOAC	Complies
Yeast and mould count	<100 CFU/g	AOAC	Complies
Total enterobacteria count	Absent /g	AOAC	Complies
<i>Escherichia coli</i>	Absent /g	AOAC	Complies
<i>Salmonella species</i> ¹	Absent /10g	USP	Complies
<i>Staphylococcus aureus</i>	Absent /g	AOAC	Complies
Pesticide residues ¹ :	Complies with USP	USP	Complies
Phytonutrients ² :			
Fucoidan	≥ 75%	Marinova C05	84.6

Notes:

1. Tested annually
2. Methods available for review

Quality Approval:

Date:

Dr Sam Karpiniec MRACI CChem
R&D Chemist

Release Approval:

Date:

Dr Damien Stringer MRACI CChem
Product Development Manager

Issued: 05 Jul. 2013



249 Kennedy Drive • Cambridge • Tasmania 7170 • Australia
phone +61 3 6248 5800 • fax +61 3 6248 4062 • info@marinova.com.au • www.marinova.com.au

000054

Certificate of Analysis

75% GFS *Undaria* Fucoidan

Batch number: GFS2013514
Botanical name: *Undaria pinnatifida*
Fresh/dry: Dry
Manufactured: Australia

Common name: Mekabu
Extract solvent: 100% water
Extraction Date: May 2013
Expiry Date: May 2018

Storage conditions: Store in well sealed containers in a cool position. Protect from light, moisture and heat.

Test	Specification	Method	Result
Appearance:	Off white to brown powder	Visual	Off white powder
Odour and taste:	Bland odour and taste	Organoleptic	Complies
Moisture:	<10%	USP	6.40%
pH:	4.0 - 7.0 (1% suspension at 25°C)	pH meter	5.41
Particle size:	≥80% less than 300 microns	USP	99%
Heavy metals:			
Lead	<3 ppm	ICP	0.2 ppm
Cadmium	<3 ppm	ICP	2.7 ppm
Mercury	<0.1 ppm	ICP	0.015 ppm
Arsenic (inorganic)	<2 ppm	ICP	0.38 ppm
Microbiology:			
Total aerobic microbial count	<1,000 CFU/g	AOAC	Complies
Yeast and mould count	<100 CFU/g	AOAC	Complies
Total enterobacteria count	Absent /g	AOAC	Complies
<i>Escherichia coli</i>	Absent /g	AOAC	Complies
<i>Salmonella species</i> ¹	Absent /10g	USP	Complies
<i>Staphylococcus aureus</i>	Absent /g	AOAC	Complies
Pesticide residues ¹ :	Complies with USP	USP	Complies
Phytonutrients ² :			
Fucoidan	≥ 75%	Marinova C05	77.9%

Notes:

1. Tested annually
2. Methods available for review

Quality Approval:

Date:

Dr Sam Karpinić MRACI CChem
Senior Chemist

Release Approval:

Date:

Dr Damien Stringer MRACI CChem
Operations Manager

Issued: 08 Aug. 2013



249 Kennedy Drive • Cambridge • Tasmania 7170 • Australia
phone +61 3 6248 5800 • fax +61 3 6248 4062 • info@marinova.com.au • www.marinova.com.au

000055

Certificate of Analysis

75% GFS *Undaria* Fucoidan

Batch number: GFS2013523
Botanical name: *Undaria pinnatifida*
Fresh/dry: Dry
Manufactured: Australia

Common name: Mekabu
Extract solvent: 100% water
Extraction Date: August 2013
Expiry Date: August 2018

Storage conditions: Store in well sealed containers in a cool position. Protect from light, moisture and heat.

Test	Specification	Method	Result
Appearance:	Off white to brown powder	Visual	Off-white powder
Odour and taste:	Bland odour and taste	Organoleptic	Complies
Moisture:	<10%	USP	6.30%
pH:	4.0 - 7.0 (1% suspension at 25°C)	pH meter	5.58
Particle size:	≥80% less than 300 microns	USP	96%
Heavy metals:			
Lead	<3 ppm	ICP	0.36 ppm
Cadmium	<3 ppm	ICP	2.4 ppm
Mercury	<0.1 ppm	ICP	0.020 ppm
Arsenic (inorganic)	<2 ppm	ICP	0.5 ppm
Microbiology:			
Total aerobic microbial count	<1,000 CFU/g	AOAC	Complies
Yeast and mould count	<100 CFU/g	AOAC	Complies
Total enterobacteria count	Absent /g	AOAC	Complies
<i>Eschericia coli</i>	Absent /g	AOAC	Complies
<i>Salmonella species</i> ¹	Absent /10g	USP	Complies
<i>Staphylococcus aureus</i>	Absent /g	AOAC	Complies
Pesticide residues ¹ :	Complies with USP	USP	Complies
Phytonutrients ² :			
Fucoidan	≥ 75%	Marinova C05	76.5%

Notes:

1. Tested annually
2. Methods available for review

Quality Approval:

Date:

Dr Sam Karpiniec MRACI CChem
Senior Chemist

Release Approval:

Date:

Dr Damien Stringer MRACI CChem
Operations Manager

Issued: 30 Sep. 2013



249 Kennedy Drive • Cambridge • Tasmania 7170 • Australia
phone +61 3 6248 5800 • fax +61 3 6248 4062 • info@marinova.com.au • www.marinova.com.au

000056

SUBMISSION END

000057

**Notifier Responses to FDA Questions Received on April 24, 2025
(Supplement to GRN 565 on fucoidan derived from *Undaria pinnatifida*)**

1. Marinova provides a list of the intended uses of fucoidan derived from *Undaria pinnatifida*.
 - a. Please confirm whether the intended use levels are on the basis of fucoidan or on the article of commerce, which is specified to contain 75 to 95% fucoidan.

Notifier Response: Marinova confirms the intended use levels are on the basis of fucoidan.

2. In Appendix C (page 116), there are two footnotes that state 1) “Only the proportion of the food mixture corresponding to the intended food use was included in the analysis,” and 2) “Non-reconstituted amount adjusted to the reconstituted/prepared amount and included in the analysis.” We note that none of the food codes or sections of Appendix C are marked to correspond to the footnote(s).
 - a. Please clarify what information these footnotes apply to.

Notifier Response: Thank you for bringing this to our attention. We have updated Appendix C (please see the revised Appendix C) to reflect the footnotes.

3. Marinova provides specifications with the corresponding methods of analysis in Table 2 (page 13).
 - a. Please provide complete citations for any published or compendial methods used and provide a statement to confirm that all methods, including any internally developed methods, are validated and appropriate for their intended purposes.

Notifier Response: Please see below an updated Table 2 which includes complete citations for any published or compendial methods. Please find attached in Appendix F, a statement from the Quality Assurance Manager confirming all analytical methods, including internally developed methods, are validated and are appropriate for use. Additionally, we have added a footnote to Table 2 confirming that all methods, including any internally developed methods, are validated and appropriate for their intended purposes.

Revised Table 1. Current specifications for Maritech® *Undaria pinnatifida* fucoidan^a

Analytical Parameter	Acceptable Target/Range	Methods of Analysis*
Appearance	Off-white to brown powder	Visual (in-house method)
Moisture	< 10%	USP <731>
pH (1% suspension at 25 °C)	4.0 – 7.0	USP <791>
Particle Size	≥ 80 % less than 300 µm	USP <786>
Heavy Metals¹		
Arsenic (As; inorganic)	< 0.5 ppm	ICP-MS
Cadmium (Cd)	< 3 ppm	USP <233> by ICP-MS
Lead (Pb)	< 1 ppm	USP <233> by ICP-MS
Mercury (Hg)	< 0.5 ppm	USP <233> by ICP-MS
Microbiology^{1,2}		
Total aerobic microbial count	< 10,000 CFU/g	USP <61> ¹ AOAC ²
Total yeast and mold count	< 100 CFU/g	USP <61> ¹ AOAC ²
Total enterobacteria count	Not detected /g	USP <62> ¹ AOAC ²
<i>Escherichia coli</i>	Not detected /g	USP <62> ¹ AOAC ²
<i>Salmonella</i> species	Not detected /10g	USP <62> ¹
<i>Staphylococcus aureus</i>	Not detected /g	USP <62> ¹ AOAC ²
Pesticide Residues¹	Complies with USP	GCMS/LCMSMS
Phytonutrients³		
Fucoidan	75% – 95%	Marinova LP-03

AOAC = Association of Official Analytical Chemists; CFU = colony forming units; ICP-MS = inductively coupled plasma-mass spectrometry; ppm= parts per million; USP = United States Pharmacopeia

^a Based on information provided by Marinova.

¹Tested annually; ² Monitored by random sampling; ³ Method available for review.

* All methods, including any internally developed methods, are validated and appropriate for their intended purposes.

4. Marinova acknowledges that the intended uses evaluated in GRN 000565 included seasonings and flavors and that estimates of dietary exposure provided in GRN 000565 for this use were based on data from the Market Research Corporation of America (MRCA, 1965).
 - a. Please indicate what data or information were used in the current assessment to estimate the dietary exposure to fucoidan derived from *Undaria pinnatifida* from the intended use in this category.

Notifier Response: Because WWEIA/NHANES does not provide seasoning or spice data, it was conservatively assumed that each respondent consumed a daily serving of seasonings/flavors containing fucoidan at 10 mg/serving. This was considered conservative given that mean consumption of seasonings and flavors reported in GRN

565 based on MRCA data was 0.01 g/day, which is below the FDA Reference Amount Customarily Consumed (RACC)¹ of 0.5 g/serving. Therefore, 10 mg fucoidan was added to each person's total background exposure estimate.

5. Marinova indicates that the estimates of dietary exposure provided for the previously notified intended uses and the cumulative dietary exposure include exposure from use in dietary supplements.
 - a. Please describe the intended use in dietary supplements and what data and information were used to estimate the dietary exposure to fucoidan derived from *Undaria pinnatifida* from this use.

Notifier Response: Background exposure estimates of fucoidan included (1) seaweed intake from the diet, (2) existing GRAS uses, and (3) dietary supplement sources. In order to estimate exposure from dietary supplements, the 24-hour dietary supplement use data from NHANES 2017-March 2020 was used. The NHANES Dietary Supplement Database (DSD) files that contain detailed data on individual supplement products, including supplement ingredients and amounts, were reviewed to identify supplements containing fucoidan or seaweed ingredients, or fucoidan-or-seaweed-containing blends. The list of supplement ingredients and blends included in the analysis are provided below in Appendix E.

The two-day average intake of fucoidan from dietary supplement uses by each respondent was added to the intake of fucoidan from GRAS uses and background seaweed intake to estimate the total background intake of fucoidan per person.

6. We note that for the selection of food codes that were included in the dietary exposure assessment, in some cases a limited number of codes are selected. For example, the intended uses in Table 3 (page 16) include “cakes, heavyweight,” “cakes, mediumweight,” and “cakes, lightweight;” however, only two food codes for cakes are included in Appendix C (53101100 Cake, angel food and 53118100 Cake, sponge). We note, for example, that Table 3 includes, as examples, pineapple upside-down cake and cheesecake; however, the corresponding food codes for these examples were not included (e.g., 53119000 - Cake, pineapple, upside down, 53104500 - Cheesecake).
 - a. Please provide any additional information on Marinova's rationale on the selection of appropriate food codes and revise the dietary exposure accordingly to include all uses of fucoidan derived from *Undaria pinnatifida*.

Notifier Response: Thank you for identifying the inconsistency between Table 3 and Appendix C. We have removed the medium and heavy weight cakes from Table 3, as they were not included in the Dietary Intake analysis. Only light weight cakes were included in the analysis, considering the serving size of 55 g for baked goods identified

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-reference-amounts-customarily-consumed-list-products-each-product-category>

in GRN 565. The “Grain-based bars with or without filling or coating” category name has been changed to “Snack bars” for consistency.

Revised Table 2. Current and new proposed food uses and use levels of fucoidan derived from *Undaria pinnatifida*

Main category	Food Uses	Maximum Use Level (mg/serving)	Summary of Food Selection
GRN 565*			
Baked goods (bread, cakes, noodles)	Breads, rolls, bagels, English muffins	30	All breads and rolls; pita bread; cornbread; soft pretzels ; all sizes and flavors of bagels; English muffins.
	Cakes, lightweight		Angel food or sponge cake without icing or filling or other heavy ingredients (e.g., chocolate chips, fruit, nuts, vegetables).
	Pastas and noodles		All plain, dry, and ready-to-eat pastas (e.g., spaghetti, vermicelli, lasagna, macaroni, gnocchi) and noodles (e.g., Mung bean noodles, rice noodles, fried canned chow mein noodles).
	Snack bars		All types of breakfast bars, granola bars, multi-grain bars, trail mix bars, and similar types of products that are made of cereal-grains with or without filling or coating and with or without nuts.
Soups	All varieties	30	All soups (e.g., oriental style soup, tomato soup, chicken, split pea soup).
	Dry soup mixes, bouillon		All types of dry soup mixes, bouillon.
Snack Foods	All varieties	25	Salty snacks such as potato chips, corn chips, tortilla chips, popcorn, pretzels, other starch-based extruded snacks; popped and un-popped popcorns, sweetened and unsweetened, flavored and unflavored, with or without nuts; fruit-based snacks; dehydrated vegetable chips, veggie crisps; and other grain-based snack mixes.
	Crackers that are usually used as snacks		All crackers with the exception of those listed in the "Crackers that are not usually used as snacks; melba toast, hard bread sticks, ice cream cones" product category. This product category includes sweet crackers (e.g., graham or animal crackers), sandwich crackers (e.g., cheese and peanut butter sandwich crackers, and rice cake.
Imitation Dairy Products	Non-dairy cheese, cream cheese, sour cream, frozen desserts, milks, creamers, and yogurt	25	All types of non-dairy based products and dairy product substitutes.
Seasonings & Flavors**	Spices and herbs (other than dietary supplements)	10	All spices and herbs (except those that contain salt) used to flavor food.
<i>New Proposed Uses (Current Amendment)</i>			
Non-Alcoholic Beverages	Sports drinks, regular and diet	30	All sports drinks, including Gatorade, Powerade, etc.; fluid replacement.

* The daily intake calculations in GRN 565 were based on USDA data (CSFII) and mean portion size.

** As CSFII did not report consumption, Market Research Corporation of America data (MRCA, 1965) was used for this category previously in GRN 565. [For the current GRN 565 Supplement, it was conservatively assumed that each survey respondent consumed a daily serving of seasonings/flavors containing fucoidan at 10 mg/serving.](#)

7. The specifications provided for arsenic, cadmium, lead, and mercury in fucoidan derived from *Undaria pinnatifida* are high. We note that specifications help to ensure that the ingredient is being manufactured in accordance with good manufacturing practices, and we would like to remind the manufacturer of FDA’s “Closer to Zero”^[1] initiative that focuses on reducing dietary exposure to lead, arsenic, cadmium, and mercury from food. Further, we request that specifications for heavy metals be as low as possible and consistent with the methods used. We acknowledge that Marinova provided the results of batch analyses (Appendix B) that demonstrate the presence of heavy metals in the notified substance at significant levels, in some cases at levels close to or even exceeding the specified limit (e.g., the level of cadmium in batch GFS2014527 is reported to be 3.3 mg/kg).
 - a. Please provide a discussion of the source of these heavy metals in fucoidan derived from *Undaria pinnatifida* and the estimated dietary exposure to these heavy metals from the intended uses of fucoidan derived from *Undaria pinnatifida*. In addition, please provide a discussion of any mitigation efforts that are in place to reduce the heavy metal content of this ingredient, and the actions taken when batches are found to exceed specifications.

Notifier Response: Marinova acknowledges the FDA’s “Closer to Zero” initiative that focuses on reducing the heavy metals such as inorganic arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) in food. In the case of *Undaria pinnatifida*, the organism naturally absorbs and sequesters heavy metals from its surrounding environment. These heavy metals are present in the water column where *Undaria pinnatifida* is harvested due to natural environmental factors (atmospheric deposition, ocean upwelling and currents, etc.). Cadmium, particularly, is known to be present in high concentrations in the Southern Atlantic Ocean where much of Marinova’s *Undaria pinnatifida* is harvested. The intrinsic ability of seaweeds, including *Undaria pinnatifida*, to sequester metals, specifically cadmium, from the ocean has long been recognized.

To mitigate the risk of prevalence of heavy metal in fucoidan extracted from *Undaria pinnatifida*, Marinova has the following proactive measures in place throughout its supply chain, from site selection to post-harvest handling. These efforts focus on source control, monitoring, and quality assurance:

1. Careful Harvest Site Selection

- Marinova’s contracted licensed divers prioritize harvesting locations in clean, low-industrial-impact coastal waters, away from ports, mining runoff, and urban wastewater outflows which is achieved by conducting survey and harvest site risk assessments prior to harvesting.

^[1] <https://www.fda.gov/food/environmental-contaminants-food/closer-zero-reducing-childhood-exposure-contaminants-foods>

2. Post-Harvest Testing and Segregation

- Marinova applies batch-based heavy metal screening on harvested material prior to processing and rejects any batch that exceeds specific thresholds for inorganic As, Cd, Pb and Hg.

3. Supplier Audits and Certification

- For imported sources of raw material, Marinova engages only with suppliers who can demonstrate compliance with third-party certification, such as organic certification that includes environmental monitoring components and provide traceability records.

4. Processing

- Marinova's processing facility is solely dedicated to organic seaweed processing. The seaweed raw material undergoes an aqueous extraction and ultrafiltration processes that reduces its heavy metal contents. Additionally, organically certified processing aids such as citric acid are utilized for high chelation affinity of As, Cd, Pb and Hg.

5. Quality Control and Product release

- Marinova implements rigorous testing of finished products prior to release and rejects batches exceeding heavy metal limits.

6. Regulatory Alignment and Organic certification

- Marinova aligns its testing limits to strict applicable regulations (e.g. EU regulation and US FDA).
- Marinova's extracts including fucoidan from *Undaria pinnatifida* are organically certified which includes approval of inputs (raw materials and processing aids), environmental monitoring components and provides traceability records.

7. Continuous Improvement

- Marinova is ISO 9001 certified and as part of maintaining its certification, a continuous improvement program is implemented based on trends in test results, customer feedback, and scientific updates.

However, in recognition of the importance of the FDA's "Closer to Zero" initiative, in consideration of the natural growing environment, the organic extraction process, and detailed review of all historic data on inorganic As, Cd, Pb and Hg concentrations in *Undaria pinnatifida* fucoidan extracts, Marinova proposes to lower the inorganic As and Hg specifications further from 1 ppm to 0.5 ppm (refer to Revised Table 2 above for the proposed heavy metal specifications).

The intended use level of fucoidan is up to 30 mg/serving (Table 3 of the submission). Based on the data presented in Table 7 of the submission, the 90th percentile cumulative

estimated daily intake (CEDI) of fucoidan from all background sources and intended uses has been calculated to be 131 mg/day for individuals aged 2 years and older, and 132 mg/day for individuals aged 19 years and older. Using the conservative assumptions associated with 90th percentile intake estimates, no safety concerns have been identified for the heavy metals inorganic arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) in relation to the intended uses of fucoidan. At the cadmium specification limit of 3 ppm (equivalent to 3 µg/g), the theoretical dietary exposure to cadmium from the CEDI of fucoidan at the 90th percentile is conservatively calculated to be approximately 0.4 µg/day for the general population aged 2 years and older.

The FDA has proposed an oral toxicological reference value (TRV) for cadmium ranging from 0.21 to 0.36 µg/kg body weight/day (Schaefer et al., 2023). Applying the upper bound of this range to an average body weight of 60 kg for individuals aged 13 - 18 years yields a cadmium TRV of 21.6 µg/day (60 kg × 0.36 µg/kg bw/day). This value is more than 50-fold (approximately 55-fold) higher than the estimated maximum theoretical cadmium exposure of 0.4 µg/day from all intended uses of fucoidan, indicating a substantial margin of safety and supporting the conclusion that cadmium exposure from fucoidan use does not pose a health risk under the proposed conditions of use.

8. On page 62, you state:

“The current 90th percentile CEDI of fucoidan for the total U.S. population (131 mg/day) is below the maximum safe intake level of 250 mg/day approved by the European Commission ...”

- a. Please briefly provide a narrative describing the publicly available data and information that led to European Commission to conclude that up to 250 mg/day of fucoidan derived from *Undaria pinnatifida* is safe.

Notifier Response: The maximum authorized level of fucoidan extract from the seaweed *Undaria pinnatifida* in foods (250 mg/day) as identified in the Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 is consistent with Opinion No. 9427 of the Superior Health Council (SHC) of Belgium² regarding the substantial equivalence of Marinova’s fucoidan extracted from *Undaria pinnatifida* to the fucoidan present in seaweed which is consumed as food. As part of the substantial equivalence evaluation, the SHC reviewed Marinova’s proposed maximum daily intake of 250 mg/day for fucoidan and publicly available data and information demonstrating that a) background dietary intake of fucoidan from consumption of seaweed is consistent with the estimated intake of fucoidan from Marinova’s intended use, and b) exposure estimates for fucoidan constituents and potential contaminants of toxicological concern (e.g. heavy metals) are below levels of background dietary exposure and below regulatory limits.

² https://food.ec.europa.eu/system/files/2018-06/novel-food_notifications_en.pdf

Importantly, the current 90th percentile CEDI of fucoidan for the total U.S. population (131 mg/day) is sufficiently below the NOAELs for fucoidan determined from published clinical studies and non-clinical toxicology studies (Table 11 of GRN 565 Supplement), that are not associated with any potential concerns around anticoagulation properties. The margin between the CEDI and the EC authorized maximum daily intake level (250 mg/day) provides corroborative evidence of safety.

9. On page 54, you state:

“... orally administered low molecular weight (LMW) fucoidan derived from Laminaria japonica exhibited excellent antithrombotic activity at doses of 400 and 800 mg/kg body weight per day for 30 days in male Wistar rats, suggesting its potential as an oral antithrombotic agent (Zhao et al., 2016).”

Although you indicate that “the subject of this amended GRAS notice, *Undaria pinnatifida* fucoidan, has a high molecular weight of 100-700 kDa,” you do not provide analytical data to indicate whether or not the subject of the notice contains any smaller/low molecular weight fucoidan and if so, at what level.

a. Please provide a brief explanation as to why data potentially showing that LMW fucoidan may have antithrombotic effects would not impact your safety conclusion.

Notifier Response: Reported antithrombotic effects for fucoidan have been demonstrated to be mostly associated with low molecular weight (LMW) preparations of fucoidan specifically produced through manufacturing processes such as acid hydrolysis, enzymatic degradation, ultrasonic assisted degradation, and microwave-assisted degradation to disrupt the native polymerized state of fucoidan (Zhao *et al.* 2016, Qi *et al.* 2022, Sun *et al.* 2024).

The Marinova manufacturing method for fucoidan remains as described in GRN 565; “The unique Maritech® extraction process has been specifically designed to extract fucoidan from brown seaweed without the use of organic solvents. For the extraction of fucoidan, wild-grown seaweed, hand-harvested from the cleanest ocean waters is collected. The seaweed thus obtained is dried, milled and suspended in pure water. The acidification of water is carried out with food-grade, organic certified acid to mildly acidic pH and the suspension is subjected to agitation. The suspension is filtered to remove seaweed residue (fucoidan-rich filtrate retained) with organic certified, food grade filtration aid. The filtrate thus obtained is neutralized with food-grade, organic certified base and subjected to secondary filtration to remove salts (mechanical only). This extraction process ensures the chemical constituent of the fucoidan molecule remains unaltered and equivalent to their natural state. The secondary filtrate is concentrated, dried and milled to produce the powdered fucoidan extract.”

The Maritech® extraction process is designed to extract fucoidan without altering its intrinsic composition or enhancing the *in vivo* absorption potential which is associated with fucoidan ingredients that demonstrate effective *in vivo* antithrombotic effects. Therefore, published data indicating that LMW fucoidan may have antithrombotic effects does not impact the safety conclusion for the Maritech® fucoidan.

10. On page 56, you state:

“... there is a margin of exposure ranging from 167 for adults to 55 for children aged 2-6 years, relative to the lowest nonclinical reported repeat dose oral NOAEL of 300 mg/kg body weight per day.”

- a. Please briefly describe your rationale for the selection of 300 mg/kg bw/d as the lowest NOAEL from animal studies (assuming this NOAEL was from the data described in Li et al. (2005)) despite the publication of numerous repeat dose oral toxicity studies since its publication.

Notifier Response: Based on the updated literature search and evaluation of relevant studies published since GRNs 565 and 661, no new research was identified that specifically assesses the safety of fucoidan derived from *Undaria pinnatifida*. Recent studies have primarily focused on the efficacy of fucoidans in general or those isolated from other seaweed species. Therefore, the NOAEL of 300 mg/kg bw/day reported by Li et al. (2005) remains the most appropriate reference for the current safety assessment and GRAS conclusion.

- b. We note that previous evaluation of the subject of the notice (e.g., GRN 000595) did not involve safety evaluation within subpopulations because of the method used to estimate dietary exposure. Given that your indicated margin of exposure (MOE) for the highest consumer per weight (e.g., 2-6 year old children) is below 100, please provide a brief rationale for why MOE of <100 is appropriate to reach a GRAS conclusion despite no existence of human studies with children as well as lack of reliability of estimating background dietary exposure of fucoidan from seaweed for children ages 2-6 as stated on Table 4.

Notifier Response: While a default uncertainty factor of 100 is typically applied to account for interspecies and intraspecies variability, this factor may be adjusted when supported by robust data and low hazard potential. Fucoidan is composed of the dietary monosaccharides fucose and galactose, which are naturally present in the human diet and not associated with toxicological concern for any population subgroup, including young children. These constituents are well-characterized and metabolized through established pathways, contributing to a low level of toxicological uncertainty. This supports the conclusion that a Margin of Exposure (MOE) of less than 100 is acceptable for children aged 2-6 years in comparison to the cumulative estimated daily intake of fucoidan.

11. As indicated in Table 10, a number of clinical studies seemed to indicate that orally introduced fucoidan (from various sources) may have physiological effects apart from the anticoagulation effects that could impact safety. For example, you state:

“Significantly reduced levels of proinflammatory cytokines, including IL-1 β , IL-6, and tumor necrosis factor- α after 2 weeks of fucoïdan ingestion.” (Takahashi et al., 2018)

“Levels of interferon and CD4 interferon cells increased in the fucoïdan group, while the proportions of CD3CD4 cells and CD3CD8 cells decreased during the treatment period. The decrease in white blood cells and blood creatinine from baseline levels was significantly greater in the fucoïdan group compared to the control group.” (Yeh et al., 2022)

“Immunological tests revealed a significant enhancement of NK cell activity at eight weeks in the fucoïdan group compared to baseline.” (Tomori et al., 2021)

- a. Please provide a brief narrative on why these study results do not raise safety concerns from your intended use.

Notifier Response: Clinical efficacy studies on fucoïdan are predominantly conducted using modified forms of fucoïdan that have undergone manufacturing processes to reduce polymer size and enhance gastrointestinal absorption. For example, the test article used in the study by Takahashi et al. (2018) was a fucoïdan extract from the brown seaweed *Cladosiphon novae-caledoniae* Kylin (Mozuku), enzymatically digested using abalone glycosidase. Similarly, the fucoïdan evaluated by Yeh et al. (2022) was identified as oligo-fucoïdan, a low molecular weight (LMW) form produced through hydrolysis.³ In the study by Tomori et al. (2021), the test article was derived from Okinawa Mozuku (South Product, Uruma, Japan), although the specific manufacturing process was not disclosed.

Overall, recent efficacy studies commonly utilize fucoïdan preparations that have been structurally modified through techniques such as acid hydrolysis, enzymatic degradation, ultrasonic-assisted degradation, or microwave-assisted degradation. These methods are employed to disrupt the native polymeric structure of fucoïdan, thereby improving its bioavailability and functional activity in clinical applications.

The Maritech® extraction process used to manufacture the fucoïdan that is the subject of this GRAS notification is designed to isolate fucoïdan from *Undaria pinnatifida* using a gentle, aqueous-based method that preserves the native molecular structure of the polysaccharide. This process does not involve chemical modification or hydrolysis steps intended to reduce molecular weight or enhance gastrointestinal absorption. Therefore, the clinical studies cited above, which utilize chemically or enzymatically modified forms of fucoïdan (e.g., low molecular weight or oligo-fucoïdan), are not directly relevant to the safety assessment of Marinova’s native fucoïdan extract. These studies do not raise safety concerns for the intended use of the unmodified fucoïdan derived from *Undaria pinnatifida*.

³ <https://www.fucoïdanhq.com/en/products/about-oligo-fucoïdan>

12. You describe a study by Hwang et al. (2024), which suggests oral fucoidan may elicit some positive reproductive effects in male rats with chemically-induced testicular dysfunction. We note that this study does not appear to contain appropriate controls to evaluate this effect in rats without concomitant testicular dysfunction, among a number of other study-design caveats. Importantly, we also note that fucoidan appears to inhibit bovine sperm motility parameters and penetrance of matured cumulus-oocyte complexes in an *in vitro* fertilization assay (Tanghe et al., 2004).^[2]
 - a. In the absence of a standardized reproductive toxicity study as outlined in FDA Redbook with fucoidan, please provide a rationale as to why these results are not a safety concern for male children, who are still undergoing reproductive development, as well as for adults of reproductive age who are pregnant or planning to become pregnant.

Notifier Response: The test article studied by Hwang *et al.* (2024) was a fucoidan provided by Simpson Biotech (Taoyuan, Taiwan) extracted from brown seaweed, *Cladosiphon okamuranus*, using a commercial enzyme. The fucoidan used for this study has been enzymically modified, which has been demonstrated to enhance its gastrointestinal absorption by decreasing the size of the fucoidan polymeric units. The fucoidan that is the subject of this GRAS notification is derived from *Undaria pinnatifida* in a manner to preserve its intrinsic form. Therefore, the test article studied by Hwang *et al.* (2024) is not directly relevant to Marinova's fucoidan from *Undaria pinnatifida*.

The experiments reported on by Tanghe *et al.* (2004) were bovine Oocyte Penetration of Cumulus–Oocyte Complexes and Total and Progressive Sperm Motility assays conducted *ex vivo/in vitro* and did not include *in vivo* exposure of cattle to fucoidan. Additionally, Tanghe *et al.* (2004) did not report the exact source of the fucoidan utilized in the studies. Based on the lack of information on the test article and *ex vivo/in vitro* nature of the experiments without *in vivo* exposure, the results of the experiments are not applicable to the safety assessment of fucoidan that is the subject of this GRAS notification.

A review of the available scientific literature did not identify any studies indicating reproductive or developmental toxicity associated with fucoidan derived from *Undaria pinnatifida* (wakame). Furthermore, wakame has a long history of dietary use, particularly in East Asian countries, where it is a traditional dietary staple. This extensive history of human consumption, combined with toxicological data from animal and *in vitro* studies, supports the conclusion that fucoidan from *Undaria pinnatifida* does not pose a reproductive or developmental risk under the conditions of intended use from which intake estimates that are consistent with normal dietary intake. No evidence has emerged from regulatory assessments or peer-reviewed studies to suggest adverse effects on reproductive health or fetal development.

^[2] Tanghe et al. (2004) Mol. Reprod. Dev. 68: 429.

Revised Part 7. List of Supporting Data and Information in GRAS Notice

Note: All references listed herein are considered generally available.

Abe S, Hiramatsu K, Ichikawa O, et al. Safety evaluation of excessive ingestion of mozuku fucoidan in human. *J Food Sci.* 2013;78(4):T648-T651. doi:10.1111/j.1750-3841.2012.02966.x

AlKahtane AA, Abushouk AI, Mohammed ET, et al. Fucoidan alleviates microcystin-LR-induced hepatic, renal, and cardiac oxidative stress and inflammatory injuries in mice. *Environ Sci Pollut Res Int.* 2020;27(3):2935-2944. doi:10.1007/s11356-019-06931-z

Araya N, Takahashi K, Sato T, et al. Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. *Antivir Ther.* 2011;16(1):89-98. doi:10.3851/IMP1699

Arijón, M, Ponce, NMA., Solana, V. et al. Monthly fluctuations in the content and monosaccharide composition of fucoidan from *Undaria pinnatifida* sporophylls from northern Patagonia. *J Appl Phycol.* 2021;33, 2433–2441. doi:10.1007/s10811-021-02465-5

Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, NHANES 2017-2020 Dietary Data, Released July 2022. <https://wwwn.cdc.gov/nchs/nhanes/Search/DataPage.aspx?Component=Dietary&CycleB>

Charboneau AJ, Delaney JP, Beilman G. Fucoidans inhibit the formation of post-operative abdominal adhesions in a rat model [published correction appears in *PLoS One.* 2019 Jan 30;14(1):e0211371. doi: 10.1371/journal.pone.0211371]. *PLoS One.* 2018;13(11):e0207797. doi:10.1371/journal.pone.0207797

Chauvierre C, Aid-Launais R, Aerts J, Chaubet F, Maire M, Chollet L, Rolland L, Bonafé R, Rossi S, Bussi S, et al. Pharmaceutical development and safety evaluation of a GMP-grade fucoidan for molecular diagnosis of cardiovascular diseases. *Marine Drugs.* 2019; 17(12):699. Doi:10.3390/md17120699

Choi JI, Raghavendran HR, Sung NY, et al. Effect of fucoidan on aspirin-induced stomach ulceration in rats. *Chem Biol Interact.* 2010;183(1):249-254. doi:10.1016/j.cbi.2009.09.015

Chung HJ, Jeun J, Hounng SJ, Jun HJ, Kweon DK, Lee SJ. Toxicological evaluation of fucoidan from *Undaria pinnatifida* in vitro and in vivo. *Phytother Res.* 2010;24(7):1078-1083. doi:10.1002/ptr.3138

Cox AJ, Cripps AW, Taylor PA, Fitton JH, West NP. Fucoïdan supplementation restores fecal lysozyme concentrations in high-performance athletes: A pilot study. *Mar Drugs*. 2020 Aug 4;18(8):412. doi: 10.3390/md18080412

Cox AJ, Speer H, Radcliffe CR, Masocha K, Ramsey R, West NP, Pyne DB. Immunomodulatory effects of fucoïdan in recreationally active adult males undertaking 3-weeks of intensified training. *J Sports Sci*. 2023 Oct;41(20):1875-1882. doi: 10.1080/02640414.2024.2305007

Derosa G, Pascuzzo MD, D'Angelo A, Maffioli P. *Ascophyllum Nodosum*, *Fucus Vesiculosus* and chromium picolinate nutraceutical composition can help to treat type 2 diabetic patients. *Diabetes Metab Syndr Obes*. 2019;12:1861-1865. doi:10.2147/DMSO.S212429

European Commission (EC). Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. Official Journal of the European Union. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R2470>

Gideon TP, Rengasamy R. Toxicological evaluation of fucoïdan from *Cladosiphon okamuranus*. *J Med Food*. 2008;11(4):638-642. doi:10.1089/jmf.2007.0127

Grasa-López A, Miliar-García Á, Quevedo-Corona L, et al. *Undaria pinnatifida* and Fucoxanthin ameliorate lipogenesis and markers of both inflammation and cardiovascular dysfunction in an animal model of diet-induced obesity. *Mar Drugs*. 2016;14(8):148. doi:10.3390/md14080148

GRN 565. GRAS Notice for Fucoïdan from *Undaria pinnatifida* submitted by Marinova Pty. Ltd. FDA Letter of No Objections issued July 2, 2015. <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=565>.

GRN 661. GRAS Notice for Fucoïdan concentrate from *Fucus vesiculosus* submitted by Marinova Pty. Ltd. FDA Letter of No Objections issued February 10, 2017. <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=661>.

Geurts KAM, Meijer S, Roeters van Lennep JE, et al. The effect of *Sargassum fusiforme* and *Fucus vesiculosus* on continuous glucose levels in overweight patients with type 2 diabetes mellitus: A feasibility randomized, double-blind, placebo-controlled trial. *Nutrients*. 2024;16(12):1837. doi:10.3390/nu16121837

Haskell-Ramsay CF, Jackson PA, Dodd FL, et al. Acute post-prandial cognitive effects of brown seaweed extract in humans. *Nutrients*. 2018;10(1):85. doi:10.3390/nu10010085

Herath KHINM, Kim HJ, Kim A, Sook CE, Lee BY, Jee Y. The role of fucoïdins isolated from the sporophylls of *Undaria pinnatifida* against particulate-matter-induced allergic airway inflammation: Evidence of the attenuation of oxidative stress and inflammatory responses. *Molecules*. 2020;25(12):2869. doi:10.3390/molecules25122869

Homer B, Barekatin R, Petrovski KR, et al. Prewaning purified fucoidan drench: Effects on growth, immune response, and intestinal morphology in weaned piglets. *Animals (Basel)*. 2024;14(10):1472. doi:10.3390/ani14101472

Hwang YY, Sudirman S, Wei EY, Kong ZL, Hwang DF. Fucoidan from *Cladosiphon okamuranus* enhances antioxidant activity and prevents reproductive dysfunction in polystyrene microplastic-induced male rats. *Biomed Pharmacother*. 2024;170:115912. doi:10.1016/j.biopha.2023.115912

Ikeguchi M, Yamamoto M, Arai Y, et al. Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer. *Oncol Lett*. 2011;2(2):319-322. doi:10.3892/ol.2011.254

Irhimeh MR, Fitton JH, Lowenthal RM. Pilot clinical study to evaluate the anticoagulant activity of fucoidan. *Blood Coagulation & Fibrinolysis*. 2009; 20 (7): 607-610. doi:10.1097/MBC.ob013e32833135fe.

Irhimeh MR, Fitton JH, Lowenthal RM. Fucoidan ingestion increases the expression of CXCR4 on human CD34+ cells. *Exp Hematol*. 2007;35(6):989-994. doi:10.1016/j.exphem.2007.02.009

Irhimeh MR, Fitton JH, Lowenthal RM, Kongtawelert P. A quantitative method to detect fucoidan in human plasma using a novel antibody. *Methods Find Exp Clin Pharmacol*. 2005;27(10):705-710. doi:10.1358/mf.2005.27.10.948919

Iwamoto K, Hiragun T, Takahagi S, et al. Fucoidan suppresses IgE production in peripheral blood mononuclear cells from patients with atopic dermatitis. *Arch Dermatol Res*. 2011;303(6):425-431. doi:10.1007/s00403-010-1115-7

Juffrie, M., Rosalina, I., Damayanti, W., Djumhana, A., Ahmad, A.H. The efficacy of fucoidan on gastric ulcer. *Indonesian J. Biotechnol*. 2006; 11(2):908-913.

Kadena K, Tomori M, Iha M, Nagamine T. Absorption study of Mozuku fucoidan in Japanese volunteers. *Mar Drugs*. 2018;16(8):254. doi:10.3390/md16080254

Kim WJ, Kim SM, Kim HG, Oh HR, Lee KB, Lee YK, Park YI. Purification and anticoagulant activity of a fucoidan from Korean *Undaria pinnatifida* sporophyll. *Algae*. 2007;22(3):247-52.

Kim KJ, Lee OH, Lee HH, Lee BY. A 4-week repeated oral dose toxicity study of fucoidan from the Sporophyll of *Undaria pinnatifida* in Sprague-Dawley rats. *Toxicology*. 2010a;267(1-3):154-158. doi:10.1016/j.tox.2009.11.007

Kim KJ, Lee OH, Lee BY. Genotoxicity studies on fucoidan from Sporophyll of *Undaria pinnatifida*. *Food Chem Toxicol*. 2010b;48(4):1101-1104. doi:10.1016/j.fct.2010.01.032

Konic Ristic A, Ryan S, Attjioui M, O'Connell S, Gibney ER. Effects of an extract of the brown seaweed *Ascophyllum nodosum* on postprandial glycaemic control in healthy

subjects: A randomized controlled study. *Mar Drugs*. 2023;21(6):337. doi:10.3390/md21060337

Lean QY, Eri RD, Fitton JH, Patel RP, Gueven N. Fucoïdan extracts ameliorate acute colitis. *PLoS One*. 2015;10(6):e0128453. doi:10.1371/journal.pone.0128453

Leite-Silva, C., Gusmao, C.L.S., Takahashi, C.S., 2007. Genotoxic and antigenotoxic effects of *Fucus vesiculosus* extract on cultured human lymphocytes using the chromosome aberration and Comet assays. *Genet. Mol. Biol.* 30(1): 105-111

Li N, Zhang Q, Song J. Toxicological evaluation of fucoïdan extracted from *Laminaria japonica* in Wistar rats. *Food Chem Toxicol.* 2005;43(3):421-426. doi:10.1016/j.fct.2004.12.001

Luthuli S, Wu S, Cheng Y, Zheng X, Wu M, Tong H. (2019). Therapeutic Effects of Fucoïdan: A Review on Recent Studies. *Mar Drugs*, 17(9):487. doi:10.3390/md17090487

Maruyama H, Tamauchi H, Hashimoto M, Nakano T. Suppression of Th2 immune responses by mekabu fucoïdan from *Undaria pinnatifida* sporophylls. *Int Arch Allergy Immunol.* 2005;137(4):289-294. doi:10.1159/000086422

Mathew L, Burney M, Gaikwad A, Nyshadham P, Nugent EK, Gonzalez A, Smith JA. Preclinical evaluation of safety of fucoïdan extracts from *Undaria pinnatifida* and *Fucus vesiculosus* for use in cancer treatment. *Integr Cancer Ther.* 2017 Dec;16(4):572-584. doi:10.1177/1534735416680744. Epub 2016 Dec 21. PMID: 29096568; PMCID: PMC5739145

McFadden BA, Vincenty CS, Chandler AJ, Cintineo HP, Lints BS, Mastrofini GF, Arent SM. Effects of fucoïdan supplementation on inflammatory and immune response after high-intensity exercise. *J Int Soc Sports Nutr.* 2023 Dec;20(1):2224751. doi:10.1080/15502783.2023.2224751. PMID: 37331983; PMCID: PMC10281294

Michel C, Lahaye M, Bonnet C, Mabeau S, Barry JL. In vitro fermentation by human faecal bacteria of total and purified dietary fibres from brown seaweeds. *Br J Nutr.* 1996;75(2):263-280. doi:10.1079/bjn19960129

Mori N, Nakasone K, Tomimori K, Ishikawa C. Beneficial effects of fucoïdan in patients with chronic hepatitis C virus infection. *World J Gastroenterol.* 2012;18(18):2225-2230. doi:10.3748/wjg.v18.i18.2225

Murray M, Dordevic AL, Cox K, Scholey A, Ryan L, Bonham MP. Twelve weeks' treatment with a polyphenol-rich seaweed extract increased HDL cholesterol with no change in other biomarkers of chronic disease risk in overweight adults: A placebo-controlled randomized trial. *J Nutr Biochem.* 2021;96:108777. doi:10.1016/j.jnutbio.2021.108777

Murray M, Dordevic AL, Ryan L, Bonham MP. A Single-Dose of a Polyphenol-Rich *Fucus Vesiculosus* Extract is Insufficient to Blunt the Elevated Postprandial Blood Glucose Responses Exhibited by Healthy Adults in the Evening: A Randomised Crossover Trial. *Antioxidants (Basel).* 2019;8(2):49. doi:10.3390/antiox8020049

Murray M, Dordevic AL, Ryan L, Bonham MP. The Impact of a Single Dose of a Polyphenol-Rich Seaweed Extract on Postprandial Glycaemic Control in Healthy Adults: A Randomised Cross-Over Trial. *Nutrients*. 2018; 10(3):270. doi:10.3390/nu10030270

MRCA, 1965. Market Research Corporation of America (MRCA), in conjunction with the "Food intake and nutritive value of the diets of men, women and children in United States, Spring 1965". A Preliminary Report by the Consumer and Food Economics Research Division, Agricultural Research Division. United States Department of Agriculture, Washington, DC.

Myers SP, Mulder AM, Baker DG, et al. Effects of fucoidan from *Fucus vesiculosus* in reducing symptoms of osteoarthritis: a randomized placebo-controlled trial. *Biologics*. 2016;10:81-88. doi:10.2147/BTT.S95165

Myers SP, O'Connor J, Fitton JH, et al. A combined Phase I and II open-label study on the immunomodulatory effects of seaweed extract nutrient complex. *Biologics*. 2011;5:45-60. doi:10.2147/BTT.S12535

Myers SP, O'Connor J, Fitton JH, et al. A combined phase I and II open label study on the effects of a seaweed extract nutrient complex on osteoarthritis. *Biologics*. 2010;4:33-44. doi:10.2147/btt.s8354

Nagamine, T., Kadena, K., Tomori, M., Nakajima, K., & Iha, M. Activation of NK cells in male cancer survivors by fucoidan extracted from *Cladosiphon okamuranus*. *Mol Clin Oncol.*, 2020; 12(1): 81–88. doi:10.3892/mco.2019.1943

Nagamine T, Nakazato K, Tomioka S, Iha M, Nakajima K. Intestinal absorption of fucoidan extracted from the brown seaweed, *Cladosiphon okamuranus*. *Mar Drugs*. 2014;13(1):48-64. doi:10.3390/md13010048

Ohnogi H, Naito Y, Higashimura Y, Uno K, Yoshikawa T. Immune efficacy and safety of fucoidan extracted from *Gagome Kombu* (*Kjellmaniella crassifolia*) in healthy Japanese subjects. *Japanese J Complement Altern Med*. 2015;12(2):87–93.

Olsthoorn SEM, Wang X, Tillema B, et al. Brown seaweed food supplementation: Effects on allergy and inflammation and its consequences. *Nutrients*. 2021;13(8):2613. doi:10.3390/nu13082613

Pozharitskaya ON, Shikov AN, Faustova NM, Obluchinskaya ED, Kosman VM, Vuorela H, Makarov VG. Pharmacokinetic and tissue distribution of fucoidan from *Fucus vesiculosus* after oral administration to rats. *Mar Drugs*. 2018 Apr 18;16(4):132. doi: 10.3390/md16040132. PMID: 29669995; PMCID: PMC5923419.

Prasad S, Lillicrap D, Labelle A, et al. Efficacy and safety of a new-class hemostatic drug candidate, AV513, in dogs with hemophilia A. *Blood*. 2008;111(2):672-679. doi:10.1182/blood-2007-07-098913

Qi Y, Wang L, You Y, et al. Preparation of Low-Molecular-Weight Fucoïdan with Anticoagulant Activity by Photocatalytic Degradation Method. *Foods*. 2022;11(6):822. doi:10.3390/foods11060822

Ramu S, Murali A, Narasimhaiah G, Jayaraman A. Toxicological evaluation of *Sargassum Wightii greville* derived fucoïdan in Wistar rats: Haematological, biochemical and histopathological evidences. *Toxicol Rep*. 2020;7:874-882. doi:10.1016/j.toxrep.2020.07.009

Ren R, Azuma Y, Ojima T, et al. Modulation of platelet aggregation-related eicosanoid production by dietary F-fucoïdan from brown alga *Laminaria japonica* in human subjects. *Br J Nutr*. 2013;110(5):880-890. doi:10.1017/S000711451200606X

Sakai C, Abe S, Kouzuki M, et al. A randomized placebo-controlled trial of an oral preparation of high molecular weight fucoïdan in patients with Type 2 Diabetes with evaluation of taste sensitivity. *Yonago Acta Med*. 2019;62(1):14-23. doi:10.33160/yam.2019.03.003

Schaefer HR, Flannery BM, Crosby LM, et al. Reassessment of the cadmium toxicological reference value for use in human health assessments of foods. *Regul Toxicol Pharmacol*. 2023;144:105487. doi:10.1016/j.yrtph.2023.105487

Song MY, Ku SK, Han JS. Genotoxicity testing of low molecular weight fucoïdan from brown seaweeds. *Food Chem Toxicol*. 2012;50(3-4):790-796. doi:10.1016/j.fct.2011.11.010

Sun X, Yan C, Fu Y, et al. Orally administrated fucoïdan and its low-molecular-weight derivatives are absorbed differentially to alleviate coagulation and thrombosis. *Int J Biol Macromol*. 2024;255:128092. doi:10.1016/j.ijbiomac.2023.128092

Takahashi H, Kawaguchi M, Kitamura K, et al. An exploratory study on the anti-inflammatory effects of fucoïdan in relation to quality of life in advanced cancer patients. *Integr Cancer Ther*. 2018;17(2):282-291. doi:10.1177/1534735417692097

Teas J, Baldeón ME, Chiriboga DE, Davis JR, Sarriés AJ, Braverman LE. Could dietary seaweed reverse the metabolic syndrome?. *Asia Pac J Clin Nutr*. 2009;18(2):145-154.

Teng QL, Sui SJ, Zhu Z, et al. A fucoïdan plant drink reduces *Helicobacter pylori* load in the stomach: a real-world study. *Transl Gastroenterol Hepatol*. 2023;8:34. doi:10.21037/tgh-23-63

Tocaciu S, Oliver LJ, Lowenthal RM, et al. The Effect of *Undaria pinnatifida* fucoïdan on the pharmacokinetics of letrozole and tamoxifen in patients with breast cancer. *Integr Cancer Ther*. 2018;17(1):99-105. doi:10.1177/1534735416684014

Tokita Y, Nakajima K, Mochida H, Iha M, Nagamine T. Development of a fucoïdan-specific antibody and measurement of fucoïdan in serum and urine by sandwich ELISA. *Biosci Biotechnol Biochem*. 2010;74(2):350-357. doi:10.1271/bbb.90705

Tomori M, Nagamine T, Miyamoto T, Iha M. Effects of ingesting fucoidan derived from *Cladosiphon okamuranus* Tokida on human NK cells: A randomized, double-blind, parallel-group, placebo-controlled pilot study. *Mar Drugs*. 2021;19(6):340. doi:10.3390/md19060340.

Tsai HL, Tai CJ, Huang CW, Chang FR, Wang JY. Efficacy of low-molecular-weight fucoidan as a supplemental therapy in metastatic colorectal cancer patients: A double-blind randomized controlled trial. *Mar Drugs*. 2017;15(4):122. doi:10.3390/md15040122

Tsai HL, Yeh YS, Chen PJ, et al. The Auxiliary effects of low-molecular-weight fucoidan in locally advanced rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy before surgery: A double-blind, randomized, placebo-controlled study. *Integr Cancer Ther*. 2023;22. doi:10.1177/15347354231187153

van den Driessche JJ, Plat J, Konings MCJM, Mensink RP. Effects of spirulina and wakame consumption on intestinal cholesterol absorption and serum lipid concentrations in non-hypercholesterolemic adult men and women. *Eur J Nutr*. 2020;59(5):2229-2236. doi:10.1007/s00394-019-02073-7

Vodouhè M, Marois J, Guay V, et al. Marginal impact of brown seaweed *Ascophyllum nodosum* and *Fucus vesiculosus* extract on metabolic and inflammatory response in overweight and obese prediabetic subjects. *Mar Drugs*. 2022;20(3):174. doi:10.3390/md20030174

Wang C, Chen W, Xu Y, et al. *Laminaria japonica* polysaccharides improves the growth performance and faecal digestive enzyme activity of weaned piglets. *Vet Sci*. 2023;11(1):11. doi:10.3390/vetsci11010011

Wang S, Tian ZB, Chen JW, et al. Effect of fucoidan on gut microbiota and its clinical efficacy in *Helicobacter pylori* eradication: A randomized controlled trial. *J Dig Dis*. 2023;24(8-9):461-471. doi:10.1111/1751-2980.13215

Wang H, Wei W, Liu F, Wang M, Zhang Y, Du S. Effects of fucoidan and synbiotics supplementation during bismuth quadruple therapy of *Helicobacter pylori* infection on gut microbial homeostasis: an open-label, randomized clinical trial. *Front Nutr*. 2024;11. doi:10.3389/fnut.2024.1407736

Wright, C.M., Bezabhe, W., Fitton J.H., Stringer D.N., Bereznicki L.R.E., Peterson G.M., 2019. Effect of a fucoidan extract on insulin resistance and cardiometabolic markers in obese, nondiabetic subjects: A randomized, controlled trial. *J Altern Complement Med*. 25(3):346-352.

Yamanaka, R., Akiyama, K. Cultivation and utilization of *Undaria pinnatifida* (wakame) as food. *J Appl Phycol* 5, 249–253 (1993). doi:10.1007/BF00004026

Yang JH. Topical application of fucoidan improves atopic dermatitis symptoms in NC/Nga mice. *Phytother Res*. 2012;26(12):1898-1903. doi:10.1002/ptr.4658

- Yasuzawa T, Mima A, Ueshima S. Antithrombotic effect of oral administration of Mozuku (*Cladosiphon okamuranus*, brown seaweed) extract in rat. *J Nutr Sci Vitaminol (Tokyo)*. 2019;65(2):171-176. doi:10.3177/jnsv.65.171
- Yeh CW, Shih CJ, Liu TC, Chiou YL. Effects of oligo-fucoidan on the immune response, inflammatory status and pulmonary function in patients with asthma: a randomized, double-blind, placebo-controlled trial. *Sci Rep*. 2022;12(1):18150. doi:10.1038/s41598-022-21527-3
- Yoshinaga K, Nakai Y, Izumi H, et al. Oral administration of edible seaweed *Undaria Pinnatifida* (Wakame) modifies glucose and lipid metabolism in rats: A DNA microarray analysis. *Mol Nutr Food Res*. 2018;62(12):e1700828. doi:10.1002/mnfr.201700828
- Yuan L, Cheng S, Sol WMPJ, et al. Heparan sulfate mimetic fucoidan restores the endothelial glycocalyx and protects against dysfunction induced by serum of COVID-19 patients in the intensive care unit. *ERJ Open Res*. 2022;8(2):00652-2021. doi:10.1183/23120541.00652-2021
- Zaharudin N, Tullin M, Pekmez CT, Sloth JJ, Rasmussen RR, Dragsted LO. Effects of brown seaweeds on postprandial glucose, insulin and appetite in humans - A randomized, 3-way, blinded, cross-over meal study. *Clin Nutr*. 2021;40(3):830-838. doi:10.1016/j.clnu.2020.08.027
- Zaragozá MC, López D, P Sáiz M, et al. Toxicity and antioxidant activity in vitro and in vivo of two *Fucus vesiculosus* extracts. *J Agric Food Chem*. 2008;56(17):7773-7780. doi:10
- Zhang Z, Till S, Jiang C, et al. Structure-activity relationship of the pro- and anticoagulant effects of *Fucus vesiculosus* fucoidan. *Thromb Haemost*. 2014;111(3):429-437. doi:10.1160/TH13-08-0635.1021/jf8007053
- Zhao X, Guo F, Hu J, et al. Antithrombotic activity of oral administered low molecular weight fucoidan from *Laminaria Japonica*. *Thromb Res*. 2016;144:46-52. doi:10.1016/j.thromres.2016.03.008

Appendix C. *Revised* WWEIA/NHANES 2017-2020 Food Codes Included in Current Intake Analysis

Food code	Food description
Seaweed	
41601070	Soybean soup, miso broth*
58151100	Sushi, NFS*
58151170	Sushi roll, avocado*
58151180	Sushi roll, California*
58151190	Sushi roll, eel*
58151200	Sushi roll, salmon*
58151210	Sushi roll, shrimp*
58151220	Sushi roll tuna*
58151230	Sushi roll, vegetable*
58151450	Sushi, topped with egg*
59003000	Meat substitute, cereal- and vegetable protein-based, fried*
75127500	Seaweed, raw
75232000	Seaweed, dried
75232110	Seaweed, cooked, no added fat
75232120	Seaweed, cooked, fat added
75513010	Seaweed, pickled*
75647000	Seaweed soup*
Beverages (non-alcoholic)	
<i>Sports Drinks</i>	
92900300	Sports drink, dry concentrate, not reconstituted**
95320200	Sports drink (Gatorade G)
95320500	Sports drink (Powerade)
95321000	Sports drink, NFS
95322200	Sports drink, low calorie (Gatorade G2)
95322500	Sports drink, low calorie (Powerade Zero)
95323000	Sports drink, low calorie
95330100	Fluid replacement, electrolyte solution
Soups	
14710100	Cheddar cheese soup, home recipe, canned or ready-to-serve
28310110	Beef, broth, bouillon, or consomme
28310150	Oxtail soup
28310320	Beef noodle soup, Puerto Rican style*
28310330	Pho*
28311010	Pepperpot soup

Food code	Food description
28311030	Menudo soup, canned, prepared with water or ready-to-serve
28315050	Beef vegetable soup with potato, pasta, or rice, chunky style, canned, or ready-to-serve
28315160	Italian Wedding Soup*
28320160	Pork vegetable soup with potato, pasta, or rice, stew type, chunky style
28320300	Pork with vegetable excluding carrots, broccoli and/or dark-green leafy; soup, Asian Style
28321130	Bacon soup, cream of, prepared with water
28340110	Chicken or turkey broth, bouillon, or consomme
28340180	Chicken or turkey broth, less or reduced sodium, canned or ready-to-serve
28340210	Chicken rice soup, Puerto Rican style
28340220	Chicken soup with noodles and potatoes, Puerto Rican style*
28340310	Chicken or turkey gumbo soup, home recipe, canned or ready-to-serve
28340510	Chicken or turkey noodle soup, chunky style, canned or ready-to-serve
28340550	Sweet and sour soup
28340580	Chicken or turkey soup with vegetables, broccoli, carrots, celery, potatoes and onions, Asian style
28340600	Chicken or turkey vegetable soup, canned, prepared with water or ready-to-serve
28340610	Chicken or turkey vegetable soup, stew type
28340630	Chicken or turkey vegetable soup with rice, stew type, chunky style
28340640	Chicken or turkey vegetable soup with noodles, stew type, chunky style, canned or ready-to-serve
28340750	Hot and sour soup
28340800	Chicken or turkey soup with vegetables and fruit, Asian Style
28345110	Chicken or turkey soup, cream of, NS as to prepared with milk or water
28345120	Chicken or turkey soup, cream of, prepared with milk
28345130	Chicken or turkey soup, cream of, prepared with water
28345160	Chicken or turkey mushroom soup, cream of, prepared with milk
28350050	Fish chowder
28350120	Crab soup, tomato-base
28350210	Clam chowder, NS as to Manhattan or New England style
28350220	Clam chowder, Manhattan
28351110	Fish and vegetable soup, no potatoes, Mexican style
28351160	Codfish, rice, and vegetable soup, Puerto Rican style
28355110	Clam chowder, New England, NS as to prepared with water or milk
28355120	Clam chowder, New England, prepared with milk
28355130	Clam chowder, New England, prepared with water
28355140	Clam chowder, New England, reduced sodium, canned or ready-to-serve
28355210	Crab soup, cream of, prepared with milk
28355250	Lobster bisque
28355310	Oyster stew
28355350	Salmon soup, cream style
28355410	Shrimp soup, cream of, NS as to prepared with milk or water

Food code	Food description
28355420	Shrimp soup, cream of, prepared with milk
28355450	Seafood soup with potatoes and vegetables including carrots, broccoli, and/or dark-green leafy
28355460	Seafood soup with potatoes, and vegetables excluding carrots, broccoli, and dark-green leafy
28355470	Seafood soup with vegetables including carrots, broccoli, and/or dark-green leafy; no potatoes
28355480	Seafood soup with vegetables excluding carrots, broccoli, and dark-green leafy; no potatoes
32300100	Egg drop soup
32301100	Garlic egg soup, Puerto Rican style*
41601010	Bean soup, NFS
41601020	Bean with bacon or ham soup, canned or ready-to-serve
41601030	Black bean soup, home recipe, canned or ready-to-serve
41601040	Lima bean soup, home recipe, canned or ready-to-serve
41601070	Soybean soup, miso broth
41601080	Pinto bean soup, home recipe, canned or ready-to-serve*
41601090	Bean soup, with macaroni, home recipe, canned, or ready-to-serve
41601130	Bean soup, mixed beans, home recipe, canned or ready-to-serve
41602010	Pea and ham soup, chunky style, canned or ready-to-serve
41602020	Garbanzo bean or chickpea soup, home recipe, canned or ready-to-serve
41602030	Split pea and ham soup
41602050	Split pea soup
41603010	Lentil soup, home recipe, canned, or ready-to-serve
58400000	Soup, NFS
58400100	Noodle soup, NFS*
58400200	Rice soup, NFS
58401010	Barley soup, home recipe, canned, or ready-to-serve
58401200	Barley soup, sweet, with or without nuts, Asian Style
58402010	Beef noodle soup, canned or ready-to-serve
58402030	Beef rice soup, home recipe, canned or ready-to-serve
58403010	Chicken or turkey noodle soup, canned or ready-to-serve
58403040	Chicken or turkey noodle soup, home recipe*
58403050	Chicken or turkey noodle soup, cream of, home recipe, canned, or ready-to-serve
58403060	Chicken or turkey noodle soup, reduced sodium, canned or ready-to-serve
58404010	Chicken or turkey rice soup, canned, or ready-to-serve
58404040	Chicken or turkey rice soup, reduced sodium, canned, prepared with water or ready-to-serve
58404500	Matzo ball soup
58404510	Chicken or turkey soup with dumplings and potatoes, home recipe, canned, or ready-to-serve
58404520	Chicken or turkey soup with dumplings, home recipe, canned or ready-to-serve
58407010	Instant soup, noodle*
58407030	Soup, mostly noodles*

Food code	Food description
58407035	Soup, mostly noodles, reduced sodium
58408010	Wonton soup
58408500	Noodle soup with vegetables, Asian style*
58409000	Noodle soup, with fish ball, shrimp, and dark green leafy vegetable*
58421010	Sopa Seca de Fideo, Mexican style, made with dry noodles, home recipe*
58421020	Sopa de Fideo Aguada, Mexican style noodle soup, home recipe*
63415100	Soup, fruit
71801000	Potato soup, NS as to made with milk or water
71801010	Potato soup, cream of, prepared with milk
71801020	Potato soup, prepared with water
71801100	Potato and cheese soup
71803010	Potato chowder
71851010	Plantain soup, Puerto Rican style
72302000	Broccoli soup, prepared with milk, home recipe, canned or ready-to-serve
72302020	Broccoli soup, prepared with water, home recipe, canned, or ready-to-serve
72302100	Broccoli cheese soup, prepared with milk, home recipe, canned, or ready-to-serve
72307000	Spinach soup
72308000	Dark-green leafy vegetable soup with meat, Asian style
72308500	Dark-green leafy vegetable soup, meatless, Asian style
73502000	Squash, winter type, soup, home recipe, canned, or ready-to-serve
74601000	Tomato soup, NFS
74601010	Tomato soup, cream of, prepared with milk
74602010	Tomato soup, prepared with water, or ready-to-serve
74602050	Tomato soup, instant type, prepared with water
74602200	Tomato soup, canned, reduced sodium, prepared with water, or ready-to-serve
74602300	Tomato soup, canned, reduced sodium, prepared with milk
74603010	Tomato beef soup, prepared with water
74604010	Tomato beef noodle soup, prepared with water
74604100	Tomato beef rice soup, prepared with water
74604500	Tomato noodle soup, canned, prepared with water or ready-to-serve
74605010	Tomato rice soup, prepared with water
74606010	Tomato vegetable soup, prepared with water
74606020	Tomato vegetable soup with noodles, prepared with water
75600150	Soup, cream of, NFS
75601000	Asparagus soup, cream of, NS as to made with milk or water
75601010	Asparagus soup, cream of, prepared with milk
75601200	Cabbage soup, home recipe, canned or ready-to-serve
75601210	Cabbage with meat soup, home recipe, canned or ready-to-serve
75601250	Kimchi soup
75603010	Celery soup, cream of, prepared with milk, home recipe, canned or ready-to-serve

Food code	Food description
75603020	Celery soup, cream of, prepared with water, home recipe, canned or ready-to-serve
75604010	Corn soup, cream of, prepared with milk
75604020	Corn soup, cream of, prepared with water
75604600	Gazpacho
75605010	Leek soup, cream of, prepared with milk
75607000	Mushroom soup, NFS
75607010	Mushroom soup, cream of, prepared with milk
75607020	Mushroom soup, cream of, prepared with water
75607040	Mushroom soup, with meat broth, prepared with water
75607060	Mushroom soup, cream of, NS as to made with milk or water
75607100	Mushroom soup, cream of, canned, reduced sodium, prepared with milk
75607140	Mushroom soup, cream of, canned, reduced sodium, prepared with water
75608100	Onion soup, French*
75609010	Pea soup, prepared with milk
75611010	Vegetable soup, cream of, prepared with milk
75647000	Seaweed soup
75649010	Vegetable soup, canned, prepared with water or ready-to-serve
75649040	Vegetable soup, reduced sodium, canned, ready to serve
75649050	Vegetable soup, made from dry mix
75649150	Vegetable noodle soup, home recipe*
75650990	Minestrone soup, reduced sodium, canned or ready-to-serve
75651000	Minestrone soup, home recipe*
75651010	Minestrone soup, canned, prepared with water, or ready-to-serve
75651020	Vegetable beef soup, canned, prepared with water, or ready-to-serve
75651030	Vegetable beef noodle soup, prepared with water
75651040	Vegetable noodle soup, canned, prepared with water, or ready-to-serve
75651070	Vegetable rice soup, canned, prepared with water or ready-to-serve
75651080	Vegetable beef soup with rice, canned, prepared with water or ready-to-serve
75651110	Vegetable chicken rice soup, canned, prepared with water or ready-to-serve
75652030	Vegetable beef soup, canned, prepared with milk
75652040	Vegetable beef soup with noodles or pasta, home recipe*
75656020	Vegetable soup, chunky style
75656040	Vegetable soup, with pasta, chunky style
75656060	Vegetable beef soup, chunky style
75657000	Vegetable broth, bouillon
Imitation Dairy Products	
<i>Non-dairy milks</i>	
11300100	Non-dairy milk, NFS
11320000	Soy milk
11320100	Soy milk, light
11320200	Soy milk, nonfat

Food code	Food description
11321000	Soy milk, chocolate
11321100	Soy milk, light, chocolate
11350000	Almond milk, sweetened
11350010	Almond milk, sweetened, chocolate
11350020	Almond milk, unsweetened
11350030	Almond milk, unsweetened, chocolate
11360000	Rice milk
11370000	Coconut milk
11512030	Hot chocolate / Cocoa, ready to drink, made with non-dairy milk*
11513310	Chocolate milk, made from dry mix with non-dairy milk*
11513395	Chocolate milk, made from no sugar added dry mix with non-dairy milk (Nesquik) *
11513750	Chocolate milk, made from syrup with non-dairy milk*
11514150	Hot chocolate / Cocoa, made with dry mix and non-dairy milk*
11514360	Hot chocolate / Cocoa, made with no sugar added dry mix and non-dairy milk*
11519215	Strawberry milk, non-dairy
56201360	Grits, instant, made with non-dairy milk, fat added*
56203075	Oatmeal, regular or quick, made with non-dairy milk, NS as to fat*
56203076	Oatmeal, regular or quick, made with non-dairy milk, no added fat*
56203077	Oatmeal, regular or quick, made with non-dairy milk, fat added*
56203106	Oatmeal, instant, plain, made with non-dairy milk, no added fat*
56203107	Oatmeal, instant, plain, made with non-dairy milk, fat added*
56207102	Cream of wheat, instant, made with non-dairy milk, no added fat*
64134025	Fruit smoothie, with whole fruit, non-dairy*
78101115	Fruit and vegetable smoothie, non-dairy*
78101118	Fruit and vegetable smoothie, non-dairy, added protein*
92101903	Coffee, Latte, with non-dairy milk
92101906	Coffee, Latte, with non-dairy milk, flavored
92101923	Frozen coffee drink, with non-dairy milk
92101960	Coffee, Cafe Mocha, with non-dairy milk
92102502	Coffee, Iced Latte, with non-dairy milk
92102505	Coffee, Iced Latte, with non-dairy milk, flavored
92161002	Coffee, Cappuccino, with non-dairy milk
<i>Non-dairy creamers and whipped topping</i>	
12210520	Coffee creamer, soy, liquid
12220200	Whipped topping
12220270	Whipped topping, fat free
12220280	Whipped topping, sugar free
63402970	Fruit salad, excluding citrus fruits, with nondairy whipped topping*
63403030	Fruit salad, including citrus fruits, with nondairy whipped topping*
<i>Non-dairy sour cream</i>	
12320100	Sour cream, imitation

Food code	Food description
<u><i>Non-dairy cheese and cream cheese</i></u>	
14502000	Imitation cheese
<u><i>Non-dairy yogurt</i></u>	
41420380	Yogurt, soy
42401100	Yogurt, coconut milk
<u><i>Non-dairy frozen desserts</i></u>	
41480020	Frozen dessert, non-dairy
Bakery Products [Baked goods]	
<u><i>Baked goods (bread, cake, noodles)</i></u>	
13210110	Pudding, bread*
14640000	Cheese sandwich, NFS*
14640002	Cheese sandwich, American cheese, on white bread*
14640004	Cheese sandwich, American cheese, on wheat bread*
14640006	Cheese sandwich, American cheese, on whole wheat bread, no spread*
14640008	Cheese sandwich, cheddar cheese, on white bread*
14640010	Cheese sandwich, cheddar cheese, on wheat bread*
14640012	Cheese sandwich, Cheddar cheese, on whole wheat bread, no spread*
14640014	Cheese sandwich, reduced fat cheese, on white bread*
14640016	Cheese sandwich, reduced fat cheese, on wheat bread*
14640018	Cheese sandwich, reduced fat American cheese, on whole wheat bread, no spread*
14640020	Cheese sandwich, reduced fat Cheddar cheese, on white bread, no spread*
14640024	Cheese sandwich, reduced fat Cheddar cheese, on whole wheat bread, no spread*
14640026	Cheese sandwich, American cheese, on white bread, with mayonnaise*
14640028	Cheese sandwich, American cheese, on wheat bread, with mayonnaise*
14640030	Cheese sandwich, American cheese, on whole wheat bread, with mayonnaise*
14640032	Cheese sandwich, Cheddar cheese, on white bread, with mayonnaise*
14640034	Cheese sandwich, Cheddar cheese, on wheat bread, with mayonnaise*
14640036	Cheese sandwich, Cheddar cheese, on whole wheat bread, with mayonnaise*
14640042	Cheese sandwich, reduced fat American cheese, on whole wheat bread, with mayonnaise*
14640050	Cheese sandwich, American cheese, on white bread, with butter*
14640052	Cheese sandwich, American cheese, on wheat bread, with butter*
14640056	Cheese sandwich, Cheddar cheese, on white bread, with butter*
14640058	Cheese sandwich, Cheddar cheese, on wheat bread, with butter*
14640062	Cheese sandwich, reduced fat American cheese, on white bread, with butter*
14640068	Cheese sandwich, reduced fat Cheddar cheese, on white bread, with butter*
14640100	Grilled cheese sandwich, NFS*

Food code	Food description
14640105	Grilled cheese sandwich, American cheese, on white bread*
14640110	Grilled cheese sandwich, American cheese, on wheat bread*
14640115	Grilled cheese sandwich, American cheese, on whole wheat bread*
14640125	Grilled cheese sandwich, cheddar cheese, on white bread*
14640130	Grilled cheese sandwich, cheddar cheese, on wheat bread*
14640135	Grilled cheese sandwich, Cheddar cheese, on whole wheat bread*
14640155	Grilled cheese sandwich, reduced fat cheese, on white bread*
14640160	Grilled cheese sandwich, reduced fat cheese, on wheat bread*
14640165	Grilled cheese sandwich, reduced fat American cheese, on whole wheat bread*
14640190	Grilled cheese sandwich, reduced fat Cheddar cheese, on wheat bread*
27212000	Beef and noodles, no sauce*
27212050	Beef and macaroni with cheese sauce*
27212100	Beef and noodles with tomato-based sauce*
27212120	Chili con carne with beans and macaroni*
27212150	Beef goulash with noodles*
27212200	Beef and noodles with gravy*
27212300	Beef and noodles with cream or white sauce*
27212350	Beef stroganoff with noodles*
27212500	Beef and noodles with soy-based sauce*
27220210	Ham and noodles, no sauce*
27242000	Chicken or turkey and noodles, no sauce*
27242250	Chicken or turkey and noodles with mushroom sauce*
27242300	Chicken or turkey and noodles with cream or white sauce*
27242310	Chicken or turkey and noodles with cheese sauce*
27242350	Chicken or turkey tetrazzini*
27242400	Chicken or turkey and noodles with tomato-based sauce*
27242500	Chicken or turkey and noodles with soy-based sauce*
27250120	Shrimp and noodles, no sauce*
27250126	Shrimp and noodles with cream or white sauce*
27250128	Shrimp and noodles with soy-based sauce*
27250130	Shrimp and noodles with cheese sauce*
27250132	Shrimp and noodles with tomato sauce*
27250610	Tuna noodle casserole with cream or white sauce*
27250630	Tuna noodle casserole with mushroom sauce*
27313010	Beef, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; no sauce*
27313020	Beef, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; no sauce*

Food code	Food description
27313110	Beef chow mein or chop suey with noodles*
27313150	Beef, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; soy-based sauce*
27313160	Beef, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; soy-based sauce*
27313220	Beef, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; tomato-based sauce*
27313410	Beef, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; gravy*
27313420	Beef, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; gravy*
27320025	Ham or pork, noodles and vegetables excluding carrots, broccoli, and dark-green leafy; no sauce*
27320027	Ham or pork, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; no sauce*
27320070	Ham or pork, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; tomato-based sauce*
27320080	Sausage, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; tomato-based sauce*
27320310	Pork chow mein or chop suey with noodles*
27343010	Chicken or turkey, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; no sauce*
27343020	Chicken or turkey, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; no sauce*
27343410	Chicken or turkey, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; gravy*
27343420	Chicken or turkey, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; gravy*
27343470	Chicken or turkey, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; cream sauce, white sauce, or mushroom sauce*
27343480	Chicken or turkey, noodles, and vegetables excluding carrots, broccoli, and/or dark-green leafy; cream sauce, white sauce, or mushroom sauce*
27343510	Chicken or turkey, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; tomato-based sauce*
27343520	Chicken or turkey, noodles, and vegetables excluding carrots, broccoli, and dark-green leafy; tomato-based sauce*
27343910	Chicken or turkey chow mein or chop suey with noodles*
27343950	Chicken or turkey, noodles, and vegetables including carrots, broccoli, and/or dark-green leafy; cheese sauce*
27350050	Shrimp chow mein or chop suey with noodles*
27350080	Tuna noodle casserole with vegetables, cream or white sauce*
27360010	Goulash, NFS*
27446355	Asian chicken or turkey garden salad with crispy noodles, chicken and/or turkey, lettuce, fruit, nuts, crispy noodles, no dressing*
27500050	Sandwich, NFS*
27500100	Meat sandwich, NFS*

Food code	Food description
27510000	Beef sandwich, NFS*
27510100	Sloppy joe sandwich, on white bun*
27510105	Sloppy joe sandwich, on wheat bun*
27510130	Barbecue beef sandwich, on white bun*
27510135	Barbecue beef sandwich, on wheat bun*
27510140	Cheeseburger slider, from fast food*
27510155	Cheeseburger, NFS*
27510160	Cheeseburger, from fast food, 1 small patty*
27510170	Cheeseburger (Burger King)*
27510171	Whopper Jr with cheese (Burger King)*
27510172	Cheeseburger (McDonalds)*
27510190	Cheeseburger, from school cafeteria*
27510191	Cheeseburger slider*
27510195	Cheeseburger, on white bun, 1 small patty*
27510196	Cheeseburger, on wheat bun, 1 small patty*
27510215	Cheeseburger, from fast food, 1 medium patty*
27510229	Quarter Pounder (McDonalds) *
27510231	Whopper with cheese (Burger King)*
27510232	Quarter Pounder with cheese (McDonalds) *
27510235	Cheeseburger submarine sandwich with lettuce, tomato and spread*
27510241	Cheeseburger, on white bun, 1 medium patty*
27510242	Cheeseburger, on wheat bun, 1 medium patty*
27510245	Cheeseburger, on white bun, 1 large patty*
27510246	Cheeseburger, on wheat bun, 1 large patty*
27510254	Double cheeseburger, on white bun, 2 small patties*
27510257	Double cheeseburger, on white bun, 2 medium patties*
27510258	Double cheeseburger, on wheat bun, 2 medium patties*
27510261	Cheeseburger, from fast food, 1 large patty*
27510262	Double cheeseburger, on white bun, 2 large patties*
27510371	Double cheeseburger, from fast food, 2 small patties*
27510386	Double cheeseburger (Burger King) *
27510387	Double cheeseburger (McDonalds) *
27510388	McDouble (McDonalds) *
27510389	Big Mac (McDonalds)*
27510401	Double cheeseburger, from fast food, 2 medium patties*
27510405	Double cheeseburger, from fast food, 2 large patties*
27510531	Hamburger, from fast food, 1 small patty*

Food code	Food description
27510551	Hamburger (Burger King)*
27510552	Whopper Jr (Burger King)*
27510553	Hamburger (McDonalds)*
27510565	Hamburger, from school cafeteria*
27510573	Hamburger slider*
27510575	Hamburger, on white bun, 1 small patty*
27510576	Hamburger, on wheat bun, 1 small patty*
27510601	Hamburger, from fast food, 1 medium patty*
27510605	Hamburger, from fast food, 1 large patty*
27510615	Whopper (Burger King) *
27510631	Hamburger, on white bun, 1 medium patty*
27510632	Hamburger, on wheat bun, 1 medium patty*
27510635	Hamburger, on white bun, 1 large patty*
27510636	Hamburger, on wheat bun, 1 large patty*
27510649	Double hamburger, on white bun, 2 small patties*
27510655	Double hamburger, on white bun, 2 medium patties*
27510657	Double hamburger, on wheat bun, 2 medium patties*
27510658	Double hamburger, on white bun, 2 large patties*
27510661	Double hamburger, from fast food, 2 small patties*
27510671	Double hamburger, from fast food, 2 medium patties*
27510675	Double hamburger, from fast food, 2 large patties*
27510700	Meatball sandwich or sub*
27510702	Meatloaf sandwich*
27510705	Chiliburger, with or without cheese, on bun*
27510910	Corned beef sandwich on white*
27510920	Corned beef sandwich on white, with cheese*
27510930	Corned beef sandwich on wheat*
27510940	Corned beef sandwich on wheat, with cheese*
27510950	Reuben sandwich*
27513010	Roast beef sandwich on white*
27513040	Roast beef submarine sandwich, with lettuce, tomato and spread*
27513041	Roast beef submarine sandwich, with cheese, lettuce, tomato and spread*
27513050	Roast beef sandwich on white, with cheese*
27513055	Roast beef sandwich on wheat*
27513065	Roast beef sandwich on wheat, with cheese*
27513070	French dip sandwich*
27514010	Steak sandwich or sub on white*

Food code	Food description
27514020	Steak sandwich or sub on wheat*
27514030	Cheese steak sandwich or sub on white*
27514040	Cheese steak sandwich or sub on wheat*
27515010	Steak sandwich, plain, on roll*
27515020	Steak and cheese submarine sandwich, with lettuce and tomato*
27515030	Steak and cheese sandwich, plain, on roll*
27515040	Steak and cheese submarine sandwich, plain, on roll*
27515070	Steak and cheese submarine sandwich, with fried peppers and onions, on roll*
27516010	Gyro sandwich*
27520140	Bacon and egg sandwich*
27520150	Bacon, lettuce, and tomato sandwich with spread*
27520155	Bacon, lettuce, and tomato submarine sandwich, with spread*
27520156	Bacon, lettuce, tomato, and cheese submarine sandwich, with spread*
27520210	Ham sandwich on white*
27520220	Ham sandwich on white, with cheese*
27520230	Ham sandwich on wheat*
27520240	Ham sandwich on wheat, with cheese*
27520255	Ham sandwich or sub, restaurant*
27520260	Ham sandwich or sub, with cheese, restaurant*
27520310	Ham sandwich with lettuce and spread*
27520320	Ham and cheese sandwich, with lettuce and spread*
27520340	Ham salad sandwich on white*
27520370	Hot ham and cheese sandwich, on bun*
27520390	Ham and cheese submarine sandwich, with lettuce, tomato and spread*
27520410	Cuban sandwich*
27520500	Barbecue rib sandwich*
27520510	Barbecue pork sandwich, on white bun*
27520515	Barbecue pork sandwich, on wheat bun*
27520520	Pork sandwich*
27520610	Bacon, lettuce, tomato sandwich on white*
27520620	Bacon, lettuce, tomato sandwich on wheat*
27540010	Turkey sandwich on white*
27540020	Turkey sandwich on white, with cheese*
27540030	Turkey sandwich on wheat*
27540040	Turkey sandwich on wheat, with cheese*
27540050	Turkey sandwich or sub, restaurant*
27540060	Turkey sandwich or sub, with cheese, restaurant*

Food code	Food description
27540090	Chicken deli sandwich or sub, with cheese, restaurant*
27540110	Sliced chicken sandwich, with spread*
27540111	Sliced chicken sandwich, with cheese and spread*
27540120	Chicken salad sandwich on white*
27540121	Chicken salad sandwich on wheat*
27540125	Club sandwich on wheat*
27540126	Club sandwich on wheat, with cheese*
27540127	Club sandwich or sub, restaurant*
27540130	Barbecue chicken sandwich, on white bun*
27540132	Chicken fillet sandwich, NFS*
27540139	Chicken fillet sandwich, from school cafeteria*
27540146	Chicken fillet sandwich, fried, from fast food*
27540147	Chicken fillet sandwich, fried, from fast food, with cheese*
27540152	Chicken fillet sandwich, grilled, from fast food*
27540153	Chicken fillet sandwich, grilled, from fast food, with cheese*
27540160	Chicken fillet sandwich, NS as to fried or grilled, from fast food*
27540175	Chicken fillet sandwich, fried, on white bun*
27540176	Chicken fillet sandwich, fried, on white bun; with cheese*
27540185	Chicken fillet sandwich, fried, on wheat bun*
27540186	Chicken fillet sandwich, fried, on wheat bun, with cheese*
27540195	Chicken fillet sandwich, grilled, on white bun*
27540196	Chicken fillet sandwich, grilled, on white bun, with cheese*
27540205	Chicken fillet sandwich, grilled, on wheat bun*
27540206	Chicken fillet sandwich, grilled, on wheat bun, with cheese*
27540285	Chicken, bacon, and tomato club sandwich, with lettuce and spread*
27540290	Chicken submarine sandwich, with lettuce, tomato and spread*
27540291	Chicken submarine sandwich, with cheese, lettuce, tomato and spread*
27540296	Buffalo chicken submarine sandwich with cheese*
27540310	Turkey sandwich, with spread*
27540350	Turkey submarine sandwich, with cheese, lettuce, tomato and spread*
27540360	Turkey and bacon submarine sandwich, with lettuce, tomato and spread*
27540361	Turkey and bacon submarine sandwich, with cheese, lettuce, tomato and spread*
27541000	Turkey, ham, and roast beef club sandwich, with lettuce, tomato and spread*
27541001	Turkey, ham, and roast beef club sandwich with cheese, lettuce, tomato, and spread*
27545100	Turkey or chicken burger, on white bun*
27545110	Turkey or chicken burger, on wheat bun*

Food code	Food description
27550000	Fish sandwich, fried, from fast food*
27550100	Fish sandwich, fried, from fast food, with cheese*
27550110	Crab cake sandwich*
27550120	Salmon cake sandwich*
27550150	Fried seafood sandwich*
27550200	Fish sandwich, from school cafeteria*
27550300	Fish sandwich, NFS*
27550400	Fish sandwich, fried, on white bun*
27550405	Fish sandwich, fried, on white bun, with cheese*
27550410	Fish sandwich, fried, on wheat bun*
27550420	Fish sandwich, grilled*
27550510	Sardine sandwich*
27550720	Tuna salad sandwich on white*
27550730	Tuna salad sandwich on white, with cheese*
27550735	Tuna salad sandwich on wheat*
27550737	Tuna salad sandwich on wheat, with cheese*
27550740	Tuna salad sandwich, on bun*
27550745	Tuna salad sandwich, on bun, with cheese*
27550800	Seafood salad sandwich*
27560120	Bologna and cheese sandwich, with spread*
27560130	Bologna sandwich on white*
27560140	Bologna sandwich on white, with cheese*
27560150	Bologna sandwich on wheat*
27560160	Bologna sandwich on wheat, with cheese*
27560350	Pig in a blanket*
27560500	Pepperoni and salami submarine sandwich, with lettuce, tomato and spread*
27560520	Salami sandwich on white*
27560530	Salami sandwich on white, with cheese*
27560540	Salami sandwich on wheat*
27560550	Salami sandwich on wheat, with cheese*
27560610	Italian sandwich on white*
27560620	Italian sandwich on wheat*
27560630	Italian sandwich or sub, restaurant*
27560670	Sausage and cheese on English muffin*
27560710	Italian sausage sandwich on white*
27560715	Italian sausage sandwich on wheat*
27560910	Cold cut submarine sandwich, with cheese, lettuce, tomato and spread*

Food code	Food description
27560920	Spam sandwich*
27564000	Hot dog sandwich, NFS, on white bun*
27564001	Hot dog sandwich, NFS, on wheat bun*
27564002	Frankfurter or hot dog sandwich, NFS, plain, on whole wheat bun*
27564010	Hot dog sandwich, NFS, on white bread*
27564020	Hot dog sandwich, NFS, on wheat bread*
27564060	Hot dog sandwich, beef, on white bun*
27564061	Hot dog sandwich, beef, on wheat bun*
27564062	Frankfurter or hot dog sandwich, beef, plain, on whole wheat bun*
27564070	Hot dog sandwich, beef, on white bread*
27564080	Hot dog sandwich, beef, on wheat bread*
27564090	Frankfurter or hot dog sandwich, beef, plain, on whole wheat bread*
27564100	Frankfurter or hot dog sandwich, beef, plain, on whole grain white bread*
27564120	Frankfurter or hot dog sandwich, beef and pork, plain, on white bun*
27564121	Frankfurter or hot dog sandwich, beef and pork, plain, on wheat bun*
27564122	Frankfurter or hot dog sandwich, beef and pork, plain, on whole wheat bun*
27564130	Frankfurter or hot dog sandwich, beef and pork, plain, on white bread*
27564140	Frankfurter or hot dog sandwich, beef and pork, plain, on wheat bread*
27564150	Frankfurter or hot dog sandwich, beef and pork, plain, on whole wheat bread*
27564180	Hot dog sandwich, meat and poultry, on white bun*
27564181	Hot dog sandwich, meat and poultry, on wheat bun*
27564182	Frankfurter or hot dog sandwich, meat and poultry, plain, on whole wheat bun*
27564190	Hot dog sandwich, meat and poultry, on white bread*
27564200	Hot dog sandwich, meat and poultry, on wheat bread*
27564210	Frankfurter or hot dog sandwich, meat and poultry, plain, on whole wheat bread*
27564240	Hot dog sandwich, turkey, on white bun*
27564241	Hot dog sandwich, turkey, on wheat bun*
27564250	Hot dog sandwich, turkey, on white bread*
27564260	Hot dog sandwich, turkey, on wheat bread*
27564270	Frankfurter or hot dog sandwich, chicken and/or turkey, plain, on whole wheat bread*
27564290	Frankfurter or hot dog sandwich, chicken and/or turkey, plain, on multigrain bread*
27564300	Hot dog sandwich, reduced fat, on white bun*
27564301	Hot dog sandwich, reduced fat, on wheat bun*
27564310	Hot dog sandwich, reduced fat, on white bread*
27564320	Hot dog sandwich, reduced fat, on wheat bread*

Food code	Food description
27564360	Frankfurter or hot dog sandwich, fat free, plain, on white bun*
27564380	Frankfurter or hot dog sandwich, fat free, plain, on wheat bread*
27564418	Frankfurter or hot dog sandwich, reduced sodium*
27564420	Hot dog sandwich, vegetarian, on bun*
27564440	Chili hot dog sandwich, on white bun*
27564441	Chili hot dog sandwich, on wheat bun*
27564450	Chili hot dog sandwich, on white bread*
27564460	Chili hot dog sandwich, on wheat bread*
27564500	Frankfurter or hot dog sandwich, with meatless chili, on white bun*
27564520	Frankfurter or hot dog sandwich, with meatless chili, on wheat bread*
27580010	Multiple meat sandwich on white*
27580020	Multiple meat sandwich on white, with cheese*
27580030	Multiple meat sandwich on wheat*
27580040	Multiple meat sandwich on wheat, with cheese*
27580050	Multiple meat sandwich or sub, restaurant*
27580060	Multiple meat sandwich or sub, with cheese, restaurant*
27580110	Turkey and ham sandwich on white*
27580120	Turkey and ham sandwich on white, with cheese*
27580130	Turkey and ham sandwich on wheat*
27580140	Turkey and ham sandwich on wheat, with cheese*
27580150	Turkey and ham sandwich or sub, restaurant*
27580160	Turkey and ham sandwich or sub, with cheese, restaurant*
28310320	Beef noodle soup, Puerto Rican style*
28310330	Pho*
28315160	Italian Wedding Soup*
28340220	Chicken soup with noodles and potatoes, Puerto Rican style*
28340590	Chicken or turkey corn soup with noodles, home recipe*
32101500	Egg, Benedict*
32105190	Egg casserole with bread, cheese, milk and meat*
32202000	Egg, cheese, ham, and bacon on bun*
32202010	Egg, cheese, and ham on English muffin*
32202025	Egg, cheese and ham on bagel*
32202030	Egg, cheese, and sausage on English muffin*
32202034	Egg, cheese, and sausage on bun*
32202045	Egg, cheese, and steak on bagel*
32202080	Egg, cheese, and bacon on English muffin*
32202085	Egg, cheese and bacon on bagel*

Food code	Food description
32202120	Egg, cheese and sausage on bagel*
32203010	Egg salad sandwich on white*
32203020	Egg salad sandwich on wheat*
32204010	Scrambled egg sandwich*
32301100	Garlic egg soup, Puerto Rican style*
34001100	Egg sandwich on white bread*
34001110	Egg sandwich on white bread, with cheese*
34001120	Egg sandwich on white bread, with meat*
34001130	Egg sandwich on white bread, with meat and cheese*
34001200	Egg sandwich on wheat bread*
34001210	Egg sandwich on wheat bread, with cheese*
34001220	Egg sandwich on wheat bread, with meat*
34001230	Egg sandwich on wheat bread, with meat and cheese*
34001300	Egg sandwich on English muffin*
34001310	Egg sandwich on English muffin, with sausage*
34001320	Egg sandwich on English muffin, with bacon*
34001330	Egg sandwich on English muffin, with ham*
34001600	Egg sandwich on bagel*
34001610	Egg sandwich on bagel, with sausage*
34001620	Egg sandwich on bagel, with bacon*
34001630	Egg sandwich on bagel, with ham*
34002000	Egg white sandwich*
34002010	Egg white sandwich, with cheese*
34002020	Egg white sandwich, with meat*
34002150	Sausage English muffin sandwich*
41601090	Bean soup, with macaroni, home recipe, canned, or ready-to-serve*
41901010	Veggie burger, on bun*
41901020	Veggie burger, on bun, with cheese*
41901030	Falafel sandwich*
42301010	Peanut butter sandwich, NFS*
42301015	Peanut butter sandwich, with regular peanut butter, on white bread*
42301020	Peanut butter sandwich, with regular peanut butter, on wheat bread*
42301025	Peanut butter sandwich, with regular peanut butter, on whole wheat bread*
42301115	Peanut butter sandwich, with reduced fat peanut butter, on white bread*
42301120	Peanut butter sandwich, with reduced fat peanut butter, on wheat bread*
42301125	Peanut butter sandwich, with reduced fat peanut butter, on whole wheat bread*
42302010	Peanut butter and jelly sandwich, NFS*

Food code	Food description
42302015	Peanut butter and jelly sandwich, with regular peanut butter, regular jelly, on white bread*
42302020	Peanut butter and jelly sandwich, with regular peanut butter, regular jelly, on wheat bread*
42302025	Peanut butter and jelly sandwich, with regular peanut butter, regular jelly, on whole wheat bread*
42302055	Peanut butter and jelly sandwich, with reduced fat peanut butter, on white bread*
42302060	Peanut butter and jelly sandwich, with reduced fat peanut butter, on wheat bread*
42302065	Peanut butter and jelly sandwich, with reduced fat peanut butter, regular jelly, on whole wheat bread*
42302105	Peanut butter and jelly sandwich, with regular peanut butter, reduced sugar jelly, on white bread*
42302110	Peanut butter and jelly sandwich, with regular peanut butter, reduced sugar jelly, on wheat bread*
42302115	Peanut butter and jelly sandwich, with regular peanut butter, reduced sugar jelly, on whole wheat bread*
42302155	Peanut butter and jelly sandwich, with reduced fat peanut butter, reduced sugar jelly, on white bread*
42302160	Peanut butter and jelly sandwich, with reduced fat peanut butter, reduced sugar jelly, on wheat bread*
42302165	Peanut butter and jelly sandwich, with reduced fat peanut butter, reduced sugar jelly, on whole wheat bread*
42303100	Peanut butter and jelly sandwich, frozen commercial product without crusts*
42304020	Almond butter sandwich, on wheat bread*
42304030	Almond butter and jelly sandwich, on white bread*
42304040	Almond butter and jelly sandwich, on wheat bread*
42305010	Nutella sandwich on white bread*
42305020	Nutella sandwich on wheat bread*
51000100	Bread, NS as to major flour
51000110	Bread, NS as to major flour, toasted
51000180	Bread, made from home recipe or purchased at a bakery, NS as to major flour
51000200	Roll, NS as to major flour
51000300	Roll, hard, NS as to major flour
51000400	Roll, bran, NS as to type of bran
51101000	Bread, white
51101010	Bread, white, toasted
51101050	Bread, white, made from home recipe or purchased at a bakery
51101060	Bread, white, made from home recipe or purchased at a bakery, toasted
51102010	Bread, white with whole wheat swirl
51102020	Bread, white with whole wheat swirl, toasted
51105010	Bread, Cuban

Food code	Food description
51106010	Bread, native, water, Puerto Rican style
51107010	Bread, French or Vienna
51107040	Bread, French or Vienna, toasted
51108010	Focaccia, Italian, plain
51108100	Bread, naan
51109010	Bread, Italian, Grecian, Armenian
51109040	Bread, Italian, Grecian, Armenian, toasted
51109100	Bread, pita
51111010	Bread, cheese
51111040	Bread, cheese, toasted
51113010	Bread, cinnamon
51113100	Bread, cinnamon, toasted
51119010	Bread, egg, Challah
51119040	Bread, egg, Challah, toasted
51121015	Garlic bread, NFS
51121025	Garlic bread, from fast food / restaurant
51121035	Garlic bread, from frozen
51121045	Garlic bread, with parmesan cheese, from fast food / restaurant
51121055	Garlic bread, with parmesan cheese, from frozen
51121065	Garlic bread, with melted cheese, from fast food / restaurant*
51121075	Garlic bread, with melted cheese, from frozen
51121110	Bread, onion
51122000	Bread, reduced calorie and/or high fiber, white or NFS
51127010	Bread, potato
51127020	Bread, potato, toasted
51129010	Bread, raisin
51129020	Bread, raisin, toasted
51133010	Bread, sour dough
51133020	Bread, sour dough, toasted
51134000	Bread, sweet potato
51135000	Bread, vegetable
51136000	Bruschetta*
51140100	Bread, dough, fried
51150000	Roll, white, soft
51153000	Roll, white, hard
51154010	Roll, white, hot dog bun
51154100	Roll, white, hamburger bun

Food code	Food description
51154510	Roll, diet
51154550	Roll, egg bread
51154600	Roll, cheese
51155000	Roll, French or Vienna
51156500	Roll, garlic
51157000	Roll, white, hoagie, submarine
51158100	Roll, Mexican, bolillo
51159000	Roll, sour dough
51180010	Bagel
51180030	Bagel, with raisins
51180080	Bagel, with fruit other than raisins
51182010	Bread stuffing*
51182020	Bread stuffing made with egg*
51183990	Breadsticks, NFS
51184200	Breadsticks, soft, NFS
51184210	Breadsticks, soft, fast food / restaurant
51184220	Breadsticks, soft, frozen
51184230	Breadsticks, soft, with parmesan cheese, fast food / restaurant
51184240	Breadsticks, soft, with parmesan cheese, from frozen
51184250	Breadsticks, soft, topped with melted cheese
51184260	Breadsticks, soft, stuffed or topped with melted cheese
51186010	Muffin, English
51186100	Muffin, English, with raisins
51186130	Muffin, English, cheese
51186160	Muffin, English, with fruit other than raisins
51300050	Bread, whole grain white
51300060	Bread, whole grain white, toasted
51300100	Bagel, whole grain white
51300110	Bread, whole wheat
51300120	Bread, whole wheat, toasted
51300140	Bread, whole wheat, made from home recipe or purchased at bakery
51300150	Bread, whole wheat, made from home recipe or purchased at bakery, toasted
51300175	Bread, chappatti or roti
51300180	Bread, puri
51300185	Bread, paratha
51300210	Bread, whole wheat, with raisins
51300220	Bread, whole wheat, with raisins, toasted

Food code	Food description
51300300	Bread, sprouted wheat
51300310	Bread, sprouted wheat, toasted
51301010	Bread, wheat or cracked wheat
51301020	Bread, wheat or cracked wheat, toasted
51301040	Bread, wheat or cracked wheat, made from home recipe or purchased at bakery
51301050	Bread, wheat or cracked wheat, made from home recipe or purchased at bakery, toasted
51301120	Bread, wheat or cracked wheat, with raisins
51301130	Bread, wheat or cracked wheat, with raisins, toasted
51301510	Bread, wheat or cracked wheat, reduced calorie and/or high fiber
51301540	Bread, French or Vienna, whole wheat
51301550	Bread, French or Vienna, whole wheat, toasted
51301600	Bread, pita, whole wheat
51301620	Bread, pita, wheat or cracked wheat
51301700	Bagel, wheat
51301750	Bagel, whole wheat
51301800	Bagel, wheat, with raisins
51301805	Bagel, whole wheat, with raisins
51301900	Bagel, wheat bran
51302500	Muffin, English, wheat bran
51303010	Muffin, English, wheat or cracked wheat
51303030	Muffin, English, whole wheat
51303050	Muffin, English, wheat or cracked wheat, with raisins
51303070	Muffin, English, whole wheat, with raisins
51303100	Muffin, English, whole grain white
51320010	Roll, wheat or cracked wheat
51320060	Roll, wheat or cracked wheat, hot dog bun
51320070	Roll, wheat or cracked wheat, hamburger bun
51320500	Roll, whole wheat
51320550	Roll, whole wheat, hot dog bun
51320560	Roll, whole wheat, hamburger bun
51320700	Roll, whole grain white
51320710	Roll, whole grain white, hot dog bun
51320720	Roll, whole grain white, hamburger bun
51401010	Bread, rye
51401020	Bread, rye, toasted
51401030	Bread, marble rye and pumpernickel

Food code	Food description
51404010	Bread, pumpernickel
51404020	Bread, pumpernickel, toasted
51404500	Bagel, pumpernickel
51404550	Muffin, English, pumpernickel
51407010	Bread, black
51420000	Roll, rye
51501010	Bread, oatmeal
51501020	Bread, oatmeal, toasted
51501040	Bread, oat bran
51501050	Bread, oat bran, toasted
51501080	Bagel, oat bran
51601010	Bread, multigrain, toasted
51601020	Bread, multigrain
51601210	Bread, multigrain, with raisins
51602020	Bread, multigrain, reduced calorie and/or high fiber, toasted
51620000	Roll, multigrain
51620030	Roll, multigrain, hamburger bun
51630000	Bagel, multigrain
51630100	Bagel, multigrain, with raisins
51630200	Muffin, English, multigrain
51801010	Bread, barley
51801020	Bread, barley, toasted
51806010	Bread, rice
51807000	Injera, Ethiopian bread
51808000	Bread, gluten free
51808010	Bread, gluten free, toasted
51808100	Roll, gluten free
52201000	Cornbread, prepared from mix
52202060	Cornbread, made from home recipe
52204000	Cornbread stuffing
52206010	Cornbread muffin, stick, round
52206060	Cornbread muffin, stick, round, made from home recipe
53101100	Cake, angel food
53118100	Cake, sponge
54408400	Pretzels, soft, NFS
54408405	Pretzels, soft, ready-to-eat, NFS
54408410	Pretzels, soft, ready-to-eat, salted, buttered

Food code	Food description
54408411	Pretzels, soft, ready-to-eat, unsalted, buttered
54408415	Pretzels, soft, ready-to-eat, salted, no butter
54408416	Pretzels, soft, ready-to-eat, unsalted, no butter
54408420	Pretzels, soft, ready-to-eat, cinnamon sugar coated
54408422	Pretzels, soft, ready-to-eat, coated or flavored
54408430	Pretzels, soft, ready-to-eat, topped with meat
54408432	Pretzels, soft, ready-to-eat, topped with cheese
54408455	Pretzels, soft, from frozen, salted
54408456	Pretzels, soft, from frozen, unsalted
54408470	Pretzels, soft, filled with cheese
54408475	Pretzels, soft, from school lunch
54408480	Pretzels, soft, multigrain
54408485	Pretzels, soft, gluten free
56104000	Pasta, vegetable, cooked*
56112000	Noodles, cooked*
56113000	Noodles, whole grain, cooked*
56117090	Rice noodles, cooked*
56130000	Pasta, cooked*
56132990	Pasta, whole grain, cooked*
56140100	Pasta, gluten free*
58127500	Vegetable submarine sandwich, with fat free spread*
58128210	Dressing with oysters*
58128220	Dressing with chicken or turkey and vegetables*
58128250	Dressing with meat and vegetables*
58130011	Lasagna with meat*
58130014	Lasagna with meat, from restaurant*
58130015	Lasagna with meat, home recipe*
58130020	Lasagna with meat and spinach*
58130140	Lasagna with chicken or turkey*
58130150	Lasagna, with chicken or turkey, and spinach*
58130310	Lasagna, meatless*
58130320	Lasagna, meatless, with vegetables*
58131110	Ravioli, NS as to filling, with tomato sauce*
58131120	Ravioli, NS as to filling, with cream sauce*
58131310	Ravioli, meat-filled, no sauce*
58131320	Ravioli, meat-filled, with tomato sauce or meat sauce*
58131330	Ravioli, meat-filled, with cream sauce*

Food code	Food description
58131510	Ravioli, cheese-filled, no sauce*
58131520	Ravioli, cheese-filled, with tomato sauce*
58131530	Ravioli, cheese-filled, with meat sauce*
58131535	Ravioli, cheese-filled, with cream sauce*
58131590	Ravioli, cheese and spinach-filled, no sauce*
58131600	Ravioli, cheese and spinach-filled, with cream sauce*
58131610	Ravioli, cheese and spinach filled, with tomato sauce*
58133110	Manicotti, cheese-filled, no sauce*
58133120	Manicotti, cheese-filled, with tomato sauce, meatless*
58134120	Stuffed shells, cheese-filled, with tomato sauce, meatless*
58134130	Stuffed shells, cheese-filled, with meat sauce*
58134160	Stuffed shells, cheese- and spinach- filled, no sauce*
58134210	Stuffed shells, with chicken, with tomato sauce*
58134610	Tortellini, meat-filled, with tomato sauce*
58134620	Tortellini, cheese-filled, meatless, with tomato sauce*
58134640	Tortellini, cheese-filled, meatless, with vinaigrette dressing*
58134650	Tortellini, meat-filled, no sauce*
58134660	Tortellini, cheese-filled, with cream sauce*
58134680	Tortellini, cheese-filled, no sauce*
58134710	Tortellini, spinach-filled, with tomato sauce*
58134720	Tortellini, spinach-filled, no sauce*
58135110	Chow fun noodles with meat and vegetables*
58135120	Chow fun noodles with vegetables, meatless*
58137220	Pad Thai, meatless*
58137230	Pad Thai with chicken*
58137240	Pad Thai with seafood*
58137250	Pad Thai with meat*
58145110	Macaroni or noodles with cheese*
58145111	Macaroni or noodles with cheese, from restaurant*
58145120	Macaroni or noodles with cheese and tuna*
58145135	Macaroni or noodles with cheese and meat*
58145140	Macaroni or noodles with cheese and tomato*
58145160	Macaroni or noodles with cheese and frankfurters or hot dogs*
58145170	Macaroni or noodles with cheese and egg*
58145190	Macaroni or noodles with cheese and chicken or turkey*
58145300	Macaroni or noodles with cheese, whole grain*
58146120	Pasta with tomato-based sauce, cheese and meat*

Food code	Food description
58146150	Pasta with tomato-based sauce and cheese*
58146160	Pasta with vegetables, no sauce or dressing*
58146210	Pasta with sauce, NFS*
58146215	Pasta with sauce, meatless, school lunch*
58146221	Pasta with tomato-based sauce, restaurant*
58146222	Pasta with tomato-based sauce, home recipe*
58146223	Pasta with tomato-based sauce, ready-to-heat*
58146301	Pasta with tomato-based sauce, and added vegetables, restaurant*
58146302	Pasta with tomato-based sauce, and added vegetables, home recipe*
58146303	Pasta with tomato-based sauce, and added vegetables, ready-to-heat*
58146315	Pasta with sauce and meat, from school lunch*
58146321	Pasta with tomato-based sauce and meat, restaurant*
58146322	Pasta with tomato-based sauce and meat, home recipe*
58146323	Pasta with tomato-based sauce and meat, ready-to-heat*
58146331	Pasta with tomato-based sauce, meat, and added vegetables, restaurant*
58146332	Pasta with tomato-based sauce, meat, and added vegetables, home recipe*
58146333	Pasta with tomato-based sauce, meat, and added vegetables, ready-to-heat*
58146341	Pasta with tomato-based sauce and poultry, restaurant*
58146342	Pasta with tomato-based sauce and poultry, home recipe*
58146343	Pasta with tomato-based sauce and poultry, ready-to-heat*
58146352	Pasta with tomato-based sauce, poultry, and added vegetables, home recipe*
58146361	Pasta with tomato-based sauce and seafood, restaurant*
58146362	Pasta with tomato-based sauce and seafood, home recipe*
58146371	Pasta with tomato-based sauce, seafood, and added vegetables, restaurant*
58146372	Pasta with tomato-based sauce, seafood, and added vegetables, home recipe*
58146381	Pasta with cream sauce, restaurant*
58146382	Pasta with cream sauce, home recipe*
58146383	Pasta with cream sauce, ready-to-heat*
58146391	Pasta with cream sauce and added vegetables, restaurant*
58146392	Pasta with cream sauce and added vegetables, from home recipe*
58146393	Pasta with cream sauce and added vegetables, ready-to-heat*
58146401	Pasta with cream sauce and meat, restaurant*
58146402	Pasta with cream sauce and meat, home recipe*
58146403	Pasta with cream sauce and meat, ready-to-heat*
58146411	Pasta with cream sauce, meat, and added vegetables, restaurant*
58146412	Pasta with cream sauce, meat, and added vegetables, home recipe*
58146413	Pasta with cream sauce, meat, and added vegetables, ready-to-heat*

Food code	Food description
58146421	Pasta with cream sauce and poultry, restaurant*
58146422	Pasta with cream sauce and poultry, home recipe*
58146423	Pasta with cream sauce and poultry, ready-to-heat*
58146431	Pasta with cream sauce, poultry, and added vegetables, restaurant*
58146432	Pasta with cream sauce, poultry, and added vegetables, home recipe*
58146433	Pasta with cream sauce, poultry, and added vegetables, ready-to-heat*
58146441	Pasta with cream sauce and seafood, restaurant*
58146442	Pasta with cream sauce and seafood, home recipe*
58146443	Pasta with cream sauce and seafood, ready-to-heat*
58146451	Pasta with cream sauce, seafood, and added vegetables, restaurant*
58146452	Pasta with cream sauce, seafood, and added vegetables, home recipe*
58146601	Pasta, whole grain, with tomato-based sauce, restaurant*
58146602	Pasta, whole grain, with tomato-based sauce, home recipe*
58146603	Pasta, whole grain, with tomato-based sauce, ready-to-heat*
58146612	Pasta, whole grain, with tomato-based sauce and added vegetables, home recipe*
58146622	Pasta, whole grain, with tomato-based sauce and meat, home recipe*
58146623	Pasta, whole grain, with tomato-based sauce and meat, ready-to-heat*
58146631	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, restaurant*
58146632	Pasta, whole grain, with tomato-based sauce, meat, and added vegetables, home recipe*
58146641	Pasta, whole grain, with tomato-based sauce and poultry, restaurant*
58146642	Pasta, whole grain, with tomato-based sauce and poultry, home recipe*
58146652	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, home recipe*
58146653	Pasta, whole grain, with tomato-based sauce, poultry, and added vegetables, ready-to-heat*
58146672	Pasta, whole grain, with tomato-based sauce, seafood, and added vegetables, home recipe*
58146682	Pasta, whole grain, with cream sauce, home recipe*
58146683	Pasta, whole grain, with cream sauce, ready-to-heat*
58146692	Pasta, whole grain, with cream sauce, and added vegetables, home recipe*
58146713	Pasta, whole grain, with cream sauce, meat, and added vegetables, ready-to-heat*
58146722	Pasta, whole grain, with cream sauce and poultry, home recipe*
58146723	Pasta, whole grain, with cream sauce and poultry, ready-to-heat*
58146731	Pasta, whole grain, with cream sauce, poultry, and added vegetables, restaurant*
58146732	Pasta, whole grain, with cream sauce, poultry, and added vegetables, home recipe*
58146733	Pasta, whole grain, with cream sauce, poultry, and added vegetables, ready-to-heat*

Food code	Food description
58147330	Macaroni or noodles, creamed, with cheese*
58147340	Macaroni or noodles, creamed, with cheese and tuna*
58147510	Flavored pasta*
58147520	Yat Ga Mein with meat, fish, or poultry*
58148110	Macaroni or pasta salad, made with mayonnaise*
58148111	Macaroni or pasta salad, made with light mayonnaise*
58148112	Macaroni or pasta salad, made with mayonnaise-type salad dressing*
58148114	Macaroni or pasta salad, made with Italian dressing*
58148118	Macaroni or pasta salad, made with any type of fat free dressing*
58148120	Macaroni or pasta salad with egg*
58148130	Macaroni or pasta salad with tuna*
58148150	Macaroni or pasta salad with shrimp*
58148160	Macaroni or pasta salad with tuna and egg*
58148170	Macaroni or pasta salad with chicken*
58148180	Macaroni or pasta salad with cheese*
58148550	Macaroni or pasta salad with meat*
58200210	Vegetable sandwich on white*
58200220	Vegetable sandwich on white, with cheese*
58200230	Vegetable sandwich on wheat*
58200240	Vegetable sandwich on wheat, with cheese*
58201005	Jelly sandwich, on white bread*
58201015	Jelly sandwich, on wheat bread*
58201025	Jelly sandwich, regular jelly, on whole wheat bread*
58201035	Jelly sandwich, reduced sugar jelly, on white bread*
58400100	Noodle soup, NFS*
58402100	Beef noodle soup, home recipe*
58403040	Chicken or turkey noodle soup, home recipe*
58407010	Instant soup, noodle*
58407030	Soup, mostly noodles*
58408500	Noodle soup with vegetables, Asian style*
58409000	Noodle soup, with fish ball, shrimp, and dark green leafy vegetable*
58421010	Sopa Seca de Fideo, Mexican style, made with dry noodles, home recipe*
58421020	Sopa de Fideo Aguada, Mexican style noodle soup, home recipe*
72202010	Broccoli casserole with noodles*
74701000	Tomato sandwich on white*
74701010	Tomato sandwich on wheat*
75460900	Chow mein or chop suey, meatless, with noodles*

Food code	Food description
75608100	Onion soup, French*
75649150	Vegetable noodle soup, home recipe*
75651000	Minestrone soup, home recipe*
75652040	Vegetable beef soup with noodles or pasta, home recipe*
<i>Snack bars</i>	
53710400	Cereal or granola bar (General Mills Fiber One Chewy Bar)
53710500	Cereal or granola bar (Kellogg's Nutri-Grain Cereal Bar)
53710502	Cereal or granola bar (Kellogg's Nutri-Grain Yogurt Bar)
53710504	Cereal or granola bar (Kellogg's Nutri-Grain Fruit and Nut Bar)
53710600	Milk 'n Cereal bar
53710700	Cereal or granola bar (Kellogg's Special K bar)
53710800	Cereal or granola bar (Kashi Chewy)
53710802	Cereal or granola bar (Kashi Crunchy)
53710810	Cereal or granola bar (KIND Fruit and Nut Bar)
53710900	Cereal or granola bar (General Mills Nature Valley Chewy Trail Mix)
53710902	Cereal or granola bar, with yogurt coating (General Mills Nature Valley Chewy Granola Bar)
53710904	Cereal or granola bar (General Mills Nature Valley Sweet and Salty Granola Bar)
53710906	Cereal or granola bar (General Mills Nature Valley Crunchy Granola Bar)
53711000	Cereal or granola bar (Quaker Chewy Granola Bar)
53711002	Cereal or granola bar (Quaker Chewy 90 Calorie Granola Bar)
53711004	Cereal or granola bar (Quaker Chewy 25% Less Sugar Granola Bar)
53711006	Cereal or granola bar (Quaker Chewy Dipps Granola Bar)
53712000	Snack bar, oatmeal
53712100	Cereal or Granola bar, NFS
53712200	Cereal or granola bar, low fat, NFS
53712210	Cereal or granola bar, nonfat
53713010	Cereal or granola bar, fruit and nut
53714200	Cereal or granola bar, chocolate coated, NFS
53714210	Cereal or granola bar, with coconut, chocolate coated
53714220	Cereal or granola bar with nuts, chocolate coated
53714230	Cereal or granola bar, oats, nuts, coated with non-chocolate coating
53714250	Cereal or granola bar, coated with non-chocolate coating
53714300	Cereal or granola bar, high fiber, coated with non-chocolate yogurt coating
53714400	Cereal or granola bar, with rice cereal
53714500	Breakfast bar, NFS
53714520	Breakfast bar, cereal crust with fruit filling, lowfat

Food code	Food description
Snack Foods	
<i>Snacks</i>	
41310900	Bean chips
53239100	Pocky
54318000	Chips, rice
54401011	Corn nuts
54401021	Corn chips, plain
54401026	Corn chips, flavored
54401031	Corn chips, plain (Fritos)
54401035	Corn chips, flavored (Fritos)
54401055	Cheese flavored corn snacks
54401065	Cheese flavored corn snacks, reduced fat
54401075	Tortilla chips, plain
54401081	Cheese flavored corn snacks (Cheetos)
54401085	Tortilla chips, flavored
54401090	Corn chips, reduced sodium
54401110	Tortilla chips, nacho cheese flavor (Doritos)
54401111	Tortilla chips, cool ranch flavor (Doritos)
54401112	Tortilla chips, other flavors (Doritos)
54401121	Tortilla chips, reduced fat, plain
54401122	Tortilla chips, reduced fat, flavored
54401170	Tortilla chips, low fat, unsalted
54402080	Tortilla chips, reduced sodium
54402200	Snack mix
54403001	Popcorn, NFS
54403005	Popcorn, movie theater, with added butter
54403006	Popcorn, movie theater, no butter added
54403010	Popcorn, air-popped, no butter added
54403040	Popcorn, air-popped, with added butter
54403045	Popcorn, popped in oil, no butter added
54403046	Popcorn, popped in oil, with added butter
54403051	Popcorn, microwave, NFS
54403052	Popcorn, microwave, plain
54403053	Popcorn, microwave, plain, light
54403054	Popcorn, microwave, low sodium
54403055	Popcorn, microwave, unsalted
54403056	Popcorn, microwave, butter flavored

Food code	Food description
54403057	Popcorn, microwave, flavored, light
54403058	Popcorn, microwave, cheese flavored
54403059	Popcorn, microwave, kettle
54403061	Popcorn, microwave, kettle corn, light
54403062	Popcorn, microwave, other flavored
54403080	Popcorn, ready-to-eat, NFS
54403081	Popcorn, ready-to-eat, plain
54403082	Popcorn, ready-to-eat, plain, light
54403083	Popcorn, ready-to-eat, low sodium
54403085	Popcorn, ready-to-eat, butter flavored
54403086	Popcorn, ready-to-eat packaged, butter flavored, light
54403087	Popcorn, ready-to-eat, cheese flavored
54403088	Popcorn, ready-to-eat, flavored, light
54403089	Popcorn, ready-to-eat, kettle
54403091	Popcorn, ready-to-eat packaged, kettle corn, light
54403092	Popcorn, ready-to-eat packaged, other flavored
54403110	Popcorn, caramel coated
54403120	Popcorn, caramel coated, with nuts
54403160	Popcorn, chocolate coated
54404000	Popcorn chips, plain
54404010	Popcorn chips, other flavors
54404020	Popcorn chips, sweet flavors
54406010	Onion flavored rings
54406200	Shrimp chips
54408000	Pretzels, NFS
54408015	Pretzels, hard, NFS
54408016	Pretzels, hard, plain, salted
54408017	Pretzels, hard, plain, lightly salted
54408030	Pretzels, hard, plain, unsalted
54408035	Pretzels, hard, flavored
54408070	Pretzels, hard, multigrain
54408081	Pretzels, hard, plain, gluten free
54408082	Pretzels, hard, flavored, gluten free
54408105	Pretzel chips, hard, plain
54408110	Pretzel chips, hard, flavored
54408115	Pretzel chips, hard, gluten free
54408190	Pretzels, hard, coated, NFS

Food code	Food description
54403057	Popcorn, microwave, flavored, light
54403058	Popcorn, microwave, cheese flavored
54403059	Popcorn, microwave, kettle
54403061	Popcorn, microwave, kettle corn, light
54403062	Popcorn, microwave, other flavored
54403080	Popcorn, ready-to-eat, NFS
54403081	Popcorn, ready-to-eat, plain
54403082	Popcorn, ready-to-eat, plain, light
54403083	Popcorn, ready-to-eat, low sodium
54403085	Popcorn, ready-to-eat, butter flavored
54403086	Popcorn, ready-to-eat packaged, butter flavored, light
54403087	Popcorn, ready-to-eat, cheese flavored
54403088	Popcorn, ready-to-eat, flavored, light
54403089	Popcorn, ready-to-eat, kettle
54403091	Popcorn, ready-to-eat packaged, kettle corn, light
54403092	Popcorn, ready-to-eat packaged, other flavored
54403110	Popcorn, caramel coated
54403120	Popcorn, caramel coated, with nuts
54403160	Popcorn, chocolate coated
54404000	Popcorn chips, plain
54404010	Popcorn chips, other flavors
54404020	Popcorn chips, sweet flavors
54406010	Onion flavored rings
54406200	Shrimp chips
54408000	Pretzels, NFS
54408015	Pretzels, hard, NFS
54408016	Pretzels, hard, plain, salted
54408017	Pretzels, hard, plain, lightly salted
54408030	Pretzels, hard, plain, unsalted
54408035	Pretzels, hard, flavored
54408070	Pretzels, hard, multigrain
54408081	Pretzels, hard, plain, gluten free
54408082	Pretzels, hard, flavored, gluten free
54408105	Pretzel chips, hard, plain
54408110	Pretzel chips, hard, flavored
54408115	Pretzel chips, hard, gluten free
54408190	Pretzels, hard, coated, NFS

Food code	Food description
54408200	Pretzels, hard, chocolate coated
54408210	Pretzels, hard, white chocolate coated
54408250	Pretzels, hard, yogurt coated
54408260	Pretzels, hard, coated, gluten free
54408300	Pretzels, hard, cheese filled
54408310	Pretzels, hard, peanut butter filled
54420210	Multigrain chips (Sun Chips)
54420220	Snack mix, plain (Chex Mix)
54440020	Cracker chips
71200010	Potato chips, NFS
71200100	Potato chips, plain
71200110	Potato chips, barbecue flavored
71200120	Potato chips, sour cream and onion flavored
71200130	Potato chips, cheese flavored
71200140	Potato chips, other flavored
71200200	Potato chips, ruffled, plain
71200210	Potato chips, ruffled, barbecue flavored
71200220	Potato chips, ruffled, sour cream and onion flavored
71200230	Potato chips, ruffled, cheese flavored
71200240	Potato chips, ruffled, other flavored
71200300	Potato chips, restructured, plain
71200310	Potato chips, restructured, flavored
71200400	Potato chips, baked, plain
71200410	Potato chips, baked, flavored
71201050	Potato chips, reduced fat
71201060	Potato chips, fat free
71201200	Potato chips, restructured, reduced fat, lightly salted
71202000	Potato chips, unsalted
71202500	Potato chips, lightly salted
71202510	Potato chips, restructured, lightly salted
71203010	Potato chips, popped, plain
71203020	Potato chips, popped, flavored
71203030	Potato chips, popped, NFS
71205020	Potato sticks, plain
71205030	Potato sticks, flavored
71205040	Potato sticks, fry shaped
71220000	Vegetable chips

Food code	Food description
71905410	Plantain chips
71980200	Taro chips
73410210	Sweet potato chips
<i>Crackers that are usually used as snacks</i>	
51185000	Croutons
53210900	Cookie, graham cracker with chocolate and marshmallow
53240000	Cookie, animal
53240010	Cookie, animal, with frosting or icing
53246000	Cookie, tea, Japanese
54001000	Crackers, NFS
54102010	Graham crackers
54102015	Graham crackers (Teddy Grahams)
54102020	Graham crackers, chocolate covered
54102050	Crackers, oatmeal
54102100	Graham crackers, reduced fat
54102200	Graham crackers, sandwich, with filling
54103000	Crackers, breakfast biscuit
54200100	Crackers, butter, reduced sodium
54201010	Crackers, matzo, reduced sodium
54204020	Crackers, wheat, reduced sodium
54204030	Crackers, woven wheat, reduced sodium
54301010	Crackers, butter, plain
54301020	Crackers, butter, flavored
54301030	Crackers, butter (Ritz)
54301100	Crackers, butter, reduced fat
54304000	Crackers, cheese
54304005	Crackers, cheese (Cheez-It)
54304020	Crackers, cheese (Goldfish)
54304100	Crackers, cheese, reduced fat
54304110	Crackers, cheese, reduced sodium
54304150	Crackers, cheese, whole grain
54305010	Crackers, crispbread
54305020	Crackers, flatbread
54305500	Crispbread, wheat or rye, extra crispy
54307000	Crackers, matzo
54318500	Rice cake
54319000	Crackers, rice

Food code	Food description
54319005	Crackers, rice and nuts
54319020	Popcorn cake
54319500	Rice paper
54326000	Crackers, multigrain
54328000	Crackers, sandwich
54328100	Crackers, sandwich, peanut butter filled
54328105	Crackers, sandwich, peanut butter filled (Ritz)
54328110	Crackers, sandwich, reduced fat, peanut butter filled
54328120	Crackers, whole grain, sandwich, peanut butter filled
54328200	Crackers, sandwich, cheese filled
54328210	Crackers, sandwich, cheese filled (Ritz)
54336000	Crackers, water
54336100	Crackers, wonton
54337010	Crackers, woven wheat
54337020	Crackers, woven wheat, plain (Triscuit)
54337030	Crackers, woven wheat, flavored (Triscuit)
54337060	Crackers, woven wheat, reduced fat
54338000	Crackers, wheat
54338010	Crackers, wheat, plain (Wheat Thins)
54338020	Crackers, wheat, flavored (Wheat Thins)
54338100	Crackers, wheat, reduced fat
54339000	Crackers, corn
54340100	Crackers, gluten free, plain
54340110	Crackers, gluten free, flavored
54402700	Pita chips
54440010	Bagel chips
56116000	Noodles, chow mein

* Only the proportion of the food mixture corresponding to the intended food use was included in the analysis.

** Non-reconstituted amount adjusted to the reconstituted/prepared amount and included in the analysis.

Appendix E. Dietary Supplement Ingredients (including blends) Included in the Background Exposure Estimate (NHANES 2017- 2020)

Ingredient ID	Ingredient Name
177	Iodine
184	Kelp
633	Herbal Blend For Multivitamin With Herbs*
641	Kelp Powder (FronD)
796	Kelp (Whole Plant)
826	Nutrilite Concentrate Blend*
841	Ocean Kelp
892	Pacific Kelp Powder (Whole)
1096	Solgar Special Natural Powdered Blend*
1147	Solaray Hawthorn Motherwort Blend*
1262	Kyo-Green Blend*
1592	Bladderwrack (Leaf)
1636	Thermochrome Proprietary Blend*
1711	T-Lite Proprietary Blend*
1739	Nature's Sunshine Zinc Proprietary Blend*
1762	Xtra-Cal Exclusive Blend*
1790	Vitalerbs Proprietary Blend*
1872	Combination Potassium Proprietary Blend*
1887	Ts-Ii Thyroid Proprietary Blend*
2010	Martrim Proprietary Blend*
2100	Super Power Trim Proprietary Blend*
2107	Dexatrim Results Proprietary Blend #1 Ephedrine Free*
2114	Dexatrim Results Proprietary Herbal Blend #1 W/ Ephedrine*
2126	Kelp (FronD)
2209	Sp Min-Chex Proprietary Blend*
2267	Electrim Diet Formula Proprietary Blend*
2356	Now Proprietary Herb Blend*
2359	Classic Proprietary Blend*
2437	Watkins Metabolic Support Blend*
2438	Bladderwrack (Kelp)
2445	Kelp (Laminaria Digitata)
2446	Kelp (Alaria Esculenta)
2450	Kelp (Ascophyllum Nodosum)
2574	Solgar Formula Vm-75 Natural Powdered Blend*
2582	Kidgreenz Superfood Complex*
2625	Fibrestore Proprietary Blend*

Ingredient ID	Ingredient Name
2648	Nature's Herbs Sea Kelp Combination Proprietary Herbal Blend*
2684	All One Base Blend*
2691	Kelp (Macrocystis Pyrifera)
2712	Nature's Sunshine Trace Mineral Concentrate*
2742	Trimspa Appetite Control Blend*
2801	Perfect Protein-Mineral Blend*
2831	Nutri Stars 4:1 Herbal Extracts*
2882	Experience Mediterranean Proprietary Blend*
3077	Power Thin Proprietary Blend*
3079	Bladderwrack
3097	Solgar Natural Powdered Blend #2*
3348	Herbalife Xtra-Cal Exclusive Blend*
3410	All In One Herbal Blend Extract Standardized 1:4*
3464	Feeling Young Fruit And Vegetable Extract Complex*
3492	Night Burner Proprietary Blend*
3537	Norwegian Sea Kelp
3645	Atkins Thyroplex Blend*
3723	Nutritionalysis Synergistic Herbal Blend*
3735	Hgh Youth Formula Proprietary Blend*
3806	Seasilver Proprietary Blend*
3875	Nature's Sunshine Thyroid Activator Proprietary Blend*
3880	Nature's Sunshine Metabomax Proprietary Blend*
3895	Nova Scotia And Pacific Kelp
3919	Barlean's Sea Vegetable Blend*
4046	Body Balance Proprietary Blend*
4171	Altrum Sea Vegetable Complex*
4189	Mega-T Metabolic Support Blend*
4191	Vision For Life Gentle Body Cleanse Proprietary Blend*
4361	Garden Of Life Phytonutrient Blend*
4374	Nature's Sunshine Energ-V Proprietary Blend*
4411	Nature's Way Akn Proprietary Blend*
4544	Reliv Classic Proprietary Blend #2*
4574	Kelp (Porphyra)
4591	Mannatech Advanced Ambrotose Complex*
4640	Reliv Arthaeffect Proprietary Blend*
4642	Reliv Now Improved Formula Proprietary Herb Blend*
4718	Sea Vegg Pristine Ocean Blend*
4774	Garden Of Life Perfect Protein Mineral Blend*
4917	Rexall Super Plenamins Plus Proprietary Blend*
5003	Nature's Way Alive! Green Food/Spirulina Blend #2*

Ingredient ID	Ingredient Name
5079	Generic8 Very Green Proprietary Green Mix Blend*
5096	Nature's Plus Kidgreenz Superfood Complex #2*
5101	Twinlab Super Food Blend*
5112	Herbalife Schizandra Plus Exclusive Blend*
5330	Nioxin Recharging Complex Proprietary Blend*
5441	Genesis Today Proprietary Sea Vegetable Blend*
5603	Whole Foods Greens Blend Sea Vegetable Blend*
5611	Super Green Tea Diet Proprietary Blend*
5670	First Cleanse Renew Life First Cleanse 1 Proprietary Blend*
5681	Awarenesslife Daily Complete Proprietary Blend*
5699	Trimform Rapid Weight Loss Solution Blend*
5729	Solaray Kidney Blend Sp-6*
5732	Solaray Liver Blend Sp-13*
5785	Solaray Whole Food And Herb Base #2*
5869	All One Green Phyto Base Multiple Vitamin & Mineral Powder Base*
5871	All One Green Phyto Base Multiple Vitamin & Mineral Powder Kelp Blend*
5960	Green Tea Fat Burner Xenedrol Blend*
5990	Roex Celltalk Proprietary Blend*
5993	Kelp Powder
6064	Liquid Health Complete Multiple Organ Cleanse & Detox Support Blend*
6246	Nature's Secret Multi-Herb Proprietary Blend #2*
6271	Reliv Classic Proprietary Blend #3*
6447	Mannatech Advanced Ambrotose Complex #2*
6462	Nsi Nutraceutical Sciences Institute Whole Food Shake Green Foods Blend*
6490	Trace Minerals Research Greens Pak Antioxidant Blend*
6493	Atlantic Kelp Powder
6512	Ephedra-Hoodia Fusion Proprietary Fusion Blend*
6648	Kelp (Whole Thallus)
6774	Rainbow Light Advanced Enzyme System Sea Vegetable Complex*
6785	Mason Natural Super Multiple Proprietary Blend*
6815	Nutrilite Concentrate Blend #2*
6896	North Atlantic Kelp
6962	Delicious Greens 8000 The Original! Xtraimmunaid Blend*
7006	Life's Fortune Multi-Vitamin & Mineral Proprietary Blend*
7025	Irwin Naturals Fruit And Vegetable Botanical Blend*
7097	Garden Of Life Poten-Zyme Sea Veggie Blend*
7134	Solaray Detox Blend Sp-25 Proprietary Blend*
7138	Mega-T Green Tea Now With South Africian Hoodia Proprietary Blend*
7224	Nutrapathic Multiple 'Plus' Proprietary Blend*
7231	Rainbow Light Protective Phyto-Nutrient Foods Blend*

Ingredient ID	Ingredient Name
7256	Atlantic Kelp
7302	Green Tea Fat Burner Essential Vitality Blend*
7305	Bladderwrack Powder
7330	Fucoxanthin Rich Seaweed
7546	Nioxin Recharging Complex Proprietary Blend #2*
7683	Migenetics African Origin Proprietary Blend*
7728	Nature's Sunshine Combination Potassium Proprietary Blend*
7729	Kelp (Stems & Leaves)
7759	All One Green Phyto Base Blend*
7815	Applied Nutrition 14-Day Fat Burn Cleanse Thermogenic Component And Antioxidant Blend*
7927	Doterra Microplex Vmz Proprietary Whole-Food Blend*
8072	Nature's Way Alive! Green Food/Spirulina Blend #4*
8211	Nature's Way Alive! Green Food/Spirulina Blend #5*
8315	Women's 73 Nutrient Soft-Gel Multi Nature's Secret Fruit And Vegetable Blend*
8370	Ultimate Youth Proprietary Greens-Veggie Blend*
8402	Juicefestiv Veggiefestiv Vegetable Blend*
8451	Symmetry Symply Magic Proprietary Blend*
8459	Gnc Ultra Mega Green Greens Blend*
8489	Solgar Natural Powdered Blend #3*
8517	Innate Response Formulas Adrenal Response Blend*
8673	Nature's Sunshine Super Supplemental Herbal And Protector Shield Proprietary Blend*
8703	Nutriline Concentrate Blend #3*
8874	Gnc Ultra Mega Green Greens Blend #2*
8889	Nature's Way Alive! Green Food/Spirulina Blend #6*
9099	21st Century Hair, Skin & Nails Proprietary Herbal Support Blend*
9135	Maritzmayer Laboratories Raspberry Ketone Lean Proprietary Formula*
9244	Stemenhance Se2 Stemrelease Proprietary Blend*
9260	Bladderwrack Leaf Extract
9346	Stemvida International Stemalive Proprietary Blend*
9461	Brown Seaweed (Whole Plant)
9512	Bladderwrack (Whole Plant)
9570	Genesis Pure Daily Build Pure Organic Sea Vegetable Blend*
9772	All One Proprietary Digestive Blend*
9991	Life's Fortune Multi-Vitamin & Mineral Proprietary Blend #2*
9994	Kelp (Thallus)
10034	Bio Slim Biolife Hc Proprietary Blend*
10039	Limu Original Proprietary Limu Original Blend*
10075	Digestzen Zendocrine Whole-Food Detox Blend*

Ingredient ID	Ingredient Name
10123	Pure Herbs, Ltd. T.-W Proprietary Blend*
10226	Default Proprietary Digestive Blend*
10253	Solgar Natural Powdered Blend #4*
10269	Ivl Institute For Vibrant Living All Day Energy Greens Proprietary Blend*
10359	Rainbow Light Advanced Enzyme System Sea Vegetable Complex #2*
10367	Solaray Whole Food And Herb Base #3*
10466	Tone Clinical Tone Gt Adipoblast Blend*
10745	Nature's Plus Source Of Life Animal Parade Kidgreenz Superfood Complex*
10754	Nature's Sunshine Super Supplemental Herbal And Protector Shield Proprietary Blend*
10819	Garden Of Life Mykind Organics Certified Organic Food Blend #2*
10857	Doterra Microplex Vmz Proprietary Whole-Food Blend #2*
10906	Natrol Juicefestiv Daily Veggie Organic Vegetable Blend*
10916	Premium Nutrition Thyroprime Food & Spice Blend*
10930	Brown Algae Extract (Stem & Leaf)
10939	Young Living Essential Oils Multigreens Proprietary Multigreens Blend*
10983	Dr. Christopher's Original Formulas Kid-E-Mins Proprietary Blend*
11072	Sp Standard Process Trace Minerals-B12 Proprietary Blend*
11179	It Works! Hair Skin Nails Proprietary Blend*
11196	Walgreens Green Tea Metabolism Enhancer Blend*
11263	Garden Of Life Mykind Organics Certified Organic Food Blend #4*
11332	Rainbow Light Nutri Stars Herbal Tonics 4:1 Extracts*
11377	Ascophyllum Nodosum Powder
11455	Mediplan Diet Services Lipo Caps Proprietary Blend*
11582	Mp Musclepharm Armor-V Superfood Blend*
11598	Arnold Iron Pack Super Food Blend*
11612	Nutrilite Concentrate Blend #4*
11640	Thyromend Douglas Laboratories Proprietary Blend*
11737	Dynamic Fruits & Greens Vegetable Antioxidant Blend*
11761	Transformations Weight Loss Multi-Vitamin And Mineral Proprietary Blend*
11786	Generic48 Advanced Formula Hair, Skin & Nails Proprietary Herbal Support Blend*
11850	Le-Vel Thrive M Proprietary Blend*
11857	Le-Vel Thrive W Proprietary Blend*
11858	Marked Maximum Nutrition Daily Pack Whole Food Enhanced Multivitamin Greens Blend*
11871	Only Natural For Women Only Super Food Proprietary Blend*
11914	Pure Essence Labs One 'N' Only Superfood Complex*
12055	Nature's Way Alive! Daily Greens Blend #2*
12298	Solgar Herbal Powdered Blend*
12312	Natrol Juicefestiv Daily Veggie Organic Vegetable Blend #2*

Ingredient ID	Ingredient Name
12347	Modere Trimblend*
12417	Optim Nutrition Supreme Liquid Multivitamin Fruit And Vegetable Blend*
12605	Liquid Health Complete Multiple Super-Phyto Food Complex #2*
12623	Nature's Sunshine Herbal Trace Minerals Proprietary Blend*
12634	Nature's Sunshine Thyroid Activator Proprietary Blend #2*
13080	The Mane Choice Manetabolism Plus Proprietary Blend*
13133	Floradix Iron + Herbs Liquid Extract Formula Proprietary Blend Aqueous Extract*
13167	Generic50 Mega Source Green Tea Metabolism Enhancer Blend*
13315	Young Living Essential Oils Proprietary Master Formula Capsule Blend*
13371	Kelp Thallus Extract
13393	Rainbow Light Nutri Stars Herbal Tonics 4:1 Extracts #2*
13450	Mix Rx Apple Cider Vinegar With Garcinia Cambogia Proprietary Formula*
13539	Ivl All Day Energy Greens Proprietary Blend*
13785	Zenwise Health Daily Digestive Enzymes Sea Vegetable Complex*
13806	Nature's Way Alive! Daily Greens Blend #3*
13865	Hair La Vie Revitalizing Hair Blend Hair La Vie Proprietary Blend*
13915	Paleoethics Pe Sport Organic Greens Greens Blend*
14074	Reliv Now Proprietary Blend*
14276	Nutrilite Concentrate Blend #5*
14300	Life's Fortune Multi-Vitamin & Mineral Proprietary Blend #4*

* It was assumed that blends contained equal parts all ingredients and only the fucoidan-containing ingredient of the blend was included.

Note: It was assumed fucoidans make up 25% of the seaweed ingredients in supplements.

Appendix F. Analytical Method Validation and Approval for their Intended purpose



ABN 17 103 342 801

249 Kennedy Drive
Cambridge Tasmania
Australia 7170

Phone: +61 3 6248 5800

Fax: +61 3 6248 4062

info@marinova.com.au

www.marinova.com.au

30 April 2025

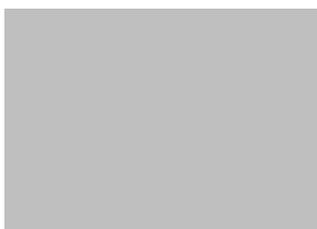
Re: Analytical Method Validation and Approval for their Intended purpose

Dear Sir/Madam:

I confirm that all methods of analysis, including internally developed methods, have been fully validated and are appropriate for their intended purposes.

Should you require any further information, please do not hesitate to contact us.

Sincerely,



Dr Michelle Mendoza

Quality Manager

For and on behalf of Marinova Pty Ltd