GRAS Notice (GRN) No. 545
http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm

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ORIGINAL SUBMISSION

Original Submission

GRN 000545

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FOOD ADDITIVE SAFETY

September 23, 2014

Dr. Paulette Gaynor
DBGNR/OFAS/CFSAN, HSF-255
Food and Drug Administration
5100 Paint Branch Pkwy.
College Park, MD 20740

Dear Dr. Gaynor:

The attached GRAS Notice for the use of a phosphatidylserine product derived from sunflower, trade named SharpPS® Green, is submitted on behalf of Enzymotec, who has determined that SharpPS® Green is GRAS based on scientific procedures.

As the agent for Enzymotec, we request that all correspondence be directed to my attention at the address below:

Mr. Edward A. Steele,
Chairman & CEO
EAS Consulting Group, LLC
1700 diagonal, Suite 750
Alexandria, VA 22314
571-447-5500
esteele@easconsultinggroup.com

The data and information that are the basis for Enzymotec's GRAS determination are available for the Food and Drug Administration's review and copying at reasonable times at the address above or will be sent to FDA upon request.

A summary and discussion of the basis for this GRAS determination is presented in the pages below.

Thank you for your prompt attention and consideration of this GRAS Notice.

Sincerely,

(b) (6) [redacted]

Edward A. Steele
Chairman & CEO

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GRAS DETERMINATION FOR SharpPS® Green

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)

Phosphatidylserine, derived from sunflower, for use as a nutrient, has been determined by Enzymotec, Sagi 2000 Industrial Park, P. O. Box 6, Migdal HaEmeq, ISRAEL 23106 (Enzymotec), to be Generally Recognized As Safe, and therefore, is exempt from the requirement of premarket approval, under the conditions of its intended use as described below. This determination is based on scientific procedures as described in the following sections.

B. Name and Address of Responsible Individual:

Iris Meiri-Bendek
Regulatory Affairs
Enzymotec
Sagi 2000 Industrial Park
P. O. Box 6, Migdal HaEmeq
Israel 23106
Telephone: + 972 74 717 7177
Facsimile: + 972 74 717 7001
Email: iris@enzymotec.com

Enzymotec accepts responsibility for the GRAS determination that has been made for phosphatidylserine derived from sunflower (hereinafter referred to as SharpPS® Green) as described in the subject notification; consequently, phosphatidylserine derived from sunflower (SharpPS® Green) meeting the conditions described herein is exempt from premarket approval requirements for food ingredients.

C. Common or usual name of the notified substance:

The common name of the substance of this notification is phosphatidylserine derived from sunflower. The product will be marketed under the trade name SharpPS® Green.

D. Conditions of use:

Phosphatidylserine derived from sunflower (SharpPS® Green) is intended for use as a nutrient in the same foods and levels as those for soy phosphatidylserine which was the subject of a GRAS Notice No. 000223 submitted to FDA on May 15, 2007 and for which FDA issued a "No Questions" letter dated December 20, 2007 [See Letter to Mr.

Edward A. Steele, EAS Consulting Group, LLC from Laura M. Taurantino: available at: http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm153874.htm]. These foods include milk, flavored milk, milk drinks (excluding milk, fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink at use levels of 100 mg phosphatidylserine *per* serving and in breakfast cereals and milk, fluid at 50 mg/serving.

Thus, Enzymotec proposes to use SharpPS® Green as a nutrient [21 CFR §170.3(o)(20)] at levels up to 100 mg phosphatidylserine/serving in milk, flavored milk, milk drinks (excluding milk fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink, and at use levels of 50 mg phosphatidylserine/serving in breakfast cereals and milk fluid.

In addition to the above described categories, SharpPS® Green is also intended for use under the supervision of a physician in Medical Food at levels not to exceed 300 mg phosphatidylserine/person/day. Under Section 5(b) of the Orphan Drug Act (ODA), a Medical Food is defined as a food that is formulated to be consumed or administered enterally under the supervision of a physician and that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. The intended use of SharpPS® Green in Medical Food will be as per these and other applicable regulations.

The estimated daily intake of phosphatidylserine from the intended uses of SharpPS® Green at the 90^{th} percentile of 98.73 mg/person (2.51 mg/kg/day) is below the safe levels of intake in humans of 300 mg of phosphatidylserine/person *per* day (5 mg/kg bw/day). The estimated daily intake, if ingested daily over a lifetime, is considered safe.

E. Basis for GRAS Determination:

In accordance with 21 CFR § 170.30, the intended use of SharpPS® Green has been determined to be generally recognized as safe (GRAS) based on scientific procedures. A comprehensive search of the scientific literature was also utilized for this review.

In addition to above mentioned GRN 223, FDA has received four other GRAS Notices for phosphatidylserine derived from various sources. These GRNs are listed below:

GRN 000186 – Soy lecithin enzymatically modified to have increased phosphatidylserine (July 20, 2006); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=186&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000197 – Phosphatidylserine (Soy) (September 20, 2006); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=197&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000279 – Phosphatidylserine derived from fish (July 25, 2009); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=279&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000311 – Krill-based phosphatidylserine (June 15, 2010); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=311&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

In all of these GRAS Notices, after review, FDA issued a letter informing the notifier that the agency had "No questions" concerning the notifier's conclusion that their products containing phosphatidylserine were GRAS. The fact that FDA has not expressed any concerns with these products coming from different sources and different production processes indicates that FDA is comfortable with the safety of these products. As the phosphatidylserine derived from the sources above is similar in nature and composition to phosphatidylserine derived from sunflower, the safety information that FDA considered in its evaluation of the above GRAS Notices can be used to further support the safety of phosphatidylserine derived from sunflower. Therefore, the information in these GRAS Notices is incorporated by reference into this GRAS assessment.

There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to determine safety-in-use for SharpPS® Green. The safety determination of SharpPS® Green is primarily based on human clinical trials and a variety of animal studies as well as *in vitro* studies that further corroborate the human data. Results from over 42 human clinical trials show that phosphatidylserine, from any source, is well-tolerated at doses from 100 to 800 mg *per* day. In animal studies no significant toxicity was noted at doses of up to 1000 mg/kg body weight (bw)/day. The adverse effects noted in animal studies at 1000 mg/kg bw/day were considered minor as these changes were small in magnitude, not supported by any histological damage, and lack of dose-response. On the basis of scientific procedures[1], and history of exposure from natural sources, the consumption of sunflower phosphatidylserine as an added food ingredient is considered safe at levels up to 300 mg/day. Recently, FDA has agreed to exercise enforcement discretion with a Health Claim Petition[2] on phosphatidylserine, in which the petitioner demonstrated that soy-derived phosphatidylserine is safe at levels up to 500 mg/day.[3]

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[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.
[2] Letter Regarding Dietary Supplement Health Claim for Phosphatidylserine and Cognitive Dysfunction and Dementia" (2003) Available at: http://www.cfsan.fda.gov/~dms/ds-ltr33.html
[3] Petition for Health Claim: Phosphatidylserine and Cognitive Dysfunction, Phosphatidylserine and Dementia (2002) Available at: http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091302/80027351.pdf

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

A. Chemical name

Phosphatidylserine. Per IUPAC-CBN nomenclature, it is a 1,2-diacyl-*sn*-glycero-3-phospho-L-serine.

B. Trade Name:

The subject of this notification will be marketed as SharpPS® Green.

C. Chemical Abstract Registry Number:

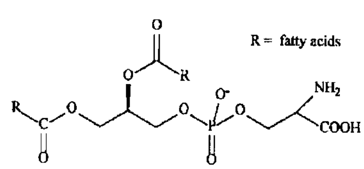
There is no CAS Reg. No. assigned specifically to phosphatidylserine derived from sunflower. The generic CAS Reg. No. assigned to phosphatidylserine is: 84776-79-4.

D. Chemical Formula:

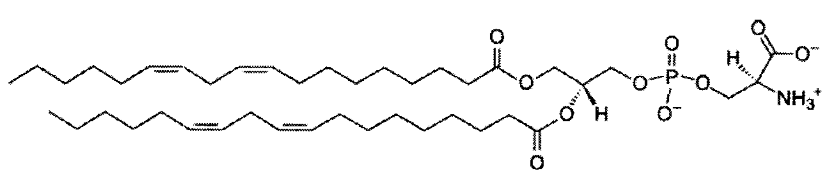
The empirical formula of the most abundant phosphatidylserine molecule in SharpPS® Green (comprising two linoleic acids) is $C_{42}H_{73}O_{10}PNCa$

E. Structure:

Phosphatidylserine consists of a glycerophosphate skeleton conjugated with 2 fatty acids and L-serine *via* a phosphodiester linkage. The structural diagram below shows the general representation of glycerophosphate backbone with R as fatty acids. The counter ion for the phosphate moiety is Ca^{++}.



General structure of phosphatidylserine



Most abundant form (the counter ion for the phosphate moiety is Ca^{++})

F. Fatty Acid Profile:

The mean percentage of the fatty acids in SharpPS® Green is presented in Table F.1.

Table F.1. Fatty Acid Profile for SharpPS® Green

Fatty acid	Percentage (as % of total fatty acids)
Palmitic acid	11.0
Stearic acid	2.9
Oleic acid	15.8
Linoleic acid	70.1
Linolenic acid	0.2
Total	100

G. Molecular weight

SharpPS® Green is not a single pure compound. Therefore, an exact molecular weight cannot be provided.

H. Physical and Chemical Characteristics

SharpPS® Green is produced as a light yellow to brown-colored powder. The typical composition and specifications are shown in Tables H.1 and H.2 below. Analytical data from five different manufacturing lots are presented in Table H.3. Enzymotec also analyzed its product for tocopherol content (Table H.4), heavy metals (Table H.5), ethanol residues (Table H.6), pesticides (Table H.7) and dioxin congeners (Table H.8). These data are shown below. Enzymotec considers the levels for the pesticides and heavy metals to be safe in this product.

Table H.1. Typical Composition and Specifications of SharpPS® Green

Parameter	Typical values	Assay method
Phosphatidylserine	66.8% w/w	^{31}P-NMR
Phosphatidic acid	9.2 % w/w	^{31}P-NMR
Phosphatidylcholine	0.4 % w/w	^{31}P-NMR
Lyso phosphatidylserine	0.9 % w/w	^{31}P-NMR
Lyso phosphatidic acid	0.7 % w/w	^{31}P-NMR
Phosphatidyl inositol	1.3 % w/w	^{31}P-NMR
Other phospholipids	8 % w/w	^{31}P-NMR
Glyceride (Tr-, Di-and Mono -)	4.9 % w/w	GC-FID
Sodiun (Na^{+})	14.5 ppm	ICP-OES
Calcium (Ca^{++})	2.5 % w/w	ICP-OES

Chloride (Cl^-)	<0.1 %w/w	Potentiometric titration
Free L-serine	0.4 % w/w	Ninhydrin reaction
Total sterols	ND	GC-FID
Tocopherols	0.17 % w/w	HPLC-FLD
Ash	14.6 %w/w	Gravimetric
Heavy metals		
Lead	<0.05 ppm	ICP-MS
Arsenic	<0.1 ppm	ICP-MS
Cadmium	<0.01	ICP-MS
Mercury	<0.005 ppm	ICP-MS

Table H.2. Product specifications for SharpPS® Green

Parameter	**Specifications**	**Assay method**
Consistency	Powder	Visual
Color	Light-yellow to brown	Visual
Peroxide value	< 5 meq/Kg	AOCS official method Cd 8-53
Loss On Drying	<2.0 % w/w	USP <731>
Phosphatidylserine	Not less than 60% w/w	^{31}P-NMR
Ethanol residues	<1000 ppm	GC-FID
Microbiological assays		
Total plate count	<1000 cfu/g	Israeli Standard SI 885 Part 3 (1999)
Yeast and Mold	<100 cfu/g	Israeli Standard SI 885 Part 3 (1999)
Molds	<100 cfu/g	Israeli Standard SI 885 Part 3 (1999)
Coliforms	Negative (cfu/g)	USP 61 (2000)
Staphylococcus aureus	Negative (cfu/g)	USP 61 (2000)
Salmonella	Negative (cfu/20g)	Israeli Standard SI 885 Part 3 (1999)
Shelf life	24 months	
cfu=colony forming units		

Table H.3. Analytical data from five different manufacturing lots of SharpPS® Green

Parameter	Typical Level/specifications	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28	Lot SF-31
Phosphatidylserine	66.8 % w/w	67.12	67.3	66.71	68.43	64.27
Phosphatidic acid	9.2 % w/w	8.37	9.32	9.44	9.79	9.3
Phosphatidylcholine	0.4 % w/w	0.17	0.1	0.48	0.67	0.53
Lyso phosphatidylserine	0.9 % w/w	0.7	0.77	0.96	1.13	1.07
Lyso phosphatidic acid	0.7 % w/w	0.51	0.61	0.75	0.85	0.47
Phosphatidyl inositol	1.3 % w/w	1.62	1.5	0.94	1.02	ND
Other phospholipids	8 % w/w	7.46	7.61	7.94	7.49	8.86
Glyceride (Tr-, Di- and Mono -)	4.9 % w/w	4.05	3.22	4.24	5.31	
Sodium (Na^+)	14.5 ppm	24	17	10	7	
Calcium (Ca^{++})	2.5 % w/w	2.2	2.4	2.4	3	
Chloride (Cl^-)	<0.1 %w/w	<0.1	<0.1	<0.1	<0.1	
Free L-serine	0.4 % w/w	0.4	0.5	0.3	0.2	
Total sterols	ND %w/w	ND	ND	ND	ND	
Tocopherols	0.17 % w/w	0.18	0.16	0.17	0.18	
Ash	14.6 % w/w	15	15.1	15.4	12.8	
Peroxide value	< 5 meq/Kg	<0.2	<0.2	<0.2	<0.2	<0.2
Loss on Drying	<2.0 % w/w	0.61	0.61	0.59	0.53	0.4

Table H.4. Tocopherols breakdown from four manufacturing lots

	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28
Alpha tocopherol (mg/100g)	179	157	171	184
Beta tocopherols (mg/100g)	<0.5	<0.5	<0.5	<0.5
Gamma tocopherols (mg/100g)	<0.5	<0.5	<0.5	<0.5
Delta tocopherols (mg/100g)	<0.5	<0.5	<0.5	<0.5

Table H.5. Heavy metal analysis from four manufacturing lots

	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28
Lead (ppm)	<0.05	<0.05	<0.05	<0.05
Arsenic (ppm)	<0.1	<0.1	<0.1	<0.1
Cadmium (ppm)	<0.01	<0.01	<0.01	<0.01
Mercury (ppm)	<0.005	<0.005	<0.005	<0.005

Table H.6. Ethanol residues from four manufacturing lots

	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28
Residual ethanol (ppm)	<50	101	<50	<50

Table H.7. Dioxins and Dioxin-like PCBs[1]

	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28
Dioxins and Furans (pg/g WHO-PCDD/F TEQ)	0.103	0.103	0.101	0.102
Sum of Dioxins & dioxin-like PCBs (pg/g WHO-PCDD/F+PCB-TEQ)	0.163	0.163	0.16	0.163
Dioxin-like PCBS (pg/g WHO-PCB TEQ)	0.06	0.06	0.059	0.059

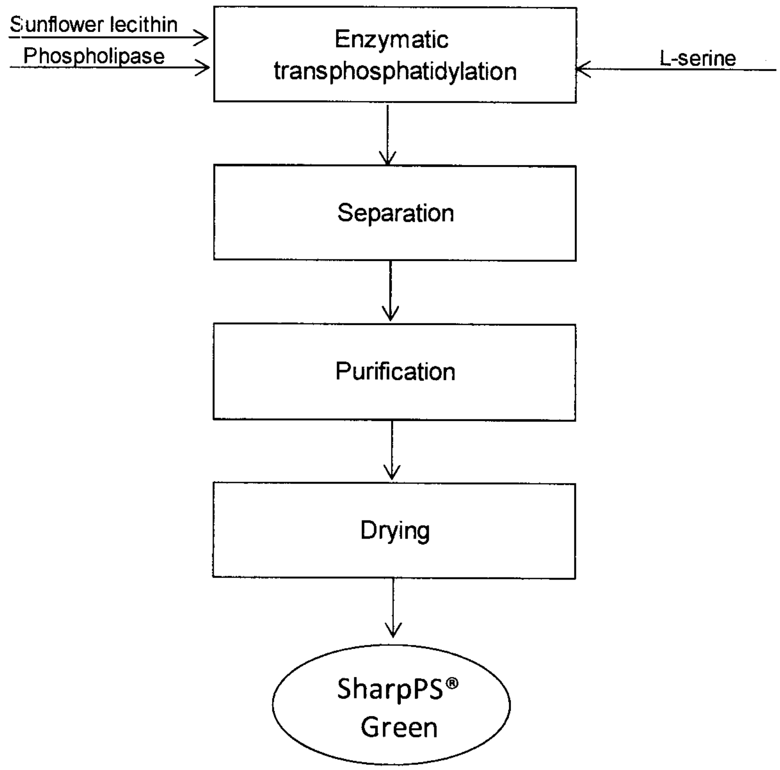
[1]Upperbound concentrations calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification

Table H.8. Pesticides

	Lot SF-25	Lot SF-26	Lot SF-27	Lot SF-28
Organochlorine pesticides	ND	ND	ND	ND
Organophosphorus pesticides	ND	ND	ND	ND

I. Manufacturing process

Phosphatidylserine (SharpPS® Green) is manufactured from high phosphatidylcholine enriched sunflower lecithin (See flowchart). The phosphatidylcholine-enriched lecithin is enzymatically transphosphatidylated with L-serine using a phospholipase enzyme. The enzyme used for transphosphatidylation is derived from a microorganism that is nonpathogenic and nontoxicogenic. This enzymatic process catalyzes the substitution of the choline head-group with serine to form phosphatidylserine. The enzyme treatment does not alter the fatty acids attached to the molecule or its stereochemistry. Following the enzymatic reaction, the solid product is separated from the reaction mixture, purified and dried. Food grade antioxidants are added to the product in accordance with good manufacturing practices. Processing aids used such as acetic acid, sodium methoxide, calcium chloride, and ethyl alcohol are food grade quality as specified in Food Chemical Codex.



J. Intended Technical Effects

While there is no Reference Daily Intake for phosphatidylserine, the nutritive contribution of phosphatidylserine is widely recognized. It is a naturally occurring nutritive component in a variety of foods, but is found at high levels only in certain fish, poultry and meats (especially organ meats). The supplementation of phosphatidylserine through foods is to provide a nutrient for brain function. Although phosphatidylserine is present at certain levels in the diet, its supplementation to food is aimed at gaining certain health benefits. The level of phosphatidylserine required to achieve the health benefits was determined through intervention trials in which people consumed phosphatidylserine as a supplement to their diet (whether from marine, bovine or plant source).

III. Summary of the Basis for Enzymotec's Determination that Phosphatidylserine (SharpPS® Green) is GRAS

Enzymotec has determined, based upon scientific procedures, that SharpPS® Green is GRAS for its use as a nutrient at levels up to 100 mg phosphatidylserine/serving in milk, flavored milk, milk drinks (excluding milk fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink, at use levels of 50 mg phosphatidylserine/serving in breakfast cereals and milk fluid and in Medical Food at levels not to exceed 300 mg phosphatidylserine/person/day. The intended use levels and food categories are the same as those for soy phosphatidylserine which was the subject of a GRAS Notice No. 000223. SharpPS® Green will also serve as a substitute for soy phosphatidylserine in many instances. Thus, the exposure to phosphatidylserine from SharpPS® Green will be the same as from soy phosphatidylserine, i.e., 98.73 mg/person/day which is well below the safe levels of intake for humans at 300 mg phosphatidylserine /person/day.

Based on a critical evaluation of the pertinent data and information summarized here, Enzymotec has determined by scientific procedures that the addition of SharpPS® Green to milk, flavored milk, milk drinks, milk analogs (soy milk), milk-based meal replacement, yogurt, breakfast bars, breakfast cereals ,fruit flavored drink and Medical Food, meeting the specifications cited above and manufactured according to current Good Manufacturing Practice, is Generally Recognized As Safe (GRAS) under the conditions of intended use in the selected foods, as specified herein.

In arriving at this decision that phosphatidylserine is GRAS, Enzymotec relied upon the fact that neither SharpPS® Green or any of its degradation products pose any toxicological hazards or safety concerns at the intended use levels, the similarity, and safety profiles of other sources of phosphatidylserine products, as well as published toxicology studies and other articles relating to the safety of the product. It is also the opinion of Enzymotec that other qualified and competent scientists, reviewing the same publicly available toxicological and safety information, would reach the same conclusion.

IV. **Basis for a Conclusion that Phosphatidylserine is GRAS for its Intended Use.**

DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF PHOSPHATIDYLSERINE (SharpPS® Green) AS A NUTRIENT

TABLE OF CONTENTS

DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF PHOSPHATIDYLSERINE (SharpPS® Green) AS A NUTRIENT

1. INTRODUCTION

Sunflower phosphatidylserine (SharpPS® Green), as a direct food ingredient, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Enzymotec has determined that such use is GRAS. This determination is based on scientific procedures. Enzymotec has concluded that other competently trained scientists, upon reviewing the information, below would reach the same conclusion. Enzymotec intends to use sunflower phosphatidylserine (SharpPS® Green) as a nutrient [21 CFR § 170.3(o)(20)][4] in milk, flavored milk, milk drinks (excluding milk, fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink at use levels of 100 mg phosphatidylserine *per* serving, in breakfast cereals and milk, fluid at 50 mg/serving and in Medical Food at levels not to exceed 300 mg phosphatidylserine/person/day. A comprehensive search of the scientific literature for safety and toxicity information on phosphatidylserine was conducted through July 2014. Enzymotec independently and critically evaluated these materials and other information deemed appropriate or necessary. A detailed discussion of this data is discussed below. In addition, Enzymotec also reviewed and evaluated the publicly available data from GRAS Notices that had been submitted to FDA for the use of phosphatidylserine in which FDA has issued "No Questions" letters. The composition and similarity of these products with SharpPS® Green was compared. The GRAS Notices that FDA received, reviewed, and issued "No Questions" letters are listed below:

GRN 000186 – Soy lecithin enzymatically modified to have increased phosphatidylserine (July 20, 2006); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=186&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000197 – Phosphatidylserine (Soy) (September 20, 2006); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=197&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000223 – Phosphatidylserine (Soy) (December 20, 2007); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

GRN 000279 – Phosphatidylserine derived from fish (July 25, 2009); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=279&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

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[4] "Nutrient supplements": Substances which are necessary for the body's nutritional and metabolic processes.

GRN 000311 – Krill-based phosphatidylserine (June 15, 2010); [Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=311&sort=GRN_No&order=DESC&startrow=1&type=basic&search=phosphatidylserine].

The fact that FDA has not expressed any concerns with these products coming from different sources and different production processes indicates that the agency is comfortable with the safety of these products. As the phosphatidylserine derived from the sources above is similar in nature and composition to phosphatidylserine derived from sunflower, the safety information that FDA considered in its evaluation of the above GRAS Notices can be used to further support the safety of phosphatidylserine derived from sunflower. Therefore, the information in these GRAS Notices is incorporated by reference here.

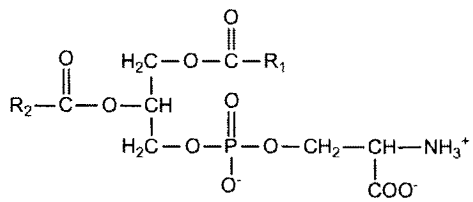
1.1. Occurrence

Phosphatidylserine, a member of the class of phospholipids and structural component of cells, is commonly found in all biological membranes of plants, animals and other life forms (Hendler and Rorvik, 2001). The fatty acid composition of endogenous phosphatidylserine depends on its localization and function in the cell. Approximately 30 g of phosphatidylserine is found in the human body and about half of this amount (~13 g) is present in the brain (Horrocks *et al.,* 1982). In the brain, phosphatidylserine comprises 15% of the total phospholipid pool. Other organs containing phosphatidylserine include skeletal muscle (~3.3 g; 3.3%), liver (~2.4 g; 3.8%), lung (~0.2 g; 7.4%), and kidney (~0.3 g; 5.7%).

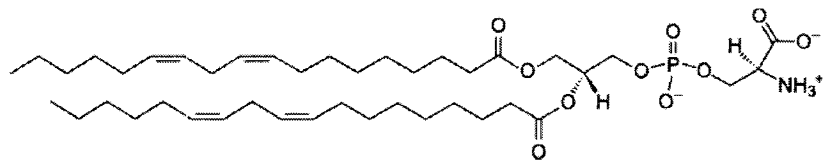
The commercial sources of phosphatidylserine today are soy, krill and fish. Historically, the source was from cow brains. With the discovery of "Mad Cow" disease, this source has been restricted. Today the major source of PS is soy. However, Sunflower PS is a replacement for soy PS for many people because it is derived from non-GMO sources where it offers two contrasting advantages: 1. It is not derived from bovine sources; and, 2. It is not a soy derivative which removes concerns about allergies and GMO sources.

1.2. Chemistry and Biological Activity

Structurally, phosphatidylserine comprises three different parts: a glycerol backbone, a polar head group, and a hydrophobic moiety (Figure 1). The head group consists of the amino acid serine, which is attached to the 3-carbon backbone *via* a phosphate group; the two other hydroxy groups of the glycerol are each esterified with a fatty acid. The fatty acid moiety in position 2 is usually more unsaturated and has more carbon atoms than the fatty acid moiety in position 1. The term phosphatidylserine refers to a group of molecules due to the fact that the fatty acyl residues can vary considerably, depending on the natural source. Phosphatidylserine is amphiphilic in nature because of the negatively charged head group (hydrophilic) and the fat-soluble fatty acid tails (lipophilic) (Hendler and Rorvik, 2001). Phosphatidylserine cannot be synthesized by the human body *de novo*. It is produced only *via* exchange of the head group from phosphatidylcholine (PC) and/or phosphatidylethanolamine (PE), catalyzed by phosphatidylserine synthase-1 or -2. Thus, phosphatidylserine is formed from phosphatidylethanolamine by exchange of the ethanolamine head for L-serine.



General structure



Most abundant form (the counter ion for the phosphate moiety is Ca^{++})

Figure 1. Chemical structure of phosphatidylserine

Phosphatidylserine is primarily located in the internal layer of the cell membrane and performs a variety of structural and regulatory functions. It is involved in governing membrane fluidity and therefore in the regulation of biological cell activities. Aside from the regulation of many metabolic processes (such as activation of cell-membrane bound enzymes), phosphatidylserine is involved in neuronal signaling. Moreover, the sodium-potassium-stimulated enzyme ATPase is also activated by phosphatidylserine. Another enzyme activated by phosphatidylserine is tyrosine hydroxylase, which is involved in neurotransmitter synthesis thus influencing dopaminergic and adrenergic signal transduction in the brain. Phosphatidylserine facilitates the calcium uptake into the nerve cells that decreases in the aging brain. It is also involved in the processes of cell repair and removal. In addition to its role in brain glucose metabolism, it can stimulate synthesis of the neurotransmitter acetylcholine to improve receptor functioning and to restore nerve signal transduction.

A comparison of Sunflower PS and soy PS (Table 1) shows that they contain essentially the same fatty acid profile with varying percentages for the different fatty acids. A similar comparison is also evident for the other PS sources (GRNs 186, 197, 279, and 311), but to a lesser extent than for soy PS.

Table 1. Comparison of Fatty Acid Profile for sunflower PS and Soy PS (GRN 223)

Acid Fatty	SharpPS® Green (sunflower PS) (as % of total fatty acids)	SharpPS® (soy PS) (as % of total fatty acids)
Palmitic acid	11.0	14

Stearic acid	2.9	4
Oleic acid	15.8	15
Linoleic acid	70.1	62
Linolenic acid	0.2	5
Total	100	100

1.3. Description, Manufacturing Process and Specifications

General descriptive parameters and properties of phosphatidylserine manufactured as SharpPS® Green by Enzymotec are summarized in Table 2. SharpPS® Green occurs as light yellow to brown colored powder.

Table 2. General descriptive characteristics of phosphatidylserine from SharpPS® Green

Parameter	Description
Chemical name	1,2-diacyl-*sn*-glycero-3-phospho-L-serine
CAS Number	84776-79-4
Chemical formula	$C_{42}H_{73}O_{10}PNCa$
Physical state	Powder
Solubility	Chloroform: methanol 95:5
Stability	24 months
Color	Light yellow to brown
Odor	Light sunflower lecithin-like odor
Flavor	None
Storage	Below 25°C, in sealed containers, protected from light and moisture.

1.3.1. Manufacturing Process

Phosphatidylserine (SharpPS® Green) is manufactured from high phosphatidylcholine enriched sunflower lecithin (Figure 2). The phosphatidylcholine-enriched lecithin is enzymatically transphosphatidylated with L-serine using a phospholipase enzyme. The enzyme used for transphosphatidylation is derived from a microorganism that is nonpathogenic and nontoxicogenic. This enzymatic process catalyzes the substitution of the choline head-group with serine to form phosphatidylserine. The enzyme treatment does not alter the fatty acids attached to the molecule or its stereochemistry. Following the enzymatic reaction, the solid product is separated from the reaction mixture, purified and dried. Food grade antioxidants are added to the product in accordance with good manufacturing practices. Processing aids used such as acetic acid, sodium methoxide, calcium chloride, and ethyl alcohol are food grade quality as specified in the Food Chemicals Codex.

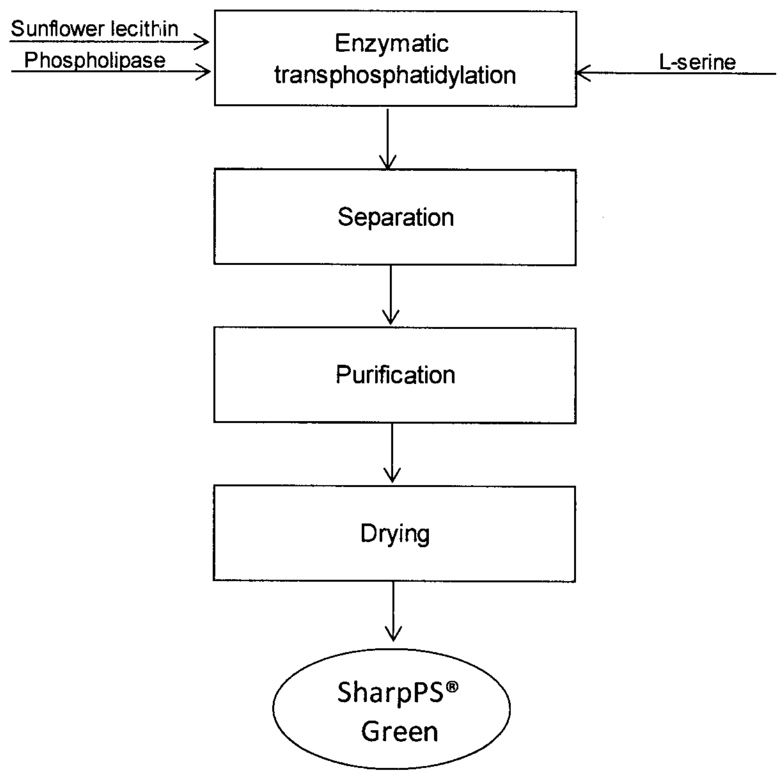


Figure 2. Manufacturing process of phosphatidylserine (SharpPS® Green)

1.4. Identity and Specifications

Typical compositional analysis and specifications of SharpPS® Green from Enzymotec are presented in Tables 3 and 4, respectively, also in comparison with phosphatidylserine from soy (SharpPS®, subject of GRN000223). Analytical results of five lots from non-consecutive batches indicate that the SharpPS® Green produced meets these specifications (see section H. Physical and Chemical Characteristics).

Table 3. Typical Composition and Specifications for SharpPS® Green in comparison with phosphatidylserine from soy (SharpPS®)

Parameter	Typical values for SharpPS® Green	Assay method	Typical values for SharpPS® (soy PS)
Phosphatidylserine	66.8% w/w	^{31}P-NMR	72 %
Phosphatidic acid	9.2 % w/w	^{31}P-NMR	10.6 %
Phosphatidylcholine	0.4 % w/w	^{31}P-NMR	-
Lyso phosphatidylserine	0.9 % w/w	^{31}P-NMR	0.5 %
Lyso phosphatidic acid	0.7 % w/w	^{31}P-NMR	0.3 %
Phosphatidylethanolamine	-	^{31}P-NMR	1 %
Phosphatidyl inositol	1.3 % w/w	^{31}P-NMR	-
Other phospholipids	8 % w/w	^{31}P-NMR	3.3 %
Glyceride (Tri-, Di- and Mono -)	4.9 % w/w	GC-FID	2.8 %
Sodiun (Na^{+})	14.5 ppm	ICP-OES	277 ppm
Calcium (Ca^{++})	2.5 % w/w	ICP-OES	2.5 %
Chloride (Cl^{-})	<0.1 %w/w	Potentiometric titration	0.2 ppm
Free L-serine	0.4 % w/w	Ninhydrin reaction	<0.1 %
Total sterols	ND	GC-FID	0.028 %
Tocopherols	0.17 % w/w	HPLC-FLD	0.2 %
Ash	14.6 %w/w	Gravimetric	12.7 %
Heavy metals			
Lead	<0.05 ppm	ICP-MS	<0.2 ppm
Arsenic	<0.1 ppm	ICP-MS	<0.2 ppm
Cadmium	<0.01 ppm	ICP-MS	<0.03 ppm
Mercury	<0.005 ppm	ICP-MS	<0.2 ppm

Table 4. Product specifications in comparison with phosphatidylserine from soy (SharpPS®)

Parameter	Specifications for SharpPS® Green	Assay method	Specifications for SharpPS® (Soy PS)
Consistency	Powder	Visual	Powder
Color	Light-yellow to brown	Visual	Off-white to light yellow
Peroxide value	< 5 meq/Kg	AOCS official method Cd 8-53	< 5 meq/kg
Loss On Drying	<2.0 % w/w	USP <731>	<2.0 % w/w
Phosphatidylserine	Not less than 60% w/w	^{31}P-NMR	60-80 %
Ethanol residues	<1000 ppm	GC-FID	<1000 ppm

Microbiological assays			
Total plate count	<1000 cfu/g	Israeli Standard SI 885 Part 3 (1999)	<1000 cfu/g
Yeast and Mold	<100 cfu/g	Israeli Standard SI 885 Part 3 (1999)	<100 cfu/g
Molds	<100 cfu/g	Israeli Standard SI 885 Part 3 (1999)	<100 cfu/g
Coliforms	Negative (cfu/g)	USP 61 (2000)	Negative (cfu/g)
Staphylococcus aureus	Negative (cfu/g)	USP 61 (2000)	Negative (cfu/g)
Salmonella	Negative (cfu/20g)	Israeli Standard SI 885 Part 3 (1999)	Negative (cfu/g)
Shelf life	24 months		24 months
cfu=colony forming units			

The comparison of the composition and specifications of SharpPS® Green (derived from sunflower) and SharpPS® (derived from soy) demonstrates the similarity of these products. As such, the safety data for SharpPS® can be used to support the safety of SharpPS® Green.

1.5. Technical Effects

SharpPS® Green is intended for use in food as a nutrient for individuals who wish to increase their daily intake of phosphatidylserine. While there is no Reference Daily Intake, the nutritive contribution of phosphatidylserine is well recognized. It is naturally present in a wide variety of foods with relatively higher amounts in specific foods such as fish, poultry and meats. Although phosphatidylserine is present at a certain level in the diet, its supplementation to food is aimed at gaining certain health benefits. The level of phosphatidylserine required to achieve the health benefits was determined through intervention trials in which people consumed phosphatidylserine to supplement their diet (whether from marine, bovine or plant sources). The supplementation of phosphatidylserine through foods is intended to assist in maintaining acuity and to aid in preventing age-related mental deterioration.

1.6. Current Uses

Phosphatidylserine is extensively marketed as a dietary supplement. FDA has concluded that "the use of phosphatidylserine as a dietary supplement is safe and lawful under 21 CFR § 101.14 provided that bovine-derived sources, if used, are not derived from bovine tissues from cattle born, raised, or slaughtered in any country where BSE exists[5]."

In reply to five separate GRAS notices, FDA had no questions on the use of phosphatidylserine in different food categories under the conditions described in the notifications. In one of the GRAS notifications from Degussa Food Ingredients GmbH (2006)[6], the use of phosphatidylserine at levels of 20 mg/serving in yogurt, powdered milk, ready-to-drink soymilk, meal replacement, cereal bars, powdered beverage mixes, chewing gum, and breakfast cereals was considered as GRAS. In the second GRAS notice submitted by Lipogen (2006)[7], the use of phosphatidylserine in 28 different food products resulting in estimated mean and 90th percentile intake of approximately 140 and 240 mg/person/day, respectively, was determined to be GRAS.

1.7. Intake from Natural Presence in Food

As mentioned earlier, phosphatidylserine is virtually present in all biological membranes of plants and animals. As such, phosphatidylserine is a typical constituent of the human diet. It is found in small amounts in foods such as meats, eggs, soy products, certain legumes, and milk. Bruni *et al.* (1989) reported an estimated daily intake of phosphatidylserine of about 75 mg/day. On the basis of a scientific analysis of phosphatidylserine exposure, Hamm (2004) determined an average intake of phosphatidylserine as 130 mg/day, with light eaters of meat and fish consuming about 100 mg and vegans consuming less than 50 mg/day. In a GRAS notification, Degussa (2006) determined estimated dietary intake of phosphatidylserine in the US population. Based on the analysis, limited to the foods in which the presence of phosphatidylserine has been reported, the estimated average and 90th percentile intake of phosphatidylserine for an adult from natural sources was determined as 98 and 184 mg/person/day, respectively. In another notification, Lipogen (2006) reported the background intake of phosphatidylserine from natural sources. In this report, it was estimated that consumers of meat ingest approximately 80 mg of naturally occurring phosphatidylserine *per* day. These reports show that dietary intake of phosphatidylserine, from its natural presence in diet, ranges from 75 to 184 mg/day.

1.8. Intended Use Levels and Food Categories

Enzymotec proposes to use SharpPS® Green as a nutrient [21 CFR § 170.3(o)(20)], and as an alternative to soy PS, at levels up to 100 mg phosphatidylserine/serving in milk, flavored milk, milk drinks (excluding milk, fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink, at use levels of 50 mg phosphatidylserine/serving in breakfast cereals and milk, fluid and in Medical Food at levels not to exceed 300mg

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[5]Phosphatidylserine and Cognitive Dysfunction and Dementia (Qualified Health Claim: Final Decision Letter); available at: http://www.cfsan.fda.gov/~dms/ds-ltr36.html.

[6] GRAS notice No. GRN 000197; available at: http://www.cfsan.fda.gov/~rdb/opa-g197.html.
[7] GRAS notice No. GRN 000186; available at: http://www.cfsan.fda.gov/~rdb/opa-g186.html.

phosphatidylserine/person/day. Although some foods with standards of identity are included in the list of foods, at present the use of SharpPS® Green is intended for foods without a standard of identity. Estimates of possible daily intake from the proposed use levels of SharpPS® (soy PS) have been determined as part of GRN 000223 using CSFII 1994-96 (USDA, 1998) database (as determined by CanTox; see below) of the food product. Based on the maximum proposed use levels of SharpPS®, the resulting daily intake at the mean and 90th percentile level of phosphatidylserine is determined. Since SharpPS® Green will be used in the same food categories and at levels as those for Sharp•PS®, these exposure calculations are valid for SharpPS® Green as well.

1.8.1. Estimated Daily Intake from the Intended Uses [Also Applies to SharpPS® Green]

Earlier in 2007, at the request of Enzymotec, CanTox Health Sciences International (CanTox) performed intake estimates for phosphatidylserine derived from soy. These previous intake estimates that are also applicable to sunflower derived phosphatidylserine are summarized here. Based on the exposure estimates prepared by CanTox (Appendix I), approximately 60% of the total U.S. population was identified as consumers of phosphatidylserine (12,341 actual users identified). Although, infants are included in the intake determinations, phosphatidylserine is not intended to be used in products such as baby foods or infant formula that are specifically marketed for use by infants. Consumption of types of food categories intended for addition of phosphatidylserine by the total U.S. population resulted in estimated mean all-person and all-user intakes of phosphatidylserine of 24.61 mg/person/day (0.52 mg/kg body weight/day) and 44.75 mg/person/day (0.95 mg/kg body weight/day), respectively. The 90th percentile all-person and all-user intakes of phosphatidylserine from all intended food-uses by the total population were 70.00 mg/person/day (1.46 mg/kg body weight/day) and 98.73 mg/person/day (2.51 mg/kg body weight/day), respectively. For details of the consumption analysis, please see Appendix I. The FDA commonly uses the estimated daily intake for the 90th percentile consumer of a food additive as a measure of high chronic dietary intake. Hence, for the safety determinations, the resulting 90th percentile intake of phosphatidylserine (98.73 mg/person/day) from its intended uses in the above described food categories is considered. A summary of the estimated daily intake of phosphatidylserine from the intended food categories is presented in Table. 5.

Table 5. Intake of phosphatidylserine (mg/person/day) based on USDA data

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
				Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Infant	0 to 2	52.5	1,880	16.23	6.23	46.25	27.39	17.43	60.49
Child	3 to 11	79.8	5,030	33.03	23.24	80.81	41.90	29.88	91.10
Female Teenager	12 to 19	54.1	380	25.37	11.62	70.00	45.80	33.20	89.15
Male Teenager	12 to 19	55.0	383	33.50	14.53	98.98	60.73	45.46	117.80

Female Adult	20 and Up	53.3	2,438	22.71	8.16	63.66	42.16	27.29	96.42
Male Adult	20 and Up	46.9	2,230	22.76	NA	66.40	49.62	33.20	105.00
Total Population	**All Ages**	59.9	12,341	24.61	9.96	70.00	44.75	30.30	98.73
NA = Not applicable									

1.9. Summary of Consumption

The estimated daily intake of phosphatidylserine from SharpPS® for the various food categories identified above was determined using CSFII 1994-96 database (USDA, 1998). From these determinations, the high users only 90th percentile consumption value of phosphatidylserine ingredients for food uses in different products [milk, flavored milk, milk drinks, milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, breakfast cereals and fruit flavored drink] was considered as the estimated daily intake resulting from the intended use of SharpPS®. Based on these considerations, the intended uses of phosphatidylserine will result in daily 90th percentile exposure of 98.73 mg/person (2.51 mg/kg body weight/day). Phosphatidylserine is naturally present in food and its intake from diet ranges from 75 to 184 mg/day. Based on the available scientific information and as discussed below, the estimated daily intake, if ingested daily over a lifetime, is considered as safe. Although this intake was performed for soy derived phosphatidylserine, it is also applicable to sunflower derived phosphatidylserine or SharpPS® Green. This exposure consideration is used in the safety considerations of SharpPS® Green as well.

2. Toxicology

The safety of phosphatidylserine is supported by multiple human clinical trials. A variety of animal as well as *in vitro* experimental studies further corroborate the human observations. Because of its physiological role and health benefits, there has been considerate effort to elucidate the biological role of phosphatidylserine in the human body. As a result, the literature is full of information on phosphatidylserine. Relevant biological and toxicological studies on phosphatidylserine are included in the following section in the order of their importance in support of the conclusions drawn in this determination.

2.1. Human Studies

The clinical database of phosphatidylserine intake includes over 42 clinical trials of which 25 have been identified as double-blind protocols. The objective of the majority of these studies was to examine the effect of phosphatidylserine in reducing the symptoms of dementia and cognitive dysfunction in geriatric individuals as well as improvement of cognitive functions and improve ADHD symptoms in children. Although these investigations were designed to study the efficacy of phosphatidylserine, clinical observations also included any adverse effects. In the clinical trials with phosphatidylserine, over 1600 subjects participated and the treatment lasted for periods of up to 6 months. The doses used in these trials ranged from 100 to 800 mg/day. Results from these studies show that oral administration of phosphatidylserine at doses of up to 600 mg/day for up to 3 months were without any significant adverse effects. In the largest double-blind, placebo-controlled trial (Cenacchi et al., 1993), of the 494 participants', only one subject (out of the 215 subjects treated with PS) dropped out because of a treatment-related adverse effect as compared to seven drop-outs from the placebo group that were considered as treatment-related. The reason for drop-out for these subjects was reported as dizziness. In the majority of the clinical trials (Table 6), phosphatidylserine derived from bovine cortex was used. In 15 trials, the source of phosphatidylserine was soy and in 7 trials a marine-based phosphatidylserine was used. As discussed earlier, the source of phosphatidylserine is unlikely to affect its safety. A summary of clinical trial design, doses and adverse effects noted in these investigations is presented in Table 6.

In a review article, Pepping (1999) reported that phosphatidylserine is well-tolerated at a dosage up to 300 mg/day. The only adverse effects reported were stomach upset in some individuals at doses higher than 300-400 mg/day and sleeplessness at doses ≥600 mg taken before bedtime. There are no reported drugs, nutritional supplement, food or herbal interactions with phosphatidylserine. Hendler and Rorvik (2001) reported occasional gastrointestinal side effects (nausea and indigestion) following phosphatidylserine ingestion. These effects were attributed to the oily nature of the ingested phosphatidylserine and vehicle used. These symptoms can be minimized by consuming phosphatidylserine with food.

The safety of plant-based phosphatidylserine is supported by a large number of clinical trials. In two large trials, the safety of soy-based PS was assessed. The first was a randomised, double-blind, placebo-controlled, parallel group study design with elderly subjects with age associated memory impairment (Jorissen et al., 2002). Following a 1-week placebo run-in period, 132 elderly (aged greater than 57 years) male and female subjects were randomised to receive 300 or 600 mg/day of the soya-derived PS or placebo to be consumed as 2 capsules with each daily meal for a period of 12 weeks, followed by a 3-week placebo washout period. The soya-derived PS was Leci-PS-40P, and contained 40% PS, 13% phosphatidylcholine, 9% phosphatidyl-ethanolamine, 5% phosphatidylinositol, 5% phosphatidic acid, and 28% poly-unsaturated fatty acids. Biochemical (ALAT, ASAT, alkaline phosphatase, calcium, glucose, potassium, creatinine, sodium, urea, uric acid, and bilirubin) and haematological (white blood count, lymphocytes, monocytes, neutrophils, platelet count, basophils, eosinophils, red blood cell count, haematocrit, and haemoglobin) examinations were performed and resting DBP, SBP, and heart rate were measured at baseline and after 6 and 12 weeks of soya-PS consumption. Adverse events were assessed using a 27-item questionnaire with a 4-point rating system to evaluate the frequency of each adverse event. In addition, a summed side effects score was calculated to serve as a global measure of side effects due to the low frequency of the individual items. One hundred and twenty (120) subjects completed the trial (39, 40, and 41 in the placebo, 300, and 600 mg soya-PS/day groups, respectively) and the drop-outs (the reasons for which were unrelated to treatment) were distributed evenly over the 3 groups. There were no significant differences between groups at week 12 for any of the biochemical or haematological parameters or SBP, DBP, or heart rate after Bonferroni-Holme correction for multiple hypothesis testing. In addition, there were no significant differences in the summed total side effects scores between groups. The authors concluded that soya-PS is safe for elderly subjects to consume at levels of up to 200 mg 3 times daily.

In the second randomised, double-blind, placebo-controlled, parallel-designed study (Kato-Kataoka et al., 2010), seventy-eight elderly subjects (38 men, 35 women; mean age of 59 years) with mild cognitive impairment (described as having a Rivermead Behavioural Memory Test standard profile score of less than 22) were randomised to receive 0 (placebo), 100, or 300 mg/day of soya-derived PS for 6 months. Safety endpoints included adverse event reporting, vital signs (heart rate, systolic and diastolic blood pressure), and haematological (including red blood cell count, white blood cell count, platelet count, haemoglobin, and haematocrit), blood biochemical (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactose dehydrogenase, gamma-glutamyltransferase, creatinine phosphokinase, creatinine, blood urea nitrogen, uric acid, HDL cholesterol, LDL cholesterol, triglycerides, and blood glucose), and urinalysis (including glucose, protein, occult blood, and pH) parameters. No adverse events attributed to the test article were observed during the study. No clinically significant changes in vital signs, haematological, or urinalysis parameters were observed. Although a statistically significant decrease in blood glucose was observed in subjects receiving 100 mg/day of soya-derived PS compared to placebo controls, a similar change was not observed in subjects receiving the higher dose, and thus the decrease in blood glucose in the low-dose group was deemed to be clinically insignificant. No other statistically significant differences in blood biochemical parameters were observed. The authors concluded that the soya-derived PS was considered safe as a food ingredient.

Table 6. Clinical Trials with phosphatidylserine

Reference; study design	PS Source	Number Subjects (PS-treated)	Dose (mg/day); Duration	Adverse effects reported
Allegro et al., 1987 OL	BC-PS	30 (30)	300; 60 days	No symptoms of adverse reactions were observed
Amaducci et al., 1988; DB-PC	BC-PS	142 (70)	200; 90 days	No change noted in pre- and post-dose clinical exams, clinical chemistries, and blood counts; no adverse events
Baumeister et al., 2008; DB-PC	S-PS	16 (8)	200 in Bars; 42 days	None reported. PS-supplementation has no effect on heart rate values.
Benton et al., 2001; DB-PC	S-PS	48 (22)	300, 1mos.	No side effect in treatment group (2 in placebo).
Caffarra et al., 1987 OL	BC-PS	30 (30)	300; 60 days	None reported
Cenacchi et al., 1987; DB-PC	BC-PS	130	300; 60 days	No treatment related clinically significant adverse effects.
Cenacchi et al., 1993; DB-PC	BC-PS	425 (215)	300; 180 days	Dizziness, vomiting and dyspepsia reported in a few patients, mainly in the

Reference; study design	**PS Source**	**Number Subjects (PS-treated)**	**Dose (mg/day); Duration**	**Adverse effects reported**
				placebo group. No pharmacological interactions
Crook et al., 1991; DB-PC	BC-PS	149 (74)	300; 12 wks.	Well tolerated; no adverse events
Crook et al., 1992; DB-PC	BC-PS	51 (51)	300; 12 wks.	Well tolerated; no adverse events
Crook, 1998	S-PS	50 (50)	300; 12 wks	No adverse effects noted
Delwaide et al., 1986; DB-PC	BC-PS	35 (17)	300; 6 wks.	No significant side effects noted
Engel et al., 1992; DB-PC	BC-PS	33 (33)	300; 8 wks.	None reported
Fahey and Pearl, 1998; DB	S-PS	11 (11)	800; 2 wks.	None reported
Funfgeld et al., 1989; DB-PC	NA	62 (31)	300; NA	None reported
Granata & Michele, 1987 OL	BC-PS	35(35)	300; 60 days	None reported
Gindin et al., 1993; DB-PC	S-PS	72(31)	300 mg; 3 mos.	No adverse effects noted
Heiss et al., 1993 OL	BC-PS	80 (20)	400; 6 mos.	None reported
Heiss et al., 1994 OL	BC-PS	70 (18)	400; 6 mos.	None reported
Hellhammer et al, 2004 DB-PC	S-PS	80 (59)	400, 600, 800; 4wks. (*each 100 mg PS contains additional: 125 mg phosphatic acid, 270mg of other PL, 5mg of silicon dioxide*)	Not reported
Hellhammer et al, 2012 DB-PC	M-PS	60 (30)	300; 12 wks	No significant adverse events reported, Weight gain, high blood pressure and uneasiness were reported by two subjects from the treatment group. Blood pleasure was without measurable abnormalities.
Hershkowitz et al., 1989; DB-PC + OL	BC-PS	58 (24); OL(30)	300; 6 mos.	None reported
Hirayama et al, 2006; OL	S-PS	15	200; 2 mos.	None reported
Hirayama et al, 2013 DB-PC	S-PS	36(19)	200; 2 mos.	The treatment was well-tolerated and no adverse effects were observed.
Jäger et al., 2007 DB-PC	S-PS	20 (10)	200, bars	None reported. No influence on mean heart rate.

Reference; study design	**PS Source**	**Number Subjects (PS-treated)**	**Dose (mg/day); Duration**	**Adverse effects reported**
Jorissen et al. 2002 DB-PC	S-PS	120 (81)	300 or 600; 12 wks.	No adverse events and no significant differences were found in standard biochemical and hematological safety parameter, blood pressure and heart rate.
Kato Kataoka et al, 2010; DB-PC	S-PS	73 (50)	100 or 300; 6 mos.	No adverse event was observed. No clinically significant change in vital signs, hematological and biological blood or urine parameters. Differences in blood glucose levels were considered clinically insignificant.
Maggioni et al., 1990; PC-CO	BC-PS	10 (10)	300; 30 days	None reported
Manor et al, 2013; DB-PC+ OL	M-PS	200(137)	300; 15 wks blinded +15 wks open label	Well tolerated. No major adverse events. Adverse events reported included – gastrointestinal discomfort, atopic dermatitis, hyperactivity, tics, nausea, elevated SGOT, tantrum episodes, insomnia, high triacylglyceride level, and soft stools.
Monteleone et al., 1992 DB-PC	BC-PS	9 (9)	800; 10 days	None reported; BP unchanged
Palmieri et al., 1987; DB-PC	BC-PS	87 (44)	300; 60 days	No change noted in pre- and post-dose clinical and neurological exams, clinical chemistries, and EEG.
Parker et al, 2011 OL	S-PS	18 (18)	400; 14 days	Not effected on cortisol, total testosterone, or mood.
Puca et al., 1987 OL	BC-PS	27 (27)	300; 60 days	No change in pre- and post-dose blood biochemistry parameters.
Rabboni et al., 1990 OL	BC-PS	30 (30)	400; 60 days	No reported changes in liver and kidney function blood biochemistry or blood counts.
Ransmayr et al., 1987; DB-PC	BC-PS	39 (20)	300; 60 days	Few patients with epigastric pain associated with oil or gelatin caps.
Richter et al, 2010 OL	M-PS	8 (8)	300; 6wks	Not reported
Richter et al, 2011 OL	M-PS	26 (26)	100; 12wks *(in combination with 600mg GPC, 20mg vinpocetine,50 mg uridine-5'-monophosphate (disodium),*	No significant changes were found in resting BP,pulse and weight during the study period. In addition, no major adverse events were reported.

Reference; study design	PS Source	Number Subjects (PS-treated)	Dose (mg/day); Duration	Adverse effects reported
			550mg plant extracts (150 mg wild blueberry, 125 mg ashwagandha, 150 mg grape seed, 125 mg hops, ginger and rosemary).	
Richter et al, 2013 OL	S-PS	30 (30)	300; 12 wks	S-PS significantly reduces BP. S-PS consumption was well tolerated and no serious adverse events were reported
Schreiber et al., 2000 OL	S-PS	15 (15)	300; 12 wks	No changes noted in serum electrolytes, glucose, thyroid function, and differential blood counts; no adverse effects noted.
Sinforiani et al., 1987 OL	BC-PS	34 (34)	300; 60 days	No remarkable side effects
Starks et al., 2008, DB-PC	S-PS	10 (10)	600: 10 days	None reported
Villardita et al., 1987; DB-PC	BC-PS	170 (85)	300; 90 days	None reported
Vaisman et al., 2008; DB-PC	M-PS	60(18)	300; 90 days	No side effects. Well tolerated
Vakhapova V, 2011 DB-PC+OL	M-PS	121 (121)	300mg for 15wks followed by 100mg for 15 wks	No side effects. Well tolerated. A reduction in resting diastolic blood pressure and a slight weight gain among participants who consumed M-PS for 30 weeks
PS = phosphatidylserine; DB-PC = double-blind placebo-controlled; OL- open labeled, BC-PS = Bovine cortex derived phosphatidylserine; S-PS = soy derived phosphatidylserine; M-PS = Marine-based PS; wks = weeks; mos = months				

2.2. Source of Phosphatidylserine and Safety

Historically, phosphatidylserine is derived from animal sources such as bovine cortex. In recent years because of potential contamination concerns from bovine spongiform encephalopathy (BSE) prions, this has been supplanted by plant and marine sources. The safety database contains studies with both bovine, marine and plant derived phosphatidylserine. Hence, it is important to compare the composition of these forms of phosphatidylserine for an understanding of the applicability of the various studies in safety assessment. Sunflower- and soy-derived phosphatidylserine mainly contain polyunsaturated fatty acids. Bovine cortex derived phosphatidylserine (BCPS) primarily contains saturated and monounsaturated fatty acids, as well as some docosahexaenoic acid (Hendler and Rorvik, 2001) and marine derived phosphatidylserine mainly contain omega-3 polyunsaturated fatty acids and saturated fatty acids. A comparison of fatty acid profiles of phosphatidylserine derived sunflower and other sources such as soy, fish, krill and bovine is presented in Table 7.

Table 7 - Comparison of the Fatty Acid Profiles of Sunflower- Soy-, Fish-, Krill- and Bovine-Derived PS

Fatty Acid	Typical Fatty Acid composition (as % of total fatty acids)				
	Sunflower-derived PS	Soy-Derived PS[1]	Fish-derived PS[2]	Krill-Derived PS[3]	Bovine-derived PS[4]
Caprylic acid (C8:0)			1		
Myristic acid (C14:0)			2	2	
Palmitic acid (C16:0)	11	14	23	23.5	3
Palmitoleic acid (C16:1)			2	1.8	
Stearic acid (C18:0)	2.9	4	2	1	40
Oleic acid (C18:1 n-9)	15.8	15	13	13	35
Vaccenic acid (C18:1n-11)					
Linoleic acid (C18:2n-6)	70.11	62	2	1.2	
alpha-Linolenic acid (C18:3 n-3)	0.2	5	1	1	
Octadecatetraenoic acid (C18:4n-3)				2	
Eicosenoic (C20:1n-9)			2	0.6	6
Arachidonic acid (C20:4n-6)			1	0.7	
Eicosapentaenoic acid (C20:5n-3; EPA)			12	31	
Erucic acid (C22:1)				1.3	6
Docosapentaenoic acid (C22:5)			1	0.7	
Docosahexaenoic acid (C22:6n-3; DHA)			33	14	7
Nervonic acid (C24:1n-9)				0.3	3
Others			5	5	

[1] GRN No. 000223
[2] GRN No. 000279
[3] GRN No. 000311
[4] Adopted from Claro et al. 1999.

Although, fatty acid composition between bovine cortex-derived ,soy-, marine- or sunflower-derived phosphatidylserine differs, as discussed below, these differences are unlikely to affect the safety profile. Following ingestion, phosphatidylserine of any origin is modified in the gastrointestinal mucosa. In the human body, ingested phosphatidylserine, particularly its fatty acid composition, from different sources is modified depending on the body need. Secondly, depending on the target tissue requirements, the fatty acid profile of phosphatidylserine is modified to meet the need of the tissue/organ. These facts demonstrate that the fatty acid composition of phosphatidylserine and thus the source is unlikely to play a role in its safety.

2.3. Absorption, Metabolism and Excretion

Following dietary ingestion of phosphatidylserine, pancreatic digestive enzymes cleave specific fatty acids. The lysophospholipids thus formed are absorbed by the mucosal cells of the intestine and could be reacylated into phosphatidylserine. The fatty acids released can be further used for triglyceride synthesis (Tso, 1994). Because of the high activity of decarboxylases in the mucosal cells, the majority of the phosphatidylserine is converted into other phospholipids. Phosphatidylserine is decarboxylated mainly to phosphatidylethanolamine (Wise *et al.,* 1965). The reacylated phosphatidylserine, phosphatidylethanolamine and other phospholipids enter the lymph and circulation, and are redistributed. Available evidence indicates that only part of the ingested phosphatidylserine reaches systemic circulation as part of the phospholipid pool. The exact fatty acid profile of the phosphatidylserine that is ingested is unlikely to limit its final disposition in the nerve cells, and *in situ,* the most active form of phosphatidylserine in membranes is the lyso form, which lacks a tail in the 2-position. Unlike phosphatidylcholine, phosphatidylserine does not tend to accumulate in the body (Toffano *et al.,* 1987). Approximately 60% of the ingested phosphatidylserine is excreted in feces, while 10% is eliminated in urine. The major metabolite recovered was lysophosphatidylcholine and to a lesser extent lysophosphatidylserine (Toffano *et al.,* 1987).

Pharmacokinetic studies of phosphatidylserine in rats and mice show good bioavailability. Following intravenous administration of 20 mg/kg of phosphatidyl L-[U-^{14}C]-serine to mice, blood levels of radioactivity declined in biphasic manner. A rapid increase in brain radioactivity was noted. At 20 minutes after the injection, the amount of radioactivity peaked in the brain and was 0.25% of the dose. The amount of radioactivity in liver was 36% of the dose and reached a peak also after 20 minutes (Mazzari *et al.,* 1982). Following a bolus intravenous injection of radio-labeled phosphatidylserine (2 mg/kg) to rats, plasma concentration showed a biphasic decline with half-lives of 0.85 and 40 min (Palatini *et al.,* 1991). The initial decline was found to be due to the irreversible uptake of phosphatidylserine liposomes by the mononuclear phagocyte system, as demonstrated by the almost exclusive accumulation of phosphatidylserine in liver and spleen. The slow decline phase reflects the elimination of that fraction of phosphatidylserine, which has been incorporated into high density plasma lipoproteins. Comparative analysis of the biotransformation products found in tissues following either [^{3}H]-glycerol- or [^{14}C]-serine-phosphatidylserine injection show that parenterally administered phosphatidylserine follows two pathways: decarboxylation to phosphatidylethanolamine and extensive hydrolytic degradation with release of the individual components of the molecule.

2.4. Subchronic Studies

Results from repeat-dose safety studies in rats and dogs show that oral administration of phosphatidylserine at doses up to 1000 mg/kg/day for up to 6 months was without any significant adverse effects.

2.4.1. Rat Study

In a repeat-dose study, groups of Sprague-Dawley rats (20/sex/group) were administered daily with 0 (vehicle control), 10, 100, and 1000 mg/kg BCPS *via* gavage for 26 weeks (Heywood *et al.,* 1987). Compared to controls, BCPS administration did not significantly affect survival, weight gain and, feed, or water consumption. In some of the animals receiving 1000 mg/kg/day, post-dose salivation was noted. No significant hematological changes attributable to BCPS treatment were noted. In male and female rats receiving the highest dose of BCPS, a slight increase in alkaline phosphatase levels was observed. At week 13, in males receiving the highest dose of BCPS, serum albumin levels were slightly lowered, potassium levels were elevated and serum sodium values were decreased. In males and females receiving the highest dose, lower urine pH values were recorded. Terminal necropsy did not reveal any adverse macroscopic or microscopic treatment related findings. In the absence of dose-related effects, minimal changes, and lack of histological changes, the adverse effects noted in this study were considered minor. The results of this study show that the no-observed-adverse-effect level (NOAEL) is lower than 1000 mg/kg/day but is closer to this dose.

2.4.2. Dog Studies

Groups of pure-bred beagle dogs (5/sex/group) were administered BCPS at dosage levels of 0 (vehicle control; corn oil), 10, 100, and 1000 mg/kg/day *via* gavage for 26 weeks (Heywood *et al.,* 1987). No deaths were recorded in any of the groups during the treatment. During the first eight weeks of the study, animals in the high-dose group consumed less feed. Following week 9, animals were given moistened feed and the intake was matched with the control group. Compared to controls, animals receiving the highest dose showed a decrease in body weight gain. In dogs receiving 1000 mg/kg/day dose, the blood glucose and cholesterol levels were significantly decreased. No treatment related macroscopic findings or changes in organ weights were noted. Histological examinations of tissues did not reveal any treatment related changes. Similar to the 26-week rat study, the adverse effects noted were minor and the results show that NOAEL is lower than 1000 mg/kg/day but is closer to this dose.

In another repeat-dose study, groups of pure-bred beagle dogs (4/sex/group) were administered BCPS at dosage levels of 0 (vehicle control), 5, 10, and 15 mg/kg/day *via* intramuscular injection for 13 weeks (Heywood *et al.,* 1987). BCPS administration did not affect body weight gain. In animals receiving 10 and 15 mg/kg/day dose, pain reaction during the dosing procedure and subcutaneous hardening of injection site was noted. Hematological examinations revealed elevations in erythrocyte sedimentation rates and total white blood cell counts in animal receiving highest dose of BCPS.

Morphological examinations at termination did not reveal any changes, except for injection site changes in all groups.

2.5. Teratogenicity/Reproduction Studies

In a teratogenicity study, BCPS was administered *via* oral gavage to pregnant Sprague-Dawley rats at daily doses of 0, 10, 100, and 200 mg/kg/day from Days 6 to 15 of gestation (Heywood *et al.,* 1987). Based on the results summarized for this study, the highest dose described in methods section should be 1000 mg/kg/day, instead of 200 mg/kg/day. On day-20, animals were killed, litter values determined, and fetuses were examined for skeletal and visceral malformations. The only sign of toxicity noted in rats receiving 1000 mg BCPS/kg/day was a slight increase in salivation. BCPS treatment did not affect mean weight gain during gestation. At terminal autopsy, no treatment-related macroscopic changes were noted. BCPS treatment did not affect litter values as assessed by litter size, post-implantation loss, litter and mean fetal weights, and the embryonic and fetal development.

In another teratogenicity study, BCPS was administered *via* oral gavage to pregnant New Zealand white rabbits at daily doses of 0, 50, 150, and 450 mg/kg/day from Days 6 to 18 of pregnancy (Heywood *et al.,* 1987). At the highest dose level, BCPS administration resulted in a decrease in body weight gain during the first four days of dosing. On day-29 of pregnancy, animals were killed, litters were examined macroscopically, and fetuses were examined for skeletal and visceral abnormalities. The mean fetal weights at the highest dose were slightly lower but did not reach statistical significance. BCPS administration did not affect embryonic and fetal development.

In summary, results of teratogenicity studies in rats at doses up to 200 mg/kg/day and in rabbits at doses up to 450 mg/kg/day show that oral administration of phosphatidylserine did not affect embryonic and fetal development.

2.6. Genotoxicity

The mutagenic potential of BCPS was investigated in a human lymphocytes chromosomal damage assay, mouse-lymphoma cell mutation test, cultured human epithelial cell DNA repair assay and in an *in vivo* mouse micronucleus assay (Heywood *et al.,* 1987). Cultures of human lymphocytes were exposed to BCPS at concentrations of 0, 17, 83 and 166 μg/ml with and without metabolic activation. Compared to the control, no significant increase in chromosomal damage was noted in either the presence or absence of metabolic activation. In the *in vitro* mouse lymphoma L5178Y mammalian cell test system, which detects mutations from the heterozygous condition for the thymidine kinase locus (TK+/-) to the thymidine kinase deficient genotype (TK-/-), exposure to BCPS did not reveal any significant increases in the number of mutant colonies or mutation frequency either in the presence or absence of metabolic activation. In the DNA repair assay with autoradiographic techniques, cultured human epitheloid cells did not reveal any evidence of DNA repair synthesis in the HELA S3 cells either in the presence or absence of metabolic activation.

In the micronucleus test, BCPS was administered *via* oral gavage to mice at total dosages of 30, 150 and 300 mg/kg in two equal doses separated by 24-hours. The positive control group was treated with mytomycin C. At six hours after the second dose, mice were killed and bone marrow smears were examined for the presence of micronuclei in 1000 polychromatic erythrocytes per mouse and for the ratio of normochromatic and polychromatic erythrocytes. The results of the study did not reveal any evidence of mutagenic potential or bone marrow toxicity.

Under the conditions of the above *in vitro* and *in vivo* studies BCPC is devoid of any genotoxic or clastogenic activity.

2.7. Acute and Short-term Studies

The acute oral and subcutaneous LD_{50} of BCPS in Sprague-Dawley rats by standard methods was reported as greater than 5 g/kg body weight. The intravenous LD_{50} of BCPS in rats was reported as 236 mg/kg body weight (Heywood *et al.,* 1987). In a series of studies conducted in rats and mice to evaluate the maximum tolerated dose of phosphatidylserine derived from soy, single doses up to 2000 mg/kg body weight were well tolerated in both the species (Degussa, 2006).

In a repeat-dose short-term study, groups of 10 male and 10 female Sprague-Dawley rats were administered BCPS at dose levels of 0 (vehicle control), 5, 20, and 80 mg/kg/day *via* intravenous route for four weeks (Heywood *et al.,* 1987). In all BCPS treated groups except females at 5 mg/kg dose, reddening and swelling of paws and around the muscle region was noted. At the highest dose level, a decrease in body weight and food consumption was noted. In animals receiving the highest dose (80 mg/kg/day), a significant decrease in red blood cell counts, hemoglobin, packed cell volume and increases in neutrophil, lymphocyte counts and alkaline phosphatases were noted. Increases in the weights of spleen (in male and female rats receiving 80 mg/kg/day; and in males receiving 20 mg/kg/day), adrenal (in males and females receiving 80 mg/kg/day) and kidney (in male rats receiving 20 and 80 mg/kg/day) were noted. Injection site thrombosis was noted in some rats in all groups (Heywood *et al.,* 1987).

In another four week repeat-dose study, groups of pure-bred beagle dogs (3/sex/group) were administered BCPS at dosage levels of 0 (vehicle control), 5, 15, and 40 mg/kg/day *via* intravenous route for 28 days (Heywood *et al.,* 1987). No mortality was noted in any group. In animals receiving 15 and 40 mg/kg/day dose, generalized tremors of body muscles were noted. In male animals receiving the highest dose of BCPS, a significant reduction in weight gain, increases in white blood cell count and total serum protein were noted. BCPS treatment did not affect organ weights. Histological examinations of liver revealed centrilobular and periportal sinusoidal aggregations of polymorphonuclear leucocytes in one animal receiving 15 mg/kg/day and four animals receiving 40 mg/kg/day of BCPS.

In summary, the acute oral LD_{50} of phosphatidylserine in rats was greater than 5 g/kg body weight. Short-term intravenous administration studies in rats and dogs indicate that phosphatidylserine causes adverse effects. However, as discussed above these effects resulting from intravenous administration of phosphatidylserine were not observed in long-term studies following oral ingestion.

3. SUMMARY

Phosphatidylserine, a structural component of cells, is found in all biological membranes of plants, animals and other life forms. The human body contains about 30 g of phosphatidylserine, about half (~13 g) of which is found in brain. Phosphatidylserine plays a vital role in several metabolic processes such as activation of cell-membrane bound enzymes and is involved in neuronal signaling. Enzymotec proposes to use a standardized sunflower lecithin derived phosphatidylserine (SharpPS® Green) as a nutrient at levels up to 100 mg phosphatidylserine/serving in milk, flavored milk, milk drinks (excluding milk, fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink at use levels up to 50 mg phosphatidylserine/serving in breakfast cereals and milk, fluid and in Medical Food at a level not to exceed 300 mg phosphatidylserine/person/day. The intended use of SharpPS® Green will result in an estimated daily mean and 90th percentile intake for "users only" of 44.75 mg/person (0.95 mg/kg body weight/day) and 98.73 mg/person (2.51 mg/kg body weight/day), respectively. Phosphatidylserine has been the subject of five GRAS Notices submitted to FDA for use as a nutrient. In each case, FDA responded that they had no questions on the proposed use and did not object to the respective GRAS determination. In one of these notices, the use of phosphatidylserine was determined as GRAS at estimated daily intake levels of 240 mg/person/day.

Multiple clinical studies (> 42) with over 1600 participants revealed that oral administration of phosphatidylserine at doses of 100 to 800 mg/day is without any adverse effect. In about half of these studies, phosphatidylserine was derived from bovine cortex. In one GRAS notice submitted by Enzymotec, the phosphatidylserine was derived from soy. The available scientific evidence indicates that phosphatidylserine derived from sunflower lecithin is toxicologically equivalent to phosphatidylserine naturally found in diet or derived from bovine cortex or soy. Once inside the body, orally ingested phosphatidylserine is hydrolyzed in the intestine prior to its absorption. The absorbed phosphatidylserine is transported and rapidly converted into other endogenous constituents. In repeat-dose safety studies in rats and dogs, oral administration of phosphatidylserine at doses up to 1000 mg/kg/day for up to 6 months was without any significant toxicity. The adverse effects noted in animal safety studies at 1000 mg/kg/day were considered minor as these changes were small in magnitude, not supported by any histological damage, and lacked any dose-response correlation. In teratogenicity studies in rats and rabbits, phosphatidylserine did not affect embryonic and fetal development. Multiple genotoxicity studies show that phosphatidylserine did not reveal any genotoxic or clastogenic activity. The acute oral LD_{50} of phosphatidylserine in rats was reported as greater than 5 g/kg body weight.

4. RISK ASSESSMENT

There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to determine safety-in-use or acceptable daily intake (ADI) for phosphatidylserine. The safety data on phosphatidylserine includes over 42 human clinical trials, repeat-dose (6 month) studies in rats and dogs, teratogenicity/reproductive toxicity studies in rats and rabbits, and *in vitro* and *in vivo* genotoxicity studies.

Generally, ADIs are derived from a no-observed-adverse-effect level determined from animal studies with considerations of uncertainty factors to account for variabilities and uncertainties. The animal studies did not show any significant toxicity at doses up to 1000 mg/kg/day. Several human clinical trials (>42) and historical use supports the safety of phosphatidylserine at even higher use levels than can be determined by available animal studies. The discussion presented in this document supports a safe level of 300 mg/day.

The clinical evidence of phosphatidylserine safety is supported by:

- Phosphatidylserine is commonly found in daily-consumed foods such as meat, fish, legume, etc.
- Phosphatidylserine is an endogenous substance found in human body.
- The bioavailability of the ingested phosphatidylserine is limited due to extensive hydrolysis in the intestine prior to absorption, and that the absorbed phosphatidylserine is transported and rapidly converted into other endogenous constituents.
- In multiple (>42) human clinical studies, safety of phosphatidylserine was confirmed at doses of 300 mg/day.
- The majority of the clinical studies of phosphatidylserine included susceptible groups (elderly).
- There is no evidence that consumption of phosphatidylserine either in foods or as a dietary supplement has a cumulative effect that would affect its safety.
- A variety of animal and *in vitro* studies corroborate the human clinical safety data.

Phosphatidylserine has been marketed as a dietary supplement for over 15 years without any adverse effects (except gastrointestinal side effects such as nausea and indigestion). The typical recommended doses of phosphatidylserine as a dietary supplement are 100 mg three times a day (300 mg/day). Additionally, FDA has agreed to exercise enforcement discretion with a Health Claim Petition[8] on phosphatidylserine. The petitioner in this submission demonstrated that soy-derived phosphatidylserine is safe at levels up to 500 mg/day[9]. In a notice submitted to the FDA, use of phosphatidylserine was determined as GRAS at an estimated 90th percentile intake of 240 mg/person/day.

The intended use of SharpPS® Green will result in a daily estimated 90th percentile intake for "users only" of 98.73 mg phosphatidylserine/person (2.51 mg/kg body weight/day). The 90th percentile intake of phosphatidylserine is approximately 3-fold lower than the safe levels (300 mg/day) determined on the basis of available safety studies.

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[8] "Letter Regarding Dietary Supplement Health Claim for Phosphatidylserine and Cognitive Dysfunction and Dementia" (2003); Available at: http://www.cfsan.fda.gov/~dms/ds-ltr33.html.

[9] Petition for Health Claim: Phosphatidylserine and Cognitive Dysfunction, Phosphatidylserine and Dementia (2002); Available at: http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091302/80027351.pdf.

Therefore, Enzymotec has determined, on the basis of scientific procedures[10], and history of exposure from natural sources, that the consumption of phosphatidylserine as an added food ingredient is safe at levels up to 300 mg/day. The intended uses are compatible with current regulations, *i.e.,* phosphatidylserine is used in milk, flavored milk, milk drinks, milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, breakfast cereals, fruit flavored drink and Medical Food, and is produced according to current good manufacturing practices (cGMP).

[10] 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.

5. CONCLUSION

Based on a critical evaluation of the publicly available data summarized above, the Enzymotec has concluded that sunflower lecithin-derived phosphatidylserine, meeting the specifications cited above, and when used as a nutrient [21 CFR 170.3(o)(20)] at maximum use levels of up to 100 mg phosphatidylserine/serving in milk, flavored milk, milk drinks (excluding milk fluid), milk imitation (soy milk), milk-based meal replacement, yogurt, breakfast bars, and fruit flavored drink , at use levels of 50 mg phosphatidylserine/serving in breakfast cereals and milk fluid and in Medical Food at a use level not to exceed 300 mg phosphatidylserine/person/day, is safe.

It is also Enzymotec's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, Enzymotec has also concluded that phosphatidylserine, when used as described, is GRAS based on scientific procedures.

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7. APPENDIX I

ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE BY THE U.S. POPULATION FROM PROPOSED FOOD-USES

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ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE BY THE U.S. POPULATION FROM PROPOSED FOOD-USES

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ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE BY THE U.S. POPULATION FROM PROPOSED FOOD-USES

Table of Contents

List of Appendices

List of Tables

ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE BY THE U.S. POPULATION FROM PROPOSED FOOD-USES

1.0 INTRODUCTION

Cantox Health Sciences International (Cantox) has completed an assessment of the consumption of phosphatidylserine by the U.S. population in breakfast cereals (instant and regular hot cereals and ready-to-eat cereals), dairy product analogs (imitation milk and soy milk), grain products and pastas (nutritional bars (breakfast, granola, protein)), milk and milk products (flavored milk and milk drinks, fluid, milk, fluid (regular, filled, buttermilk, and dry reconstituted), milk-based meal replacements, and yogurt), and processed fruits and fruit juices (fruit flavored drinks).

Estimates for the intake of phosphatidylserine were based on the proposed food-uses and use-levels in conjunction with food consumption data included in the United States Department of Agriculture's (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) and the 1998 Supplemental Children's Survey (CSFII 1998) (USDA, 2000). Calculations for the mean and 90th percentile all-person and all-user intakes, and percent consuming were performed for each of the individual food-uses of phosphatidylserine. Similar calculations were used to determine the estimated total intake of phosphatidylserine from all proposed food-uses combined. In both cases, the per person and per kilogram body weight intakes were reported for the following population groups:

infants, ages 0 to 2;
children, ages 3 to 11;
female teenagers, ages 12 to 19;
male teenagers, ages 12 to 19;
female adults, ages 20 and up;
male adults, ages 20 and up; and
total population (all population and gender groups combined).

2.0 FOOD CONSUMPTION SURVEY DATA

2.1 Survey Description

Nationwide dietary intake data for the years 2001-2002 are now available for public use; however, only Day 1 interview data are included in the present release. It is well established that the length of a dietary survey affects the estimated consumption of individual users and that short-term surveys, such as the typical 1-day dietary survey, overestimate consumption over longer time periods (Anderson, 1988). Because two 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) are available from the CSFII 1994-1996, 1998 surveys, these data were used to generate estimates for the current intake analysis.

USDA CSFII 1994-1996 provides food consumption data on persons of all ages, whereas, CSFII 1998 is limited to children from birth through 9 years of age. Combined, these surveys provide the most appropriate data for evaluating food-use and food-consumption patterns in the United States, containing 4 years of data on individuals selected *via* stratified, multistage area probability sampling of American households within all 50 states.

CSFII 1994-1996, 1998 survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Data were collected in-person, a minimum of 3 days apart, on different days of the week, to achieve the desired degree of statistical independence. CSFII 1994-1996 contains 2-day dietary food consumption data for more than 15,000 individuals of all ages, and 1-day data for 16,103 individuals. CSFII 1998 contributes data from an additional 5,559 children, birth through 9 years of age, to data reported for 4,253 children of the same ages within CSFII 1994-1996. The overall CSFII 1994-1996, 1998 response rate for individuals selected for participation in the survey was 81.5 and 77.5% for Day 1 and Day 2, respectively.

In addition to collecting information on the types and quantities of foods being consumed, CSFII 1994-1996, 1998 collected physiological and demographic information from individual participants in the survey, such as sex, age, self-reported height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. USDA sample weights were developed and incorporated with CSFII 1994-1996, 1998 to compensate for the potential under-representation of intakes from specific population groups as a result of sample variability due to survey design, differential non-response rates, or other factors, such as deficiencies in the sampling frame (USDA, 2000).

2.2 Statistical Methods

Consumption data from individual dietary records, detailing food items ingested by each survey participant on each of the 2 survey days, were collated by computer and used to generate estimates for the intake of phosphatidylserine from all proposed food-uses by the U.S. population. Estimates for the daily intake of phosphatidylserine from all proposed food-uses represent projected 2-day averages for each individual from Day 1 and Day 2 of CSFII 1994-96, 1998 data. These average amounts comprised the distribution from which mean and percentile intake estimates were produced. Mean and percentile estimates were generated using ratio estimation and non-parametric techniques, respectively, incorporating USDA survey weights in order to provide representative intakes for the entire U.S. population. All-person intake refers to the estimated intake of phosphatidylserine averaged over all individuals surveyed, regardless of whether they consumed food products containing phosphatidylserine, and therefore includes "zero" consumers (those who reported no intake of phosphatidylserine during the 2 survey days). All-user intake refers to the estimated intake of phosphatidylserine by those individuals consuming food products containing phosphatidylserine, hence the 'all-user' designation. Individuals were considered users if they consumed 1 or more food products of the proposed phosphatidylserine on either Day 1 or Day 2 of the survey.

2.3 Statistical Reliability

Mean or percentile intake estimates based on small sample sizes or with high variability relative to the mean [assessed using the coefficient of variation (CV)] may be less statistically reliable than estimates based on adequate sample sizes or low variability relative to the mean (LSRO, 1995). Data presented herein for the estimated daily intake of phosphatidylserine follow the guidelines proposed by the Human Nutrition Information Service/National Center for Health Statistics Analytic Working Group for evaluating the reliability of statistical estimates adopted in the "Third Report on Nutrition Monitoring in the United States", whereby an estimated mean may be unreliable if the CV is equal to or greater than 30% (LSRO, 1995). The CV is the ratio of the estimated standard error of the mean to the estimated mean, expressed as a percentage (LSRO, 1995). Therefore, for the estimated intakes of phosphatidylserine presented herein, values were considered statistically unreliable if the CV was equal to or greater than 30%. These values were not considered when assessing the relative contribution of specific food-uses to total phosphatidylserine consumption and are marked with an asterisk.

3.0 FOOD USAGE DATA

The individual proposed food-uses and use-levels for phosphatidylserine employed in the current intake analysis are summarized in Table 3-1. Food codes representative of each proposed food-use were chosen from the CSFII 1994-1996, 1998 (USDA, 2000) and grouped in food-use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (CFR, 2006a). Product-specific adjustment factors were developed based on data provided in the standard recipe file for the CSFII 1994-1996, 1998 survey (USDA, 2000). All food codes included in the current intake assessment are listed in Appendix C.

Table 3-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Phosphatidylserine in the United States

Food Category	Proposed Food-Use	Use-Level (mg/RACC)	RACC* (g or mL)	Use-Level (%)
Breakfast Cereals	Instant and Regular Hot Cereals	50	240	0.0208
	Ready-to-Eat Cereals	50	15 to 55	0.333 to 0.0909
Dairy Product Analogs	Imitation Milk	100	240	0.042
	Soy Milk	100	240	0.042
Grain Products and Pastas	Nutritional Bars (Breakfast, Granola, Protein)	100	40	0.250
Milk Products	Flavored Milk and Milk Drinks, Fluid	100	240	0.042
	Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	50	240	0.0208
	Milk-Based Meal Replacements	100	240	0.042
	Yogurt	100	225	0.044
Processed Fruits and Fruit Juices	Fruit Flavored Drinks	100	240	0.042

* RACC – Reference Amounts Customarily Consumed Per Eating Occasion (21 CFR §101.12) (CFR, 2006b). When a range of values is reported for a proposed food-use, particular foods within that food-use may differ with respect to their RACC.

4.0 FOOD SURVEY RESULTS

Estimates for the total daily intakes of phosphatidylserine from all proposed food-uses are provided in Tables 4.1-1 and 4.1-2. Estimates for the daily intake of phosphatidylserine from individual food-uses in the U.S. are summarized in Tables A-1 to A-7 and B-1 to B-7 of Appendices A and B, respectively. Tables A-1 to A-7 provide estimates for the daily intake of phosphatidylserine per person (g/day), whereas Tables B-1 to B-7 provide estimates for the daily intake of phosphatidylserine on a per kilogram body weight basis (g/kg body weight/day).

4.1 Estimated Daily Intake of Phosphatidylserine from All Proposed Food-Uses

The estimated total intake of phosphatidylserine from all proposed food-uses in the U.S. by population group is summarized in Table 4.1-1. Table 4.1-2 presents this data on a per kilogram body weight basis.

Approximately 59.9% of the total U.S. population was identified as consumers of phosphatidylserine (12,341 actual users identified). Consumption of these types of foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of phosphatidylserine of 24.61 mg/person/day (0.52 mg/kg body weight/day) and 44.75 mg/person/day (0.95 mg/kg body weight/day), respectively (Tables 4.1-1 and 4.1-2). The 90th percentile all-person and all-user intakes of phosphatidylserine from all proposed food-uses by the total population were 70.00 mg/person/day (1.46 mg/kg body weight/day) and 98.73 mg/person/day (2.15 mg/kg body weight/day), respectively. The 50th percentile or median reports the value in the middle of the distribution. The median is less sensitive to extreme values than the mean and is useful if the overall distribution is highly skewed. In this assessment there are a low number of individuals reported for each food group causing the values of the 50th percentile to be low, as presented in Tables 4.1-1 and 4.1-2; therefore, for the purpose of this report, the 50th percentile will not be discussed further.

On an individual population basis, the greatest mean all-person and all-user intakes of phosphatidylserine on an absolute basis were determined in male teenagers, at 33.50 mg/person/day (0.56 g/kg body weight/day), and 60.73 mg/person/day (1.01 mg/kg body weight/day), respectively. Children encompassed the greatest percentage of users of any population group at 79.8%. Infants had the lowest intakes of phosphatidylserine on an absolute basis, with all-person and all-user mean intakes of 16.23 and 27.39 mg/person/day, respectively. On a body weight basis, mean all-person intake of phosphatidylserine was highest in children, at 1.36 mg/kg body weight/day, and the mean all-user intake was highest in infants, at 2.21 mg/kg body weight/day. The lowest mean all-person and all-user intakes on a per kilogram body weight basis were observed in male adults (0.28 and 0.61 mg/kg body weight/day) (Table 4.2-2).

Table 4.1-1 Summary of the Estimated Daily Intake of Phosphatidylserine from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
				Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Infant	0 to 2	52.5	1,880	16.23	6.23	46.25	27.39	17.43	60.49
Child	3 to 11	79.8	5,030	33.03	23.24	80.81	41.90	29.88	91.10
Female Teenager	12 to 19	54.1	380	25.37	11.62	70.00	45.80	33.20	89.15
Male Teenager	12 to 19	55.0	383	33.50	14.53	98.98	60.73	45.46	117.80
Female Adult	20 and Up	53.3	2,438	22.71	8.16	63.66	42.16	27.29	96.42
Male Adult	20 and Up	46.9	2,230	22.76	na	66.40	49.62	33.20	105.00
Total Population	All Ages	59.9	12,341	24.61	9.96	70.00	44.75	30.30	98.73

Table 4.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Phosphatidylserine from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
				Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Infant	0 to 2	52.5	1,880	1.32	0.55	3.80	2.21	1.35	4.86
Child	3 to 11	79.8	5,030	1.36	0.88	3.34	1.72	1.23	3.64
Female Teenager	12 to 19	54.1	380	0.47	0.22	1.35	0.83	0.60	1.67
Male Teenager	12 to 19	55.0	383	0.56	0.24	1.66	1.01	0.72	2.18
Female Adult	20 and Up	53.3	2,438	0.35	0.12	0.99	0.65	0.43	1.47
Male Adult	20 and Up	46.9	2,230	0.28	na	0.83	0.61	0.40	1.31
Total Population	All Ages	59.9	12,341	0.52	0.15	1.46	0.95	0.56	2.15

When heavy consumers (90th percentile) were assessed, all-person and all-user intakes of phosphatidylserine from all proposed food-uses on an absolute basis also were determined to be greatest in male teenagers (98.98 and 117.80 mg/person/day, respectively). The lowest 90th percentile all-person and all-users intakes of phosphatidylserine on an absolute basis were in infants (46.25 and 60.49 mg/person/day, respectively) (Table 4.1-1). On a body weight basis, infants were determined to have the greatest all-person 90th percentile intakes (3.80 mg/kg body weight/day) and the greatest all-user 90th percentile intakes of phosphatidylserine (4.86 mg/kg body weight/day) (Table 4.1-2). The lowest all-person and all-user 90th percentile intakes of phosphatidylserine on a body weight basis were observed in male adults (0.83 and 1.31 mg/kg body weight/day, respectively).

4.1.1 All-Person Intakes

Estimates for the mean and 90th percentile daily intakes of phosphatidylserine from each individual food category are summarized in Tables A-1 to A-7 and B-1 to B-7 on a mg/day and mg/kg body weight/day basis, respectively. Tables A-7 and B-7 summarize the estimates for the mean all-person intakes of phosphatidylserine by the total population (all ages) from each of the individual food-uses on a mg/person/day and mg/kg body weight/day basis, respectively. The total U.S. population was identified as being significant consumers of ready-to-eat cereals (43.7% users) and milk products (13.6% users).

Consumption of ready-to-eat cereals made the most significant contribution to the mean and 90th percentile all-person intakes of the proposed phosphatidylserine, at 9.89 mg/person/day (0.22 mg/kg body weight/day) and 33.20 mg/person/day (0.68 mg/kg body weight/day). On a body weight basis, the highest mean and 90th percentile all-person intakes were 0.22 mg/kg body weight/day and 0.68 mg/kg body weight/day, for ready-to-eat cereals, respectively. Meal replacements, fruit flavoured drinks and dairy product analogs had a negligible impact on the all-person intakes of phosphatidylserine.

Of the individual population groups, the consumption of ready-to-eat cereals made the most significant contribution to the mean all-person intakes of phosphatidylserine (Tables A-1 to A-6 and Tables B-1 to B-6). The consumption of ready-to-eat cereals also made a significant contribution to the 90th percentile intakes of phosphatidylserine in each population group. The highest mean all-person intakes of phosphatidylserine, on an absolute basis, were reported in male teenagers consuming ready-to-eat cereals, at 16.71 mg/person/day (0.28 mg/kg body weight/day), and the highest 90th percentile all-person intakes also were reported in male teenagers consuming ready-to-eat cereals, at 49.90 mg/person/day (0.86 mg/kg body weight/day). On a body weight basis, consumption of ready-to-eat cereals in children led to the highest mean and 90th percentile all-person intakes (0.67 and 1.69 mg/kg body weight/day, respectively) of phosphatidylserine. The lowest mean all-person intakes of phosphatidylserine across the various individual population groups were identified consistently for meal replacements or dairy product analogs.

4.1.2 All-User Intakes

Tables A-7 and B-7 also summarize the estimates for the mean all-user intakes of phosphatidylserine by the total population (all ages) from each of the individual food-uses on a mg/person/day and mg/kg body weight/day basis, respectively. When the number of users of each individual food-use is taken into account, consumers of ready-to-eat cereals were identified as having the greatest contribution to the mean and 90th percentile all-user intakes of phosphatidylserine at 26.61 and 49.80 mg/person/day (0.59 and 1.23 mg/kg body weight/day), respectively. Of the other food categories with a significant number of users of phosphatidylserine in the total population, consumption of yogurt, fluid milk products, and nutritional bars also made significant contributions to the estimates for the mean (49.96, 23.81, and 67.89 mg/person/day, respectively) and 90th percentile (94.33, 54.96 and 113.40 mg/person/day, respectively). The lowest all-user mean and 90th percentile percent user adjusted intakes of phosphatidylserine were observed for dairy product analogs, at 65.29 and 153.31 mg/person/day (1.99 and 4.42 mg/kg body weight/day), respectively.

On an individual population group basis, the consumption of ready-to-eat cereals made the most significant contribution to the all-user intakes of phosphatidylserine (Tables A-1 to A-6 and Tables B-1 to B-6). On an absolute basis children consuming ready-to-eat were determined to have the highest reliable mean and 90th percentile all-user intakes of phosphatidylserine of 477.62 and 604.80 mg/person/day, respectively. On a per kilogram body weight basis, infants consuming dairy product analogs experienced the highest reliable mean and 90th percentile all-user intakes of phosphatidylserine of 10.66 and 19.52 mg/kg body weight/day, respectively.

5.0 CONCLUSIONS

Consumption data and information pertaining to the individual food-uses of phosphatidylserine were used to estimate the all-person and all-user intakes of phosphatidylserine for specific demographic groups and for the total U.S. population. This type of intake methodology is generally considered to be 'worst case' as a result of several conservative assumptions made in the consumption estimates. For example, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate the consumption of food products that are consumed relatively infrequently.

In summary, on an all-user basis, the mean intake of phosphatidylserine by the total U.S. population from all proposed food-uses was estimated to be 44.75 mg/person/day or 0.95 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of phosphatidylserine by the total U.S. population from all proposed food-uses was estimated to be 98.73 mg/person/day or 2.15 mg/kg body weight/day.

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APPENDIX A

Estimated Daily Intake of Phosphatidylserine from Individual Proposed Food-Uses by Different Population Groups Within the United States

TABLE A-1 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY INFANTS AGED 0 TO 2 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.0	429	1.70	na	6.29	11.67	9.63	23.01
Ready-to-eat Cereals	39.8	1,424	6.41	na	20.13	14.33	11.62	29.05
Dairy Product Analogs								
Soy and Imitation Milk Products	0.3	9	0.40*	na	na	143.86	135.06	257.25
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	3.2	115	1.96	na	na	51.34	46.25	92.50
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	0.9	31	0.51	na	na	57.87	52.42	157.50
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	5.3	190	1.29	na	na	21.90	12.74	55.74
Milk-Based Meal Replacements	0.1	4	0.06*	na	na	48.83*	29.30*	117.42*
Yogurt	9.0	322	3.88	na	3.37	38.36	28.05	62.35
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	< 0.1	1	0.02*	na	na	37.80*	na	37.80*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000059

TABLE A-2 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY CHILDREN AGED 3 TO 11 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)								
Food-Use Category	**% Users**	**Actual # of Total Users**	**All-Person Consumption (mg)**			**All-Users Consumption (mg)**		
			Mean	**50th Percentile**	**90th Percentile**	**Mean**	**50th Percentile**	**90th Percentile**
Cereal and Cereal Products								
Instant and Regular Hot Cereals	13.2	830	1.68	na	6.08	14.87	12.22	26.10
Ready-to-eat Cereals	65.3	4,116	16.52	12.45	41.09	25.99	22.41	47.45
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	15	0.15*	na	na	99.91	77.18	154.35
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	5.8	363	3.73	na	na	58.05	46.25	105.00
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	4.3	272	3.64	na	na	62.16	52.50	105.00
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.6	858	3.94	na	12.74	25.32	19.11	50.96
Milk-Based Meal Replacements	0.2	14	0.16	na	na	62.20	52.08	117.18
Yogurt	9.5	597	2.90	na	na	36.69	27.44	54.89
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.4	27	0.31	na	na	80.44	na	126.00

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000060

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TABLE A-3 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY FEMALE TEENAGERS AGED 12 TO 19 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	5.8	41	0.94	na	na	15.61	12.79	25.17
Ready-to-eat Cereals	40.7	286	10.96	na	33.20	26.05	23.24	47.27
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	1	0.04*	na	na	51.45*	51.45*	51.45*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	5.1	36	3.43	na	na	58.37	53.75	81.25
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	4.6	32	2.97	na	na	71.80	52.50	131.04
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.5	95	3.76	na	12.74	25.74	22.30	63.70
Milk-Based Meal Replacements	0.3	2	0.24*	na	na	100.82	100.82	130.20
Yogurt	3.6	25	1.64	na	na	45.56	40.43	74.84
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.3	2	1.40*	na	na	477.62*	na	604.80*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000061

TABLE A-4 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY MALE TEENAGERS AGED 12 TO 19 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	6.0	42	1.03	na	na	19.60	16.22	38.01
Ready-to-eat Cereals	42.7	297	16.71	na	49.90	38.78	31.13	69.72
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	1	0.12*	na	na	76.97	76.97	76.97
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	4.9	34	3.24	na	na	67.19	53.75	107.50
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	5.7	40	4.95	na	na	77.52	52.50	157.50
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	12.9	90	4.81	na	12.74	37.78	25.48	92.37
Milk-Based Meal Replacements	0.1	1	0.26*	na	na	155.61	155.61	155.61
Yogurt	2.6	18	1.62	na	na	54.40	40.43	106.04
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.4	3	0.77*	na	na	186.69	na	239.40

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000062

TABLE A-5 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY FEMALE ADULTS AGED 20 AND OVER WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.8	586	1.66	na	6.29	14.30	12.17	25.27
Ready-to-eat Cereals	31.9	1,458	7.30	na	25.45	22.73	18.69	41.09
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	10	0.10*	na	na	45.43	51.45	77.18
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	2.9	134	2.21	na	na	64.20	46.25	107.50
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	1.1	50	0.81	na	na	73.72	52.50	110.04
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	19.2	876	4.09	na	15.86	20.52	15.91	44.41
Milk-Based Meal Replacements	0.9	40	0.86	na	na	88.11	71.61	136.71
Yogurt	7.8	357	4.37	na	na	52.66	49.90	99.79
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	1.1	52	1.29	na	na	115.23	na	252.00

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000063

TABLE A-6 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY MALE ADULTS AGED 20 AND OVER WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	11.8	561	1.87	na	na	18.89	13.21	36.50
Ready-to-eat Cereals	29.9	1,422	9.16	na	34.24	31.41	25.45	58.10
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	6	0.08*	na	na	62.44*	34.30*	154.31*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	2.6	123	2.73	na	na	86.10	70.88	162.50
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	0.8	36	0.64	na	na	85.95	52.50	204.96
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	14.8	702	3.86	na	12.74	25.70	19.11	57.30
Milk-Based Meal Replacements	0.5	24	0.42	na	na	107.35	103.74	195.72
Yogurt	4.0	190	2.58	na	na	57.63	49.90	107.80
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.6	129	1.12	na	na	141.57	na	252.00

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000064

TABLE A-7 ESTIMATED DAILY INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY TOTAL POPULATION (ALL AGES) WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg)			All-Users Consumption (mg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.1	2,489	1.66	na	3.97	15.88	12.58	27.55
Ready-to-eat Cereals	43.7	9,003	9.89	na	33.20	26.61	22.20	49.80
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	42	0.11	na	na	65.29	51.45	154.31
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	3.9	805	2.71	na	na	67.89	53.75	113.40
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	2.2	461	1.49	na	na	70.92	52.50	110.04
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.6	2,811	3.89	na	12.74	23.81	19.03	50.96
Milk-Based Meal Replacements	0.4	85	0.51	na	na	92.11	71.61	143.22
Yogurt	7.3	1,509	3.23	na	na	49.96	49.90	94.33
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.6	129	1.12	na	na	141.57	na	252.00

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000065

APPENDIX B

Estimated Daily Per Kilogram Body Weight Intake of Phosphatidylserine from Individual Proposed Food-Uses by Different Population Groups Within the United States

TABLE B-1 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY INFANTS AGED 0 TO 2 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.1	2,489	0.14	na	0.57	0.96	0.79	1.99
Ready-to-eat Cereals	43.7	9,003	0.50	na	1.57	1.12	0.88	2.26
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	42	0.03*	na	na	10.66	8.89	19.52
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	3.9	805	0.16	na	na	4.03	3.40	7.02
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	2.2	461	0.04	na	na	4.45	3.30	13.33
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.6	2,811	0.10	na	na	1.71	1.16	3.71
Milk-Based Meal Replacements	0.4	85	< 0.01*	na	na	4.14*	3.08*	9.94*
Yogurt	7.3	1,509	0.34	na	0.55	3.24	2.63	5.93
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.6	129	< 0.01*	na	na	2.52*	2.52*	2.52*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000067

TABLE B-2 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY CHILDREN AGED 3 TO 11 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	13.2	830	0.08	na	0.25	0.67	0.56	1.18
Ready-to-eat Cereals	65.3	4,116	0.67	0.50	1.69	1.05	0.85	1.99
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	15	0.01*	na	na	4.06	2.83	5.66
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	5.8	363	0.16	na	na	2.34	1.91	4.21
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	4.3	272	0.14	na	na	2.46	2.17	4.13
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.6	858	0.16	na	0.54	1.01	0.76	2.10
Milk-Based Meal Replacements	0.2	14	0.01	na	na	2.09	1.68	4.52
Yogurt	9.5	597	0.14	na	na	1.67	1.37	2.84
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.4	27	0.01	na	na	3.06	2.46	9.70

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

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TABLE B-3 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY FEMALE TEENAGERS AGED 12 TO 19 YEARS WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	5.8	41	0.02	na	na	0.29	0.24	0.50
Ready-to-eat Cereals	40.7	286	0.21	na	0.61	0.48	0.41	0.87
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	1	< 0.01*	na	na	1.08*	1.08*	1.08*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	5.1	36	0.06	na	na	1.04	1.03	1.67
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	4.6	32	0.05	na	na	1.30	1.04	2.40
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.5	95	0.07	na	0.24	0.46	0.35	1.08
Milk-Based Meal Replacements	0.3	2	< 0.01*	na	na	1.55	1.55	1.85
Yogurt	3.6	25	0.03	na	na	0.81	0.81	1.32
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.3	2	0.02*	na	na	8.16*	10.40*	10.40*

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000069

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TABLE B-4 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY MALE TEENAGERS AGED 12 TO 19 YEARS WITHIN THE UNITED STATES 50MG/SERVING (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	6.0	42	0.02	na	na	0.33	0.28	0.63
Ready-to-eat Cereals	42.7	297	0.28	na	0.86	0.65	0.54	1.26
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	1	< 0.01*	na	na	1.25*	1.25*	1.25*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	4.9	34	0.06	na	na	1.25	1.08	2.53
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	5.7	40	0.08	na	na	1.25	1.07	2.17
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	12.9	90	0.08	na	0.18	0.63	0.40	1.35
Milk-Based Meal Replacements	0.1	1	< 0.01*	na	na	2.36*	2.36*	2.36*
Yogurt	2.6	18	0.03	na	na	0.88	0.78	1.17
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.4	3	0.01*	na	na	1.71	1.85	2.07

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000070

TABLE B-5 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY FEMALE ADULTS AGED 20 AND OVER WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.8	586	0.03	na	0.09	0.22	0.18	0.44
Ready-to-eat Cereals	31.9	1,458	0.11	na	0.39	0.35	0.28	0.65
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	10	< 0.01*	na	na	0.76*	0.61*	1.36*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	2.9	134	0.04	na	na	1.02	0.75	2.04
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	1.1	50	0.01	na	na	1.10	0.89	1.97
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	19.2	876	0.06	na	0.24	0.32	0.24	0.67
Milk-Based Meal Replacements	0.9	40	0.01	na	na	1.27	1.18	1.95
Yogurt	7.8	357	0.07	na	na	0.82	0.72	1.46
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	1.1	52	0.02	na	na	1.62	1.28	3.00

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000071

TABLE B-6 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY MALE ADULTS AGED 20 AND OVER WITHIN THE UNITED STATES (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	11.8	561	0.02	na	na	0.24	0.19	0.46
Ready-to-eat Cereals	29.9	1,422	0.11	na	0.41	0.39	0.32	0.73
Dairy Product Analogs								
Soy and Imitation Milk Products	0.1	6	< 0.01*	na	na	1.08*	0.44*	2.42*
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	2.6	123	0.03	na	na	1.03	0.86	1.87
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	0.8	36	0.01	na	na	1.04	0.72	2.01
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	14.8	702	0.05	na	0.15	0.31	0.22	0.66
Milk-Based Meal Replacements	0.5	24	0.01	na	na	1.31	1.31	1.84
Yogurt	4.0	190	0.03	na	na	0.70	0.58	1.33
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.6	129	0.02	na	na	1.95	1.35	3.65

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000072

TABLE B-7 ESTIMATED DAILY PER KILOGRAM BODY WEIGHT INTAKE OF PHOSPHATIDYLSERINE FROM INDIVIDUAL PROPOSED FOOD-USES BY THE TOTAL POPULATION (ALL AGES) WITHIN THE UNITED STATES 50 MG/SERVING (1994-1996, 1998 USDA CSFII DATA)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption (mg/kg)			All-Users Consumption (mg/kg)		
			Mean	50th Percentile	90th Percentile	Mean	50th Percentile	90th Percentile
Cereal and Cereal Products								
Instant and Regular Hot Cereals	12.1	2,489	0.04	na	0.07	0.34	0.23	0.72
Ready-to-eat Cereals	43.7	9,003	0.22	na	0.68	0.59	0.41	1.23
Dairy Product Analogs								
Soy and Imitation Milk Products	0.2	42	< 0.01*	na	na	1.99	1.03	4.42
Grain Products and Pastas								
Nutritional Bars (Breakfast, Granola, Protein)	3.9	805	0.06	na	na	1.46	1.08	2.96
Milk and Milk Products								
Flavored Milk and Milk Drinks, Fluid	2.2	461	0.04	na	na	1.71	1.30	2.96
Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)	13.6	2,811	0.07	na	0.21	0.45	0.29	1.00
Milk-Based Meal Replacements	0.4	85	0.01	na	na	1.39	1.27	2.02
Yogurt	7.3	1,509	0.07	na	na	1.11	0.78	2.13
Processed Fruits and Fruit Juices								
Fruit Flavored Drinks	0.6	129	0.02	na	na	1.98	1.39	3.17

*Indicates an intake estimate that may not be statistically reliable, as the CV of the mean is equal to or greater than 30% (see Section 2.3).

000073

APPENDIX C

Representative CSFII 1994-1996, 1998 Food Codes for All Proposed Food-Uses of Phosphatidylserine in the United States

Representative CSFII 1994-1996, 1998 Food Codes for All Proposed Food-Uses of Phosphatidylserine in the United States

Breakfast Cereals

Instant and Regular Hot Cereals

[Phosphatidylserine] = 0.0208 %

56200300	Cereal, cooked, NFS
56200350	Cereal, cooked, instant, NS as to grain
56200990	Grits, cooked, corn or hominy, NS as to regular, quick or instant, NS as to fat added in cooking
56201000	Grits, cooked, corn or hominy, NS as to regular, quick, or instant, fat not added in cooking
56201010	Grits, cooked, corn or hominy, regular, fat not added in cooking
56201020	Grits, cooked, corn or hominy, regular, fat added in cooking
56201030	Grits, cooked, corn or hominy, regular, NS as to fat added in cooking
56201040	Grits, cooked, corn or hominy, NS as to regular, quick, or instant, fat added in cooking
56201060	Grits, cooked, corn or hominy, with cheese, NS as to regular, quick, or instant, NS as to fat added
56201061	Grits, cooked, corn or hominy, with cheese, NS as to regular, quick, or instant, fat not added in cooking
56201062	Grits, cooked, corn or hominy, with cheese, NS as to regular, quick, or instant, fat added in cooking
56201070	Grits, cooked, corn or hominy, with cheese, regular, NS as to fat added in cooking
56201071	Grits, cooked, corn or hominy, with cheese, regular, fat not added in cooking
56201072	Grits, cooked, corn or hominy, with cheese, regular, fat added in cooking
56201080	Grits, cooked, corn or hominy, with cheese, quick, NS as to fat added in cooking
56201081	Grits, cooked, corn or hominy, with cheese, quick, fat not added in cooking
56201082	Grits, cooked, corn or hominy, with cheese, quick, fat added in cooking
56201090	Grits, cooked, corn or hominy, with cheese, instant, NS as to fat added in cooking
56201091	Grits, cooked, corn or hominy, with cheese, instant, fat not added in cooking
56201092	Grits, cooked, corn or hominy, with cheese, instant, fat added in cooking
56201110	Grits, cooked, corn or hominy, quick, fat not added in cooking
56201120	Grits, cooked, corn or hominy, quick, fat added in cooking
56201130	Grits, cooked, corn or hominy, quick, NS as to fat added in cooking
56201210	Grits, cooked, corn or hominy, instant, fat not added in cooking
56201220	Grits, cooked, corn or hominy, instant, fat added in cooking
56201230	Grits, cooked, corn or hominy, instant, NS as to fat added in cooking
56201240	Grits, cooked, flavored, corn or hominy, instant, fat not added in cooking
56201250	Grits, cooked, flavored, corn or hominy, instant, fat added in cooking
56201260	Grits, cooked, flavored, corn or hominy, instant, NS as to fat added in cooking
56201300	Grits, cooked, corn or hominy, NS as to regular, quick, or instant, NS as to fat added in cooking, made with water
56201510	Cornmeal mush, made with water
56201520	Cornmeal mush, fried
56201530	Cornmeal mush, made with milk
56201540	Cornmeal, rnade with evaporated milk and sugar, Puerto Rican Style (Harina de maize con leche)
56201560	Cornmeal sticks, boiled
56201600	Cornmeal, lime-treated, cooked (Masa harina)
56201700	Cornstarch with milk, eaten as a cereal (2 tbsp cornstarch in 2-1/2 cups milk)
56201990	Millet, cooked, NS as to fat added in cooking
56202000	Millet, cooked, fat not added in cooking

56202100	Millet, cooked, fat added in cooking
56202500	Muesli, prepared, instant
56202960	Oatmeal, cooked, NS as to regular, quick or instant; NS as to fat added in cooking
56202970	Oatmeal, cooked, quick (1 or 3 minutes), NS as to fat added in cooking
56202980	Oatmeal, cooked, regular, NS as to fat added in cooking
56203000	Oatmeal, cooked, NS as to regular, quick or instant, fat not added in cooking
56203010	Oatmeal, cooked, regular, fat not added in cooking
56203020	Oatmeal, cooked, quick (1 or 3 minutes), fat not added in cooking
56203030	Oatmeal, cooked, instant, fat not added in cooking
56203040	Oatmeal, cooked, NS as to regular, quick, or instant, fat added in cooking
56203050	Oatmeal, cooked, regular, fat added in cooking
56203060	Oatmeal, cooked, quick (1 or 3 minutes), fat added in cooking
56203070	Oatmeal, cooked, instant, fat added in cooking
56203080	Oatmeal, cooked, instant, NS as to fat added in cooking
56203090	Oatmeal, fortified, cooked, instant, fat not added in cooking
56203100	Oatmeal, fortified, cooked, instant, fat added in cooking
56203110	Oatmeal with maple flavor, cooked
56203120	Oatmeal, with oat bran, fortified, cooked, instant, fat not added in cooking
56203140	Total Oatmeal, cooked, quick, fat not added in cooking
56203200	Oatmeal with fruit, cooked
56203210	Oatmeal, NS as to regular, quick, or instant, made with milk, fat not added in cooking
56203220	Oatmeal, NS as to regular, quick, or instant, made with milk, fat added in cooking
56203230	Oatmeal, NS as to regular, quick, or instant, made with milk, NS as to fat added in cooking
56203540	Oatmeal, made with evaporated milk and sugar, Puerto Rican style
56203600	Oatmeal, multigrain, cooked, NS as to fat added in cooking
56203610	Oatmeal, multigrain, cooked, fat not added in cooking
56203620	Oatmeal, multigrain, cooked, fat added in cooking
56206970	Wheat, cream of, cooked, quick, NS as to fat added in cooking
56206980	Wheat, cream of, cooked, regular, NS as to fat added in cooking
56206990	Wheat, cream of, cooked, NS as to regular, quick, or instant, NS as to fat added in cooking
56207000	Wheat, cream of, cooked, NS as to regular, quick, or instant, fat not added in cooking
56207010	Wheat, cream of, cooked, regular, fat not added in cooking
56207020	Wheat, cream of, cooked, quick, fat not added in cooking
56207030	Wheat, cream of, cooked, instant, fat not added in cooking
56207040	Wheat, cream of, cooked, made with milk
56207050	Wheat, cream of, cooked, made with milk and sugar, Puerto Rican style
56207060	Wheat, cream of, cooked, instant, fat added in cooking
56207070	Wheat, cream of, cooked, instant, NS as to fat added in cooking
56207080	Wheat, cream of, cooked, NS as to regular, quick, or instant, fat added in cooking
56207100	Wheat, rolled, cooked, fat not added in cooking
56207110	Bulgur, cooked or canned, fat not added in cooking
56207120	Bulgur, cooked or canned, fat added in cooking
56207130	Bulgur, cooked or canned, NS as to fat added in cooking
56207140	Wheat, rolled, cooked, NS as to fat added in cooking
56207150	Couscous, plain, cooked, fat not added in cooking
56207160	Couscous, plain, cooked, NS as to fat added in cooking
56207180	Couscous, plain, cooked, fat added in cooking
56207190	Whole wheat cereal, cooked, NS as to fat added in cooking
56207200	Whole wheat cereal, cooked, fat not added in cooking
56207210	Whole wheat cereal, cooked, fat added in cooking
56207220	Wheat, cream of, cooked, regular, fat added in cooking
56207230	Wheat, cream of, cooked, quick, fat added in cooking
56207290	Wheat hearts, cooked, NS as to fat added in cooking
56207300	Whole wheat cereal, wheat and barley, cooked, fat not added in cooking

56207310	Wheat hearts, cooked, fat not added in cooking
56207330	Whole wheat cereal, wheat and barley, cooked, fat added in cooking
56207340	Whole wheat cereal, wheat and barley, cooked, NS as to fat added in cooking
56207350	Wheat cereal, chocolate flavored, cooked, made with milk
56207360	Wheat cereal, chocolate flavored, cooked, fat not added in cooking
56207370	Wheat cereal, chocolate flavored, cooked, NS as to fat added in cooking
56208000	Multigrain cereal, cooked, fat not added in cooking
56208010	Multigrain cereal, cooked, fat added in cooking
56208020	Multigrain cereal, cooked, NS as to fat added in cooking
56208500	Oat bran cereal, cooked, fat not added in cooking
56208510	Oat bran cereal, cooked, fat added in cooking
56208520	Oat bran cereal, cooked, NS as to fat added in cooking
56208530	Oat bran cereal, cooked, made with milk, fat not added in cooking
56208540	Oat bran cereal, cooked, made with milk, fat added in cooking
56208550	Oat bran cereal, cooked, made with milk, NS as to fat added in cooking
56209000	Rye, cream of, cooked
56210000	Nestum cereal

Ready-to-Eat Cereals
[Phosphatidylserine] = 0.333 to 0.0909 %

57137000	Corn Puffs
57301500	Kashi, Puffed
57306100	Malt-O-Meal Puffed Rice
57306120	Malt-O-Meal Puffed Wheat
57307500	Millet, puffed
57340000	Rice, puffed
57416000	Wheat, puffed, plain
57416010	Wheat, puffed, presweetened with sugar
57000000	Cereal, NFS
57000050	Kashi cereal, NS as to ready to eat or cooked
57000100	Oat cereal, NFS
57100100	Cereal, ready-to-eat, NFS
57101000	All-Bran
57101020	All-Bran with Extra Fiber
57101500	Almond Delight
57102000	Alpen
57103000	Alpha-Bits
57103020	Alpha-bits with marshmallows
57103050	Amaranth Flakes
57103100	Apple Cinnamon Cheerios
57103400	Apple Cinnamon Oh's Cereal
57103450	Apple Cinnamon Rice Krispies
57104000	Apple Jacks
57106000	Banana Frosted Flakes
57106200	Batman
57106250	Berry Berry Kix
57106300	Bigg Mixx
57106500	Bill and Ted's Excellent Adventure
57106530	Blueberry Morning, Post
57107000	Booberry
57109000	Body Buddies, natural fruit flavor
57110000	All-Bran Bran Buds, Kellogg's (formerly Bran Buds)
57111000	Bran Chex
57111300	Bran News
57111500	Bran Muffin Crisp

57112500	Breakfast with Barbie
57113000	Buc Wheats
57113300	Bunuelitos
57114000	C-3PO's
57116100	Cabbage Patch
57117000	Cap'n Crunch
57117500	Cap'n Crunch's Christmas Crunch
57118000	Cap'n Crunch's Choco Crunch
57119000	Cap'n Crunch's Crunch Berries
57119500	Cap'n Crunch's Deep Sea Crunch
57120000	Cap'n Crunch's Peanut Butter Crunch
57123000	Cheerios
57124000	Chex cereal, NFS
57124200	Chocolate flavored frosted puffed corn cereal
57124500	Cinnamon Grahams, General Mills
57125000	Cinnamon Toast Crunch
57125900	Honey Nut Clusters (formerly called Clusters)
57126000	Cocoa Krispies
57126500	Cocoa Blasts, Quaker
57127000	Cocoa Pebbles
57128000	Cocoa Puffs
57128880	Common Sense Oat Bran, plain
57128900	Common Sense Oat Bran, with raisins
57130000	Cookie-Crisp
57131000	Crunchy Corn Bran, Quaker
57132000	Corn Chex
57134000	Corn flakes, NFS
57134090	Corn flakes, low sodium
57135000	Corn flakes, Kellogg
57138000	Total Corn Flakes
57139000	Count Chocula
57141000	Cracker Jack
57144000	Crisp Crunch
57148000	Crispix
57148500	Crispy Brown Rice Cereal
57151000	Crispy Rice
57152000	Crispy Wheats'n Raisins
57152100	Croonchy Stars
57201200	Dairy Crisp w/strawberries
57201700	Dino Pebbles
57202100	Donkey Kong
57203100	Donkey Kong Jr.
57204100	Donutz Cereal
57205100	Donutz Cereal, Chocolate
57205250	Double Chex
57205260	Double Dip Crunch, Kellogg's
57205300	E.T. Cereal
57206700	Fiber One
57206800	Fiber 7 Flakes, Health Valley
57212100	French Toast Crunch, General Mills
57213800	Frosted Bran, Kellogg's
57213850	Frosted Cheerios
57214100	Frosted Wheat Bites
57215000	Frosty O's
57216000	Frosted rice, NFS
57217000	Frosted Rice Krinkles

57218000	Frosted Rice Krispies
57219000	Fruit & Fibre (fiber), NFS
57220000	Fruit & Fibre (fiber) with apples and cinnamon
57221000	Fruit & Fibre (fiber) with dates, raisins, and walnuts
57221500	Fruit & Fibre (fiber) tropical fruit w/oat clusters
57221600	Fruit & Fibre (fiber) with peaches, raisins, almonds and oat clusters
57221700	Fruit Rings, NFS
57221800	Fruit Whirls
57222500	Fruit Wheats
57224000	Golden Grahams
57225000	Golden Harvest Proteinola
57231000	Grape-Nut Flakes
57231500	Gremlins
57232000	Halfsies
57232100	Healthy Choice Almond Crunch with raisins, Kellogg's
57232120	Healthy Choice Multi-Grain Flakes, Kellogg's
57235500	Heartwise, plain
57235600	Heartwise, with fruit nuggets
57237000	Honey Bran
57237100	Honey Bunches of Oats
57237300	Honey Bunches of Oats with Almonds, Post
57238000	Honeycomb, plain
57239000	Honeycomb, strawberry
57239100	Honey Crunch Corn Flakes, Kellogg's
57240000	Honey Graham Chex
57241000	Honey Nut Cheerios
57243000	Honey Smacks
57243600	Hot Wheels
57243900	Jetsons
57301100	Kaboom
57301700	Kenmei Rice Bran
57302100	King Vitaman
57303100	Kix
57304100	Life (plain and cinnamon)
57305100	Lucky Charms
57305150	Frosted oat cereal with marshmallows
57305170	Malt-O-Meal Coco-Roos
57305200	Malt-O-Meal Crispy Rice
57305500	Malt-O-Meal Honey and Nut Toasty O's
57306500	Malt-O-Meal Golden Puffs (formerly Sugar Puffs)
57306700	Malt-O-Meal Toasted Oat Cereal
57306800	Malt-O-meal Tootie Fruities
57307100	Fruity Marshmallow Krispies (formerly called Marshmallow Krispies)
57307550	Mini Buns Cereal (cinnamon)
57308000	Morning Funnies
57308300	Multi Bran Chex
57308400	Multi Grain Cheerios
57308410	Multi-Grain Cheerios Plus
57311600	Nintendo
57311790	Nut and Honey crunch biscuits
57311800	Nut and Honey Crunch (flakes)
57311900	Nutrific Oatmeal Flakes
57313000	Nutri-Grain Corn
57313900	Nutri-Grain Raisin Bran
57315000	Nutri-Grain Golden Wheat (formerly Nutri-Grain Wheat)
57316100	Nutri-Grain Almond Raisin

57316300	Oat Bran Flakes, Health Valley
57316350	Oat Bran Options
57316700	Oh's, Crunchy Nut
57316710	Oh's, Honey Graham
57316750	Oh's, Fruitangy, Quaker
57316800	O.J.'s
57317000	Oat flakes, fortified
57317200	Oat Flakes, Post
57322500	Oreo O's cereal, Post
57323000	Sweet Crunch, Quaker (formerly called Popeye)
57323050	Sweet Puffs, Quaker
57323200	Pop Tarts Crunch Cereal
57325000	Product 19
57327450	Quaker Oat Bran Cereal
57328000	Quisp
57328500	Rainbow Brite
57335530	Razzle Dazzle Rice Krispies
57335550	Reese's Peanut Butter Puffs cereal
57336000	Rice Chex
57337000	Rice Flakes, NFS
57339000	Rice Krispies
57339500	Rice Krispies Treats Cereal (Kellogg's)
57340200	Ripple Crisp Golden Corn
57340210	Ripple Crisp Honey Bran, General Mills
57340900	S.W. Graham
57342000	Slimer! & Ghostbusters
57342500	S'mores Crunch
57343000	Smurf Magic Berries
57344000	Special K
57344050	Spider-Man, Ralston
57344100	Sprinkle Spangles
57345000	Strawberry Krispies
57346500	Toasted Oatmeal, Honey Nut (Quaker)
57347000	Corn Pops
57347500	Strawberry Squares Mini-Wheats, Kellogg's (formerly Strawberry Squares)
57348000	Frosted corn flakes, NFS
57349000	Frosted Flakes, Kellogg
57349010	Cocoa Frosted Flakes, Kellogg's
57350000	Frosted Flakes, Ralston Purina
57352000	Sugar-Sparkled Flakes
57353000	Sugar-Sparkled Rice Krinkles
57354000	Sun Flakes
57355000	Golden Crisp (Formerly called Super Golden Crisp)
57401100	Toasted oat cereal
57402000	Team
57402250	Teddy Grahams Breakfast Bears
57402500	Teenage Mutant Ninja Turtles
57402600	Temptations, French Vanilla Almond, Kellogg's
57402610	Temptations, Honey Roasted Pecan, Kellogg's
57402750	Tiny Toon Adventures
57403100	Toasties, Post
57404100	Malt-O-Meal Toasty O's
57406100	Total
57406200	Triples
57408100	Uncle Sam's Hi Fiber Cereal
57409100	Waffle Crisp, Post

57410000	Weetabix Whole Wheat Cereal
57415000	Wheat'n Raisin Chex
57418000	Wheaties
57418200	Wheaties, Honey Frosted (formerly Wheaties Honey Gold)
57103500	Apple Cinnamon Squares Mini-Wheats, Kellogg's (formerly Apple Cinnamon Squares)
57105000	Apple Raisin Crisp
57106100	Basic 4
57207000	Bran Flakes, NFS (formerly 40% Bran Flakes, NFS)
57208000	Complete Wheat Bran Flakes, Kellogg's (formerly 40% Bran Flakes)
57210100	40+ Bran Flakes
57214000	Frosted Mini-Wheats
57229000	Granola, lowfat, Kellogg's
57229500	Granola with Raisins, lowfat, Kellogg's
57232110	Healthy Choice Multi-Grain Squares, Kellogg's
57241200	Honey Nut Shredded Wheat, Post
57244000	Just Right
57245000	Just Right Fruit and Nut (formerly Just Right with raisins, dates, and nuts)
57308180	Mueslix Crispy Blend (formerly Mueslix Five Grain Muesli Cereal)
57308200	Mueslix golden crunch cereal
57308210	Muesli with apples and almonds, Ralston Purina
57308220	Strawberry muesli with pecans and raisins, Ralston
57312100	Nutri-Grain Biscuits, Whole Grain Shredded Wheat Cereal
57316410	Apple Cinnamon Oatmeal Crisp (formerly Oatmeal Crisp with Apples)
57316450	Oatmeal Crisp with Almonds
57316500	Oatmeal Raisin Crisp
57327500	Quaker Oatmeal Squares (formerly Quaker Oat Squares)
57329000	Raisin bran, NFS
57330000	Raisin Bran, Kellogg
57330500	Raisin Bran, Nutri System
57331000	Raisin Bran, Post
57332050	Raisin Bran, Total
57332100	Raisin Nut Bran
57332300	Super Raisin Bran, New Morning
57334000	Raisin Life
57335000	Raisins, Rice and Rye
57335500	Raisin Squares Mini-Wheats, Kellogg's (formerly Raisin Squares)
57341000	Shredded Wheat'N Bran
57417000	Shredded Wheat, 100%
57417500	Shredded Wheat with Oat Bran

<u>**Dairy Product Analogs**</u>

Imitation milk and soy milk
[Phosphatidylserine] = 0.042 %

11310000	Milk, imitation, fluid, soy based
11320000	Milk, soy, ready-to-drink, not baby

<u>**Grain Products and Pastas**</u>

Nutritional Bars (Breakfast, Granola, Protein)
[Phosphatidylserine] = 0.250 %

41435010	High protein bar, soy base
41435110	High protein bar, candy-like, soy and milk base
41435200	High protein bar, cookie type, soy and milk base

53540000	Breakfast bar, nfs
53540100	Breakfast bar, cake-like
53540200	Breakfast bar, cereal crust with fruit filling, lowfat
53540250	Breakfast bar, cereal crust with fruit filling, fat free
53540500	Breakfast bar, date, with yogurt coating
53541100	Breakfast bar, diet meal type
53544450	PowerBar (fortified high energy bar)
53541200	Meal replacement bar (incl slim fast bar)
53542100	Granola bar w/ oats, sugar, raisins, coconut
53542200	Granola bar, oats, fruit, nuts, lowfat
53542210	Granola bar, nonfat
53543100	Granola bar w/ peanuts, oats, sugar, wheat germ
53544100	Granola bar, w/ nougat
53544200	Granola bar, chocolate-coated
53544210	Granola bar, w/ coconut, chocolate-coated
53544220	Granola bar w/ nuts, chocolate-coated
53544250	Granola bar, coated w/ nonchocolate coating
53544300	Granola bar, high fiber, yogurt coating, not choc
53544400	Granola bars, w/ rice cereal

__Milk Products__

Flavored Milk and Milk Drinks, Fluid
[Phosphatidylserine] = 0.042 %

11511000	Milk, chocolate, nfs
11513000	Cocoa & sugar mixture, milk added, ns type milk
11513400	Chocolate syrup milk added, ns as to type of milk
11514300	Cocoa w/ nf dry milk, lo cal sweetener, water added
11514500	Cocoa w/ whey, lo cal sweetnr, fortifd, water added
11515100	Cocoa & sugar w/ milk, fortified, Puerto Rican
11515400	Cocoa w/ nfdm, low calorie, hi calcium, water added
11516000	Cocoa, whey, lo cal sweetner mix, lowfat milk added
11518000	Milk bev w/ nf dry mlk, lo cal sweet, water, choc
11518050	Milk bev w/nf dry milk, lo cal sweet, water, not choc
11518100	Milk bev w/nfd milk, lo cal sweet, hi calcium, choc
11519000	Milk beverage, not chocolate, w/ whole milk
11519050	Milk, not chocolate, whole milk based
11519100	Milk beverage, beads, whole milk added
11551050	Milk fruit drink (incl licuado)
11551100	Milk fruit drink, Puerto Rican style (champola de frutas)
11552200	Milk-based fruit drink (incl orange julius)
11553000	Fruit smoothie drink, w/ fruit and dairy products
11553100	Fruit smoothie drink, nfs
11560000	Choc-flavored drink, whey-& milk-based (incl yoo-hoo)
11560020	Milk drink, whey & milk-base, not choc (incl yoo-hoo)
11560100	Flav milk drink, skim milk & cream-based, not choc
11560110	Chocolate flav milk drink, skim milk & cream-based

Milk, Fluid (Regular, Filled, Buttermilk, and Dry reconstituted)
[Phosphatidylserine] = 0.0208 %

11100000	Milk, nfs
11112000	Milk, cow's, fluid, not whole, ns as to % fat
11113000	Milk, cow's, fluid, skim or nonfat

Milk-Based Meal Replacements
[Phosphatidylserine] = 0.042 %

11611000	Instant breakfast, fluid, canned
11612000	Instant breakfast, powder, milk added
11613000	Instant bfast, pwdr, swt w/ lo cal swt, milk added
11621000	Diet beverage, liquid, canned
11622000	Diet beverage powder, milk added
11622010	Diet beverage, pwdr, reconst w/skim (incl carnation)
11623000	Meal supplement / replacement, prepared, rtd
11631000	High calorie bev, canned or powdered, reconstituted
11641000	Meal replacement, milk based, high protein, liquid
11651010	Meal replacement, cambridge, reconst, all flavors

Yogurt
[Phosphatidylserine] = 0.044 %

11410000	Yogurt, ns as to type of milk/flavor
11411100	Yogurt, plain, whole milk
11411200	Yogurt, plain, lowfat milk
11411300	Yogurt, plain, nonfat milk
11420000	Yogurt, vanilla, lemon, coffee, ns as to milk type
11421000	Yogurt, vanilla, lemon, coffee, whole milk
11422000	Yogurt, vanilla, lemon, coffee, lowfat milk
11423000	Yogurt, vanilla, lemon, coffee, nonfat milk
11424000	Yogurt, vanilla, lemon, coffee, nonfat milk, low cal sweet
11425000	Yogurt, chocolate, ns as to type of milk
11426000	Yogurt, chocolate, whole milk
11427000	Yogurt, chocolate, nonfat milk
11430000	Yogurt, fruit variety, ns as to milk type
11431000	Yogurt, fruit variety, whole milk
11432000	Yogurt, fruit variety, lowfat milk
11433000	Yogurt, fruit variety, nonfat milk
11433500	Yogurt, fruited, nonfat milk, low cal sweetener
11444000	Yogurt, fruit & nuts, ns as to type of milk
11445000	Yogurt, fruit & nuts, lowfat milk

Processed Fruits and Fruit Juices

Fruit Flavored Drinks
[Phosphatidylserine] = 0.042 %

92741000	Fruit-flavored drink, non-carb, from low cal powder

Submission End

SUBMISSION END