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ORIGINAL SUBMISSION

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July 14, 2010

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Division of
Biotechnology and
GRAS Notice Review

Robert L. Martin, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

RE: Sel-Plex® GRAS Notification

Dear Dr. Martin:

In accordance with proposed 21 CFR § 170.36 (a notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the agent of the notifier, Alltech, a GRAS notification for the use of Sel-Plex® as a source of selenium in the diet at a maximum consumption level of 19.2 mg/day. A GRAS expert panel dossier and amendment to the GRAS dossier, setting forth the basis for the GRAS determination, as well as *curriculum vitae* of the members of the GRAS panel, are enclosed.

Best regards,

(b) (6)

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

1. GRAS Exemption Claim

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

Alltech, on the advice of a panel of experts, has determined Sel-Plex® to be generally recognized as safe (GRAS) and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

(b) (6) [redacted] Date 14 July 2010

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
801 N. Orange Avenue Suite 710
Orlando, FL 32801

(i) Name and Address of the Notifier

Alltech
3031 Catnip Hill Pike
Nicholasville, KY 40356

Agent of the Notifier:

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition
Burdock Group
801 N. Orange Ave. Suite 710
Orlando, FL 32801
Telephone: 407-802-1400
Facsimile: 407-802-1405
Email: gburdock@burdockgroup.com

(ii) Common Name of the Notified Substance

The common name of Sel-Plex® for the purposes of this GRAS Notification has been defined as:

"selenium yeast"

(iii) Conditions of Use

Sel-Plex® may be used as an ingredient in the food groups outlined in the Amendment to the Dossier in Support of the Generally Recognized As Safe (GRAS) Status of Sel-Plex® as a Food Ingredient dated June 17, 2010 (yogurts, breads, instant cereals, breakfast and granola-type bars, soups, beverages, pastas, crackers, salty snacks, pretzels and popcorn), at levels up to 19.2 mg *per* day, to provide a source of selenium to individuals who desire additional selenium in their diet. Sel-Plex® may also be used as an ingredient for medical food such that the aggregate amount of selenium consumed in the diet will not exceed 38.4 μg/day.

(iv) Basis of GRAS Determination

Pursuant to 21 CFR § 170.3, the use of Sel-Plex® as an ingredient in food categories described in the "Dossier in Support of the Generally Recognized as Safe (GRAS) Status of Sel-Plex® as a Food Ingredient" dated July 5, 2007 and the "Amendment to the Dossier in Support of the Generally Recognized As Safe (GRAS) Status of Sel-Plex® as a Food Ingredient" dated June, 17, 2010, at an intended maximum 90th percentile consumption of 19.2 mg *per* day, has been determined GRAS by scientific procedures for its intended conditions of use. The safety of Sel-Plex® for this use is supported by acute, subchronic, reproductive, and genotoxicity studies with Sel-Plex® as well as clinical trials with other organic forms of selenium. This GRAS determination is based on the opinion of experts who are qualified by scientific training and experience to evaluate the safety-in-use of substances used as ingredients added to food.

(v) Availability of Information

Three copies of the original "Dossier in Support of the Generally Recognized as Safe (GRAS) Status of Sel-Plex® as a Food Ingredient" dated July 5, 2007 and three copies of the "Amendment to the Dossier in Support of the GRAS Status of Sel-Plex® as a Food Ingredient" dated June 17, 2010, setting forth the basis for the GRAS determination, as well as *curriculum vitae* of the members of the GRAS panel, are enclosed. The data and information (*i.e.*, documentation) that serve as a basis for this GRAS determination are available for FDA review and copying at reasonable times at:

Burdock Group
801 N. Orange Ave. Suite 710
Orlando, FL 32801
Telephone: 407-802-1400
Facsimile: 407-802-1405
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Alternatively, data and information that serve as a basis for this GRAS determination may be sent to FDA upon request.

2. Detailed Information about the Identity of the Notified Substance

A. Identity

Sel-Plex® is a dried (non-viable) baker's yeast, *Saccharomyces cerevisiae* strain CNCM I-3060, cultivated in a selenium-enriched fermentation medium prior to harvesting and drying. The general descriptive characteristics of Sel-Plex® are presented in Table 1.

Table 1. General description of Sel-Plex®

Analysis	Method	Specification
Physical aspect	N/A	Light to dark brown free-flowing powder with a slight yeast aroma
Yeast strain	N/A	*Saccharomyces cerevisiae* strain CNCM I-3060

Common or Usual Name:

The common name of Sel-Plex® is "selenium yeast".

B. Composition

The product is a dried cellular product (*i.e.*, yeast that contains selenoproteins) and as such, has no specific formula. The preparation is composed of dried yeast containing selenomethionine (SeMet), selenocysteine (SeCys) and selenoproteins, as well as food-grade fermentation medium. The structures of the major ingredients (SeMet and SeCys) are shown in Figure 1.

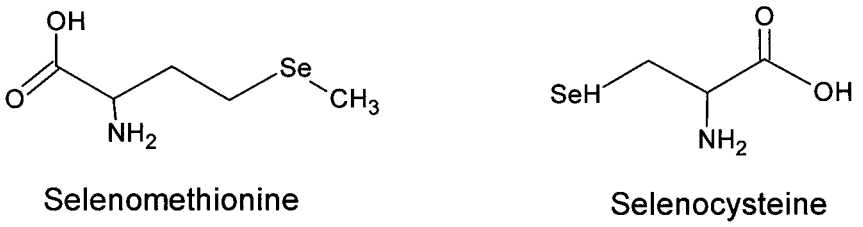

Figure 1. Selenomethionine and selenocysteine chemical structures

C. Method of Manufacture of Sel-Plex®

The manufacturing process of Sel-Plex® is conducted according to a typical batch-fed operation commonly used in the production of baker's yeast that is further used to produce a yeast biomass. This process involves incremental feeding of sugar-containing medium and represents the best practical method of producing yeast biomass without simultaneous production of sizable quantities of ethanol. During this process, the inorganic mineral source of selenium is transformed into organic forms. A graphical depiction of the manufacturing process is offered in Figure 2.

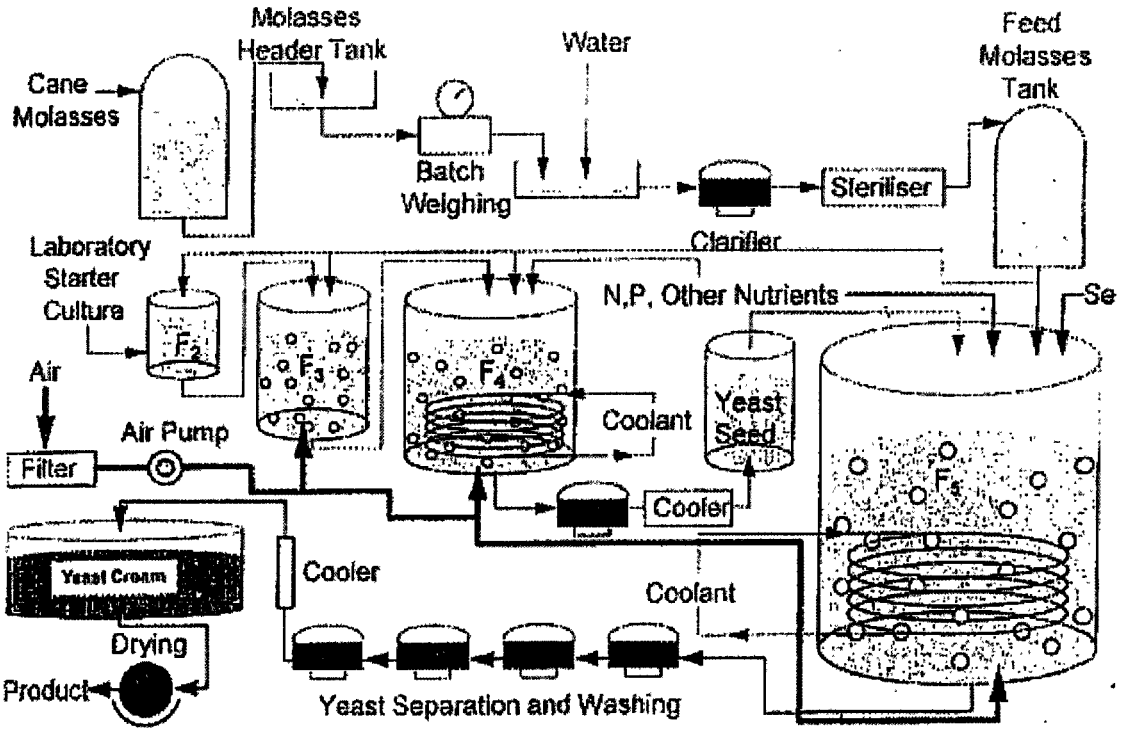

Figure 2. Schematic of the Sel-Plex® manufacturing process

D. Specifications for Food Grade Sel-Plex®

Specifications provided in Table 2 for bulk Sel-Plex® include arsenic, lead, cadmium, mercury, and the absence of coliforms, *Salmonella* and mesophilic aerobic microorganisms.

Table 2. Specifications for Sel-Plex®

Analysis	Method	Specification	Average Batch analysis results ($n = 5$)
Physical aspect	N/A	Light to dark brown free-flowing powder with a slight yeast aroma	
Yeast strain	N/A	*Saccharomyces cerevisiae* strain CNCM I-3060	
Loss on drying	2nd Directive 71/393/EC	Not more than 7.0%	5.53 ± 0.35
pH	-	-	6.39 ± 0.18
Ash (total %)	NF V 18-101	Maximum of 8%	6.55 ± 0.9
Crude protein	NF V 18-100	Minimum of 45%	46.66 ± 0.93
Mesophilic aerobic microorganisms	NF V 08-051	Less than 5.0×10^4 CFU/g	2.5×10^4 CFU/g
Coliforms	NF V 08-050	Less than 10 CFU/g	<5 CFU/g
Salmonella (search on 25 g)	NF V 08-052	Negative	Negative
Heavy metals (mg/kg)			
Arsenic	AAS	<3 ppm	0.79 ± 0.08
Lead	AAS	<1 ppm	0.07 ± 0.03
Cadmium	AAS	<3 ppm	0.022 ± 0.005
Mercury	AAS	<0.5 ppm	< 0.005
Total Selenium (mg/kg)	ICP-MS	Not less than 2000 mg/kg	2,275 ± 148.5
Total organic selenium	ICP-MS	≥ 98%	99.6 – 99.63%
Selenomethionine	ICP-MS	65% (62 – 68%)	63.4 – 66.6%
Other organic selenium compounds	ICP-MS	33% (32 – 38%)	33 – 36.2%
Inorganic selenium as Se(IV)	ICP-MS	≤ 2%	0.37 – 0.4%
Inorganic selenium as Se(VI)	ICP-MS	≤ 2% (combined with Se(IV))	Below detection limit

AAS = atomic absorption spectrometry; CFU = colony forming units; ICP-MS = inductively coupled plasma mass spectrometry; N/A = not applicable; ppm = parts *per* million.

3. Self Limiting Levels of Use

The use of Sel-Plex® is not self-limiting, but consumption is expected to be below the conservatively estimated 90th percentile level of intake.

4. Basis of GRAS Determination

The determination that Sel-Plex® is GRAS is on the basis of scientific procedures, as outlined in the attached "Dossier in Support of the Generally Recognized as Safe (GRAS) Status of Sel-Plex® as a Food Ingredient" dated July 5, 2007 and the "Amendment to the Dossier in Support of the Generally Recognized As Safe (GRAS) Status of Sel-Plex® as a Food Ingredient" dated June, 17, 2010. On the basis of the data and information described in the attached dossier and amendment and other publicly available information, there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food, that there is reasonable certainty that Sel-Plex® is GRAS under the intended conditions of use.

AMENDMENT TO THE DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

July 2, 2010

FINAL

Panel Members

G.A. Burdock, Ph.D., DABT, FACN

R. J. Cousins, Ph.D.

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AMENDMENT TO THE DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

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AMENDMENT TO THE DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

1. EXECUTIVE SUMMARY

On a prior occasion[1], an independent GRAS Expert Panel[2] critically evaluated the available information on Sel-Plex® (a selenium-enriched *Saccharomyces cerevisiae* yeast preparation by Alltech®) as an ingredient added to food to increase the amount of selenium in the diet. Based on scientific procedures according to the provision of the Federal Food Drug and Cosmetic Act (FD&C Act), the Expert Panel agreed that addition of Sel-Plex® to food resulting in a mean consumption of 0.12 mg Sel-Plex®/kg bw/day (7.2 mg/day Sel-Plex® for a 60 kg individual) and a 90th percentile consumption at 0.26 mg Sel-Plex®/kg bw/day (15.6 mg/day) is Generally Recognized As Safe (GRAS). Based on a selenium content of 2000 mg Se/kg Sel-Plex®, these consumption levels are equal to daily consumption of selenium of 14.3 and 31.2 μg/day, respectively.

On this present occasion, Alltech® requested Burdock Group to amend the original GRAS determination to: (1) include use of Sel-Plex® in salty snacks; (2) modify levels of Sel-Plex® in existing foods; and (3) include use of Sel-Plex® in medical foods. As part of this assessment, Burdock Group: (1) provided an update to the original GRAS dossier on regulatory assessment; (2) conducted a review of the relevant scientific literature since the original GRAS determination in 2007; and (3) conducted an updated consumption analysis based on the NHANES consumption dataset from 2005-2006. Alltech® assures the Expert Panel that all relevant, unpublished information in its possession has been supplied to Burdock Group and has been summarized in this monograph. A comprehensive search of the scientific literature for safety information on Sel-Plex® (and other selenized yeasts) was conducted by Burdock Group, for studies conducted between 2006 and March, 2010. Information from pertinent studies obtained from this search is included in this report. Based on new food survey data (NHANES 2003-2004)

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[1] "Dossier in support of the Generally Recognized As Safe (GRAS) status of Sel-Plex®", finalized as a GRAS determination on July 5, 2007.

[2] Modeled after that described in Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members.

and modified use levels, the mean and 90th percentile levels of Sel-Plex® consumption will be 0.16 mg Sel-Plex®/kg bw/day (9.6 mg/day Sel-Plex® for a 60 kg individual) and 0.32 mg Sel-Plex®/kg bw/day (19.2 mg/day), respectively. Based on a selenium content of 2000 mg Se/kg Sel-Plex®, these consumption levels are equal to daily consumption of selenium of 19.2 μg/day and 38.4 μg/day, respectively. Medical food products may contain Sel-Plex® such that the aggregate amount of selenium consumed in the daily diet will not exceed 38.4 μg/day.

The safety data provided in the original GRAS dossier and a critical review of the literature published since the original Sel-Plex® GRAS determination, supports a conclusion of safety of Sel-Plex® in conventional and medical foods at the proposed levels of use. Following an independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision herein.

2. INTRODUCTION

Selenium (atomic number 34) is a trace element that occurs naturally in a number of commonly ingested foods, such as meat, fish, eggs, cereals and milk (ERNA, 2004). Several areas of the world contain very little selenium in the soil, which may lead to insufficient consumption of selenium through the diet. Selenium deficiency has been associated with significantly increased mortality rates, and increased risk of developing immunodeficiency, Keshan disease (characterized by cardiomyopathy), Kashin-Beck disease (a musculoskeletal disorder) and certain types of cancer (Cheng and Qian, 1990; FSA, 2003; Whanger, 2004). Selenium is a component of several selenoproteins and selenoenzymes required for various functions, including antioxidant defense, DNA synthesis, fertility and reproduction, reduction of inflammation, and thyroid hormone production (Buettner *et al.*, 2000; Brown and Arthur, 2001; Curcio *et al.*, 2001; Hawkes *et al.*, 2001; Foresta *et al.*, 2002; Cunningham-Rundles *et al.*, 2005; Combs Jr. *et al.*, 2009).

Sel-Plex® is a preparation of the selenium-enriched (*i.e.* selenized) yeast *Saccharomyces cerevisiae* strain CNCM I-3060, composed of the intact, dried (non-viable) yeast enriched for selenium content. Selenium-enriched yeast is increasingly the subject of intense study because it contains readily bioavailable sources of selenium. Sel-Plex® has previously been determined GRAS when added to a variety of food products to provide selenium to the diet. This dossier is

an amendment to the GRAS dossier for Sel-Plex® and supports increased use levels of Sel-Plex® in conventional foods and use of Sel-Plex® in medical foods.

The term "medical food" was initially defined in the Orphan Drug Act Amendments of 1988 [21 USC 360ee (b)(3)].[3] This definition was incorporated by reference into the Nutrition Labeling and Education Act (P.L. 101-535) in November 1990, and was added to the agency's final rule on Mandatory Nutritional Labeling in January 1993. The definition for a medical food is:

> 'A food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the dietary management of a specific disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.' [4]

Medical foods are used by a select population that is under a physician's supervision. They are recommended for patients with a variety of medical conditions including, but not limited to, renal disease (*e.g.*, chronic or acute renal failure), hypermetabolic states (*e.g.*, severe burns, trauma or infections), and malabsorption (*e.g.*, inflammatory bowel disease, irritable bowel syndrome, diverticulosis and short bowel syndrome). Medical foods may be classified into the following categories: (a) nutritionally complete (*i.e.* the sole source of calories and nutrients for a patient; (b) nutritionally incomplete formulas, including individual "modular" type products that may be mixed with other medical food products before use (*e.g.*, protein, carbohydrate, or fat modulars); (c) formulas for metabolic (genetic) disorders in patients over twelve months of age; or (d) oral rehydration products.[3]

2.1. Description

Sel-Plex® consists of a dried (non-viable) baker's yeast (*Saccharomyces cerevisiae* strain CNCM I-3060) enriched with selenium during its cultivation in a fermentation medium prior to harvesting and drying. The product is a dried cellular product (*i.e.*, yeast that contains selenoproteins) and as such, has no specific formula. The preparation is composed of dried yeast

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[3] FDA (2007) U. S. Food and Drug Administration Guidance, Compliance & Regulatory Information-Medical Foods; http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/MedicalFoods/ucm054048.htm; site visited April 14, 2010.

[4] 21CFR § 101.9(j)(8)

containing selenomethionine (SeMet), selenocysteine (SeCys) and selenoproteins, as well as food-grade fermentation medium.

The structures of the major ingredients (SeMet and SeCys) are shown in Figure 1.

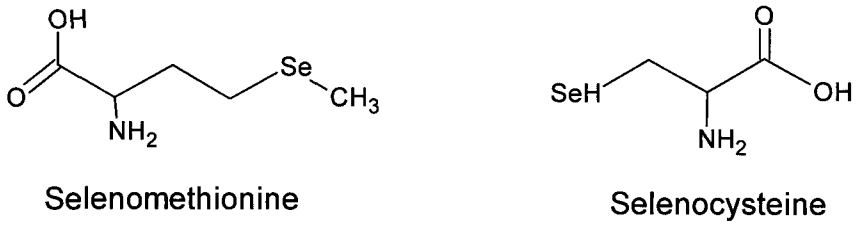

Figure 1. Selenomethionine and selenocysteine chemical structures (ChemIDplus Advanced, 2004a; 2004b)

2.2. History of use and current uses

Selenium was discovered by Berzelius and Gahn in 1817 while examining the sediment from a sulfuric acid plant at Gripsholm, Sweden (Whanger, 2002). As a natural constituent of both plant- and animal-derived foods, it has a long history of use in food. In 1957, trace levels of selenium (as little as 4 µg *per* 100 g diet) were found to protect against dietary liver necrosis in rats and pigs (Schwarz and Foltz, 1957). In the 1970's, it was determined that selenium played an essential role in the activity of glutathione peroxidase (GSH-PX), a major enzyme involved in protecting cells against oxidative damage.[5] Clinical evidence of beneficial effects of selenium supplementation on health began to emerge in the early 1990's (Yu *et al.*, 1991).

Selenized yeast is currently sold as a dietary supplement[6] and as an animal feed additive, approved by the U.S. Food and Drug Administration (FDA) for use in poultry, swine, cattle, horse, sheep and goat diets to provide supplemental sources of selenium.[7] A GRAS notification[8] for high-selenium yeast from Cypress Systems Inc. was recently filed with FDA (GRN 260),

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[5] http://www.springerlink.com/content/ju30526v6270t464/; site visited April 14, 2010.GSH-Px is a group of enzymes that share the same abbreviation.

[6] http://www.drugstore.com/products/prod.asp?pid=41590&catid=36818&aid=335933&aparam=gnc_selenium_200_mcg_tab; GNC 200 µg selenium tablets; site visited April 14, 2010.

[7] http://www.epa.gov/fedrgstr/EPA-IMPACT/2003/September/Day-03/i22358.htm; 21 CFR part 573. Food additives permitted in feed and drinking water of animals; Selenium yeast; site visited April 14, 2010.

[8] http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=260; site visited April 14, 2010.

(FDA, 2008) for use of selenized yeast in medical foods and several different types of conventional foods and beverages. The Institute of Medicine (IOM) has indicated a recommended dietary allowance (RDA) of selenium of 55 μg/day for men and women greater than 19 years of age, 60 μg/day during pregnancy, and 70 μg/day selenium for lactating women. The RDA of selenium for children progressively increases from 20 μg/day for children 1-3 years old, to 55 μg/day for both boys and girls 14-18 years of age (Institute of Medicine, 2000).

Sel-Plex® is currently used as a nutrient supplement and as an added fiber ingredient in the food categories shown in Table 1 *per* the original GRAS dossier.

Table 1. Food groups selected for Sel-Plex® supplementation per the original GRAS dossier

Food category	Intended Sep-Plex® use level (ppm)
Yogurts	10
Breads	10
Instant cereals	10
Breakfast and granola-type bars	10
Soups	10
Beverages	10

ppm = parts *per* million

2.3. Proposed use or uses

Sel-Plex® is proposed for addition to the conventional foods and beverages identified in APPENDIX 1 at 5-60 parts *per* million (ppm) for the purpose of increasing dietary organic selenium. Sel-Plex® is also proposed for addition to medical foods, which will be used under a physician's supervision, for daily intake of Sel-Plex® not to exceed the same maximum levels proposed in this GRAS determination (90th percentile consumption of 19.2 mg Sel-Plex®/day, providing 38.4 μg selenium/day). The label on the product must clearly state that the product is intended for use in the management of a specific medical disorder or condition. The addition of Sel-Plex® cannot result in a food becoming a medical food, as Sel-Plex® will be added to foods

already determined to be medical foods. Sel-Plex® may also be marketed in a modular form for addition to a medical food.[9]

2.4. Mechanism of action

Sel-Plex® contains a high level of SeMet, and several experimental studies have established that SeMet and selenized yeast increase selenium levels in humans (Clark *et al.*, 1996; Reid *et al.*, 2004; Xiaoxia *et al.*, 2006; Hawkes *et al.*, 2008; Lippman *et al.*, 2009; Schomburg *et al.*, 2009; Tsavachidou *et al.*, 2009). Cereal and forage plants convert selenium mainly into SeMet and incorporate it into protein in place of methionine (Schrauzer, 2000). In mammals, ingested SeMet is absorbed in the small intestine (Vendeland *et al.*, 1994). Once absorbed, SeMet may be incorporated into proteins in place of methionine or be metabolized to SeCys, which is catabolized into hydrogen selenide (H_2Se) by a β-lyase enzyme (Esaki *et al.*, 1982; Schrauzer, 2000; Combs Jr. *et al.*, 2001). In contrast to SeMet, inorganic forms of selenium, selenate (Na_2SeO_4) and selenite (Na_2SeO_3) are metabolized to H_2Se through reduction. H_2Se is subsequently incorporated into selenoproteins including GSH-PX, iodothyronine 5'-deiodinases (TDI), thioredoxin reductases (TR), selenophosphate synthetase (SePsyn), plasma selenoprotein P (Se-P), and muscle selenoprotein W (Se-W) (Combs Jr. *et al.*, 2001). Several of these enzymes are related to antioxidant functions (Xia *et al.*, 1989; Diwadkar-Navsariwala and Diamond, 2004; Kim *et al.*, 2004; Ebert *et al.*, 2006; Kaur and Bansal, 2006). GSH-PX is important in scavenging reactive oxygen species (ROS), potentially catalyzing the oxidation of glutathione and reduction of organic hydroperoxides or hydrogen peroxide (protecting membrane lipids and other macromolecules from oxidative damage), and has been hypothesized as the mechanism of selenium-mediated inhibition of tumorigenesis (Munz *et al.*, 1997; Bansal and Kaur, 2005; Goel *et al.*, 2006; Kaur and Bansal, 2006).

2.5. Regulatory status

A GRAS notification for high-selenium yeast from Cypress Systems Inc. was recently filed with FDA (GRN 260), for use of selenized yeast in several different types of foods and

[9] Compliance Guideline 7321.002 (September 30, 2008) page 5. Medical Foods can be classified into the following categories:...b) Nutritionally incomplete formulas, including individual "modular" type products that may be mixed with other products before use (*e.g.*, protein, carbohydrate, or fat modulars).

beverages at 5 micrograms selenium *per* serving (Table 2). Assuming that a maximum quantity of 20 servings of foods containing selenized yeast will be consumed *per* day, the maximum level of consumption of selenium from selenized yeast was estimated to be 100 μg/day (GRAS Associates, LLC, 2008). The FDA responded with a letter of no objection on March 9, 2009.[10]

As mentioned in the original 2007 GRAS dossier for Sel-Plex®, dried yeasts (*S. cerevisiae* and *S. fragilis*) and dried torula yeast (*Candida utilis*) are regulated by the FDA for safe use in food, provided the total folic acid content of the yeast does not exceed 0.04 milligrams *per* gram of yeast.[11] An extract of baker's yeast has been determined GRAS as a flavoring agent and adjuvant, not to exceed five *percent* in food.[12]

The FDA also regulates selenized yeast for addition to complete feed for chickens, turkeys, swine, beef cattle and dairy cattle, at a level not to exceed 0.3 parts *per* million (Table 2).[13] Although not stated in the regulation, FDA has also approved use of selenized yeast in horse, sheep and goat feed.[14]

The European Commission's Scientific Committee on Food (SCF) has provided an opinion on the Tolerable Upper Intake Level (UL) for selenium (EC/SCF, 2000). The SCF concluded that a selenium intake of approximately 850 μg/day could be taken as a "no observable adverse effect level (NOAEL) for clinical selenosis." Using an uncertainty factor of 3, the SCF derived a UL for selenium of 300 μg/day. EFSA's Scientific Panel on Food Additives and Nutrient Sources Added to Food has concluded that a more conservative UL of 250 μg/day should be adopted for SeMet (corresponding to 100 μg/day selenium) (EFSA, 2009).[15] Using a NOAEL of 800 μg/day for selenosis in humans and applying an uncertainty factor of 2, The IOM has established a UL for adults of 400 μg selenium/day (Institute of Medicine, 2000).

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[10] http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm155153.htm; site visited April 14, 2010.
[11] Title 21 of the US Code of Federal Regulations (CFR), section 172.896, 2006.
[12] Title 21 of the US Code of Federal Regulations (CFR), section 184.1983, 2006.
[13] Title 21 of the US Code of Federal Regulations (CFR), section 573.920, 2006.
[14] In response to a stakeholder request, FDA also provided letters permitting use of selenium yeast in complete horse, sheep or goat feed, as referenced at http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048424.htm and http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048410.htm, respectively (sites visited April 14, 2010).
[15] The selenium content of SeMet is approximately 40%, based on molecular weights of 78.96 for selenium and 196.13 for SeMet (O'Neil *et al.*, 2001a; 2001b).

Table 2. Regulatory status of yeast and selenized yeast products

Agency	Identification	Permitted functionality	Use limits	Reference
FDA	High-selenium yeast	Nutrient supplement as defined by FDA in 21 CFR 170.3(o)(20)	Baked products, non-alcoholic beverages, breakfast cereals, grain products and pastas, milk products, processed fruit and fruit juices, processed vegetables and vegetable juices, commercial soups and soup mixes, and medical foods at levels yielding 5 micrograms selenium per serving	GRN 260
FDA	Food additives permitted in feed and drinking water of animals	Selenium additive	The additive selenium yeast is added to complete feed for chickens, turkeys, swine, beef cattle and dairy cattle at a level not to exceed 0.3 parts *per* million*	21CFR §573.920(h)
FDA	Direct food substances affirmed as GRAS. Bakers yeast extract	Flavoring agent and adjuvant	Not to exceed 5% in food	21CFR §184.1983[16]
FDA	Food additives permitted for direct addition to food for human consumption. Subpart I - Multipurpose additives. Dried yeast	Multipurpose additive	Total folic acid content of the yeast does not exceed 0.04 mg/g yeast	21CFR §172.896[6]

CFR = Code of Federal Regulations; FDA = US Food and Drug Administration; GRAS = Generally Recognized As Safe; GRN = GRAS Notification; * In response to a stakeholder request, FDA also provided letters permitting use of selenium yeast in complete horse, sheep or goat feed, as referenced at http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048424.htm and http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048410.htm, respectively (sites visited April 14, 2010).

3. DESCRIPTION, SPECIFICATIONS AND MANUFACTURING PROCESS

3.1. Description and Specifications

Sel-Plex® is a dried (non-viable) baker's yeast, *Saccharomyces cerevisiae* strain CNCM I-3060, cultivated in a selenium-enriched fermentation medium prior to harvesting and drying. *S.*

[16] Title 21 of the US Code of Federal Regulations (CFR), section 184.1983, 2009.

cerevisiae strain CNCM-I-3060 was selected from a screening program for its ability to accumulate selenium in large quantities and in organic form; this strain is deposited in the Pasteur Institute[17] and its identity and purity are guaranteed by a number of methods, including DNA fingerprinting techniques, Polymerase Chain Reaction (PCR) and Pulsed-Field Gel Electrophoresis (PFGE) (Ness *et al.*, 1993).

Sel-Plex® is composed of yeast-derived selenoproteins (the major seleno amino acid is SeMet) and other proteins; there is no formula or molecular structure for the product as a whole. The physical and chemical properties and specifications for Sel-Plex®, as established by Alltech®, are provided in Table 3. As noted, the specifications are identical to the specifications presented in the GRAS dossier dated July 5, 2007.

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[17] An internationally known yeast, bacteria, and mammalian cell depository; http://www.pasteur.fr/english.html; site visited April 14, 2010.

Table 3. Specifications of Sel-Plex® (Alltech®, personal communication)

Analysis	Method	Specification	Average Batch analysis results ($n = 5$)
Physical aspect	N/A	Light to dark brown free-flowing powder with a slight yeast aroma	
Yeast strain	N/A	*Saccharomyces cerevisiae* strain CNCM I-3060	
Loss on drying	2nd Directive 71/393/EC	Not more than 7.0%	5.53 ± 0.35
pH	-	-	6.39 ± 0.18
Ash (total %)	NF V 18-101	Maximum of 8%	6.55 ± 0.9
Crude protein	NF V 18-100	Minimum of 45%	46.66 ± 0.93
Mesophilic aerobic microorganisms	NF V 08-051	Less than 5.0 x 10^4 CFU/g	2.5 x 10^4 CFU/g
Coliforms	NF V 08-050	Less than 10 CFU/g	<5 CFU/g
Salmonella (search on 25 g)	NF V 08-052	Negative	Negative
Heavy metals (mg/kg)			
Arsenic	AAS	<3 ppm	0.79 ± 0.08
Lead	AAS	<1 ppm	0.07 ± 0.03
Cadmium	AAS	<3 ppm	0.022 ± 0.005
Mercury	AAS	<0.5 ppm	< 0.005
Total Selenium (mg/kg)	ICP-MS	Not less than 2000 mg/kg	2,275 ± 148.5
Total organic selenium	ICP-MS	≥ 98%	99.6 – 99.63%
Selenomethionine	ICP-MS	65% (62 – 68%)	63.4 – 66.6%
Other organic selenium compounds	ICP-MS	33% (32 – 38%)	33 – 36.2%
Inorganic selenium as Se(IV)	ICP-MS	≤ 2%	0.37 – 0.4%
Inorganic selenium as Se(VI)	ICP-MS	≤ 2% (combined with Se(IV))	Below detection limit

AAS = atomic absorption spectrometry; CFU = colony forming units; ICP-MS = inductively coupled plasma mass spectrometry; N/A = not applicable; ppm = parts *per* million.

Sel-Plex® specifications have been extended to incorporate specific speciation (Table 4).

Table 4. Subcellular selenium distribution fingerprint for Sel-Plex®

Fraction	*Percent* total selenium (range)
Water soluble selenium species	22 – 25%
Water insoluble polysaccharide-bound selenium species	32 – 40%
Water insoluble protein-bound selenium species	28 – 37%
Residual protein-bound selenium species	1 – 2%
Residual TMAH-hydrolysable selenium species	2 – 7%

TMAH = Tetramethylammonium hydroxide

3.2. Manufacturing Process

The original manufacturing process described in the GRAS dossier for Sel-Plex® dated July 5, 2007 is still in use and has not been changed. As noted in the original GRAS dossier, Sel-Plex® is produced using a typical batch-fed operation commonly used in the production of baker's yeast, optimized to produce a biomass of *S. cerevisiae* strain CNCM-I-3060, without simultaneous production of sizable quantities of ethanol (Demirci *et al.*, 1999).

3.3. Stability

As shown in the original GRAS dossier for Sel-Plex® (dated July 5, 2007), Sel-Plex® is stable for ten months at room temperature (22-25°C) and nine months at 37°C, with minimal to no degradation of the critical component of Sel-Plex® (*e.g.*, SeMet) during these periods (Alltech, 1997). A regression analysis showed that for 24 months after the manufacturing date, at least 90% of the selenium remained in Sel-Plex®. The SeMet content was also found to remain stable for 24 months after the manufacturing date at room temperature.

4. ESTIMATED DAILY INTAKE

4.1. Conventional Foods

The general food groups designated by Alltech® to which Sel-Plex® will be added are presented in Table 5. The individual quantities that will be added to specific foods are listed in APPENDIX 1. As noted, Sel-Plex® will be added to the same food groups as specified in the original GRAS dossier for Sel-Plex®, plus salty snacks.

Table 5. Food groups selected for Sel-Plex® supplementation*

Food category	Intended Sel-Plex® use level (ppm)
Yogurts	10
Breads	60
Instant cereals	60
Breakfast and granola-type bars	60
Soups	5
Beverages	10
Salty snacks	60

*The general food categories correspond to those presented in APPENDIX 1; ppm=parts *per* million

In the original GRAS dossier dated July 5, 2007, the intake profile (amount and frequency) by individuals in USDA's What We Eat In America (WWEIA, NHANES) 2001-2002[18] data set was used to calculate the consumption of Sel-Plex® for individuals that will consume Sel-Plex®- containing foods. Use of this database resulted in mean and 90th percentile intake estimates of 7.2 and 15.6 mg Sel-Plex®/day, respectively (equivalent to 0.12 and 0.26 mg Sel-Plex®/kg bw/day, respectively). Based on a selenium content of 2000 mg Se/kg Sel-Plex®, these consumption levels are equal to daily consumption of selenium of 14.3 μg/day (0.24 μg selenium/kg bw/day) and 31.2 μg/day (0.52 μg selenium/kg bw/day), respectively.

For this GRAS amendment, a more recent dietary intake survey (WWEIA, NHANES, 2003-2004)[19] was used for determination of consumption. The foods in APPENDIX 1 are limited to foods found in the NHANES dietary database and represent examples of the types of foods to which Sel-Plex® will potentially be added. The NHANES 2003-2004 survey included two days of intake data from all respondents (n = 9,034 individuals). Comprehensive and detailed questions were posed to the participants, and the results were used to code individual foods and portion sizes consumed. The results were weighted to place more strength on foods that were consumed by more individuals, and extrapolated to the US population. If Sel-Plex® is added to the selected foods at the levels specified in Table 5, the mean and 90th percentile Sel-Plex® consumption *per* person will be 9.6 and 19.2 mg Sel-Plex®/day, respectively (equivalent to a mean and 90th percentile Sel-Plex® consumption of 0.16 and 0.32 mg Sel-Plex®/kg bw/day, respectively). These consumption levels of Sel-Plex® will provide mean and 90th percentile consumption of selenium of 19.2 and 38.4 μg/day (0.32 or 0.64 μg selenium/kg bw/day), respectively.

Combining the endogenous (current)[20] and proposed added intake levels gives the total dietary selenium consumption level. The What We Eat in America (WWEIA), NHANES 2005-

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[18] What We Eat in America, National Health and Nutrition Examination Survey (NHANES) 2001-2002, USDA, located at http://www.cdc.gov/nchs/nhanes/nhanes01-02.htm; site visited April 14, 2010.
[19] What We Eat in America, National Health and Nutrition Examination Survey (NHANES) 2003-2004, USDA, located at http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/nhanes03_04.htm; site visited April 14, 2010.
[20] Current includes selenium which is naturally part of food and does not include selenium which may he added to food.

2006 survey indicated a mean consumption of selenium from the diet of 105.7 μg/day.[21] The estimated current 90th percentile intake of dietary selenium is therefore 211.4 μg *per* day.[22] If Sel-Plex® is added to the selected foods at the levels specified in Table 5, the estimated total mean and 90th percentile consumption of selenium (from current and proposed use) would be 124.9 and 249.8 μg selenium/day (2.08 and 4.16 μg selenium/kg bw/day), respectively (Table 6).

Another possible source of selenium intake is from consumption of dietary supplements. Selenium consumption from dietary supplements is difficult to quantitate because in part of the lack of current data available on consumption of dietary supplements containing selenium. Supplements containing 30 to 200 μg selenium *per* dose unit are available (Rayman *et al.*, 2008), with the suggested daily intake at one unit *per* day. As noted, because there are no current statistical data available on consumption of dietary supplements containing selenium, we have used the levels suggested in product labels as a basis for estimating consumption.[23] Thus, the potential theoretical selenium consumption from dietary supplements would be a maximum of 200 μg/day. This estimate is added to those in Table 6 to arrive at the total potential theoretical background consumption of selenium from both conventional food and dietary supplements, with Sel-Plex® added to food as indicated. Total potential intake of selenium at the mean and 90th percentile levels will be 324.9 μg selenium/day and 449.8 μg selenium/day, respectively. This is considered to be a conservative scenario, because as noted in the report of the Institute of Medicine (2000), 50th and 90th percentile intakes of selenium from food + supplements (108.5 and 175.0 μg selenium/day, respectively) are only slightly higher than selenium consumption from food alone (106.0 and 170.0 μg selenium/day, respectively), indicating that the users of selenium supplements ingest very low concentrations of selenium from food sources.

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[21] http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/0304/Table_1_NIF.pdf; site visited April 14, 2010.
[22] http://www.fda.gov/food/guidancecomplianceregulatoryinformation/guidancedocuments/foodingredientsandpackaging/ucm074725.htm; estimating exposure to direct food additives and chemical contaminants in the diet; site visited April 14, 2010.
[23] New Chapter Selenium Food Complex; http://www.vitacost.com/New-Chapter-Selenium-Food-Complex; Schiff Natural Selenium; http://www.vitacost.com/SchiffNaturalSelenium; Solaray Selenium; http://smallplanethealth.com/solaray-selenium-1; NSI Selenium; http://www.vitacost.com/NSI-Selenium. All sites were visited April 15, 2010.

Table 6. Selenium: current intake, predicted intake following supplementation of selected foods at the indicated levels (APPENDIX 1) and total intake (predicted + current) for individuals consuming selected supplemented foods

Selenium intake from	*Per* user (µg selenium/day)	
	Mean	90th Percentile
Current food sources	105.7	211.4
Possible maximum consumption from Sel-Plex® as an added food ingredient	19.2	38.4
Total from conventional food (current + added)	124.9	249.8
Possible consumption from dietary supplements*	200	200
Total from food + dietary supplements	324.9	449.8

* Intake from dietary supplements is included to show the possible maximum intake of selenium. No selenium intake data from food + supplements was available from WWEIA NHANES 2005-2006. Value listed is the maximum intake *via* dietary supplement use (according to the label).

4.2. Medical Foods

The intended new use of Sel-Plex® is as a dietary selenium source in medical foods for use by a select population under a physician's supervision. The patient will receive instructions on the use of the medical food and the physician will determine the diet of the patient. Medical foods that are to be consumed as part of a complete, balanced diet are typically formulated to replace one or more meals throughout the day, which would have the net effect of decreasing the amount of selenium which would otherwise be derived from conventional foods. Therefore, medical food products consumed as part of a balanced diet under the direct supervision of a physician may contain Sel-Plex® such that the aggregate amount of selenium consumed in the daily diet would be limited to 38.4 µg/ day. Patients receiving such a medical food as a sole source of nutrition would not exceed this intake of selenium because of the absence of other dietary selenium sources.

In some instances, medical foods may be used to supplement the typical diet (*i.e.* the medical food is not the sole source of the diet). Supplemental use of Sel-Plex® in medical foods consistent with the safe use of Sel-Plex® for the following reasons:

- The consumption analysis for this GRAS determination assumes intake of Sel-Plex® from conventional foods and beverages at the 90th percentile (Table 5). If a patient is receiving medical food containing Sel-Plex®, it is unlikely that the patient will consume enough conventional food containing Sel-Plex® (or selenium) to achieve

greater than 90th percentile intakes of Sel-Plex® (or selenium). If a physician orders the addition of a selenium containing medical food and/or requests that the patient add a selenium source (*i.e.* a "modular") to their medical food, it is therefore likely the physician is cognizant of the need for adequate amounts of selenium and the possible overdosing of selenium and therefore, will advise the patient to avoid other dietary sources rich in selenium.

- The total possible intake of selenium shown in Table 6 assumes consumption of selenium as a dietary supplement at 200 μg/day. Because medical foods are administered under supervision of a physician, patients who receive medical food to supplement their caloric and nutritive intake would be unlikely to consume dietary supplements containing significant quantities of selenium.

In conclusion, is highly improbable that an individual would be consuming conventional foods enriched with Sel-Plex® at 90th percentile levels, medical foods containing Sel-Plex®, and dietary supplements containing 200 μg selenium on a daily basis. However, in the unlikely event that this would occur, the 90th percentile consumption of selenium would be 488.2 μg/day. This level of selenium intake is higher than the IOM established UL of 400 μg selenium/day, but lower than the NOAEL for clinical selenosis (800 μg selenium/day).

5. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION (ADME)

The primary forms of organic selenium in food are SeMet from plants and SeCys from animal-derived foods (*i.e.*, meat products). Ingestion of inorganic selenium is typically *via* dietary supplements. The bioactive constituents of Sel-Plex® are seleno amino acids, mainly SeMet and SeCys derived from selenoproteins.

5.1. Absorption and Bioavailability

Absorption of dietary organic selenium from food sources is approximately 80%, and occurs mainly in the small intestine (Reilly, 1998; Institute of Medicine, 2000). Whereas results of some previously reviewed studies indicate that evidence supports that organic selenium is absorbed more efficiently than inorganic forms (Clausen and Nielsen, 1988; Reilly, 1998; Sloth *et al.*, 2003; Burk *et al.*, 2006; Lee *et al.*, 2007), others suggest that selenium from selenized yeast is

less bioavailable than selenate (Fox *et al.*, 2004) or, similar in bioavailability to selenite (Alfthan *et al.*, 2000). An examination of the populations used in the studies conducted by Alfthan *et al.* (2000) and Clausen and Nielsen (1988) suggests that depressed selenium status results in a higher bioavailability of selenium from organic sources than from inorganic selenium supplementation.

Recent clinical studies show that in subjects receiving 200, 300 or 400 μg/kg day selenium from SeMet or selenized yeast, plasma levels of selenium increase in a dose-dependent manner up to approximately one year (from approximately 115- 146 ng/ml at baseline to approximately 180, 228 or 232 ng/ml (respectively)), where they plateau if supplementation is continued (Hawkes *et al.*, 2008; Reid *et al.*, 2008; Lippman *et al.*, 2009). In healthy men administered 300 μg/kg day selenium from selenized yeast for 48 weeks, concentrations of selenium in erythrocytes, plasma and platelets returned to baseline levels 48 weeks after discontinuing use of the supplement (Hawkes *et al.*, 2008).

5.2. Distribution

5.2.1. Humans

No new information about the distribution of selenium from Sel-Plex®, selenized yeast or SeMet in humans was located. A study mentioned in the original GRAS dossier for Sel-Plex® indicates that in men with "organ-confined" prostate cancer, selenium from SeMet accumulates preferentially in the human prostate gland, compared to the seminal vesicle (Sabichi *et al.*, 2006).

5.2.2. Other Mammals

A search of the literature published after the original GRAS Determination for Sel-Plex® revealed new information about the distribution of selenium from Sel-Plex® or selenized yeast in experimental animals (rats) and livestock.

In rats administered 1.2 mg selenium/kg in feed (as 600 mg/kg feed Sel-Plex®) for 29 days (estimated 0.12 mg selenium/kg bw), increased concentrations of selenium were found in liver and muscle compared to animals receiving basal feed (Czauderna *et al.*, 2007a; 2009).

A number of studies have been conducted in livestock to determine distribution of selenium after administration of Sel-Plex® or selenized yeast in the diet. The actual doses of Sel-Plex® or selenium that were administered in these experiments (on a mg/kg bw basis) cannot be

determined from data that were provided in the published literature because food intake was *ad libitum* and not measured. However, useful information about distribution of selenium after Sel-Plex® or selenized yeast in livestock can be obtained from these studies. In Suffolk lambs (6.87 ± 0.23 kg bw) administered reconstituted milk replacer and a pellet diet containing Sel-Plex® (6.30 ± 0.18 mg selenium/kg dry mass) for 91 days, concentrations of total selenium in skeletal muscle, liver, heart and kidney tissue were 26, 16, 8 and 3 times higher (respectively) than selenium concentrations in animals that were fed diets that were not supplemented with selenium (Juniper *et al.*, 2009a). Whereas SeCys was the predominant form of selenium in the liver and kidney, SeMet concentrations were higher than SeCys in cardiac and skeletal muscle. After placement on the diet containing Sel-Plex®, increased concentrations of SeMet and SeCys were still present in tissues after a 42 day washout period in which the lambs consumed an unsupplemented diet (Juniper *et al.*, 2008b). The rates of selenium clearance in liver, kidney, cardiac tissue and skeletal muscle were 307 µg/day, 238 µg/day, 120 µg/day and 20 µg/day, respectively. Whereas results of one study in lambs employing a lower concentration Sel-Plex® (approximately 0.11 mg selenium/kg dry matter), showed no effect of supplementation on the concentration of total selenium in liver, heart and kidney tissues (Juniper *et al.*, 2009b), another study showed that supplementation of the diet with 0.10 mg selenium/kg dry matter as selenized yeast, increased selenium concentration in the kidney and liver of lambs (Qin *et al.*, 2007). In both of these studies, an increase in selenium content of muscle and increased activity of GSH-PX activity in blood were observed. In lambs receiving feed containing Sel-Plex® (0.30 mg selenium/kg dry weight) for 63 days, there is a significant increase in SeMet content of *Latissimus dorsi* muscle compared to lambs receiving control feed (Vignola *et al.*, 2009). Lambs from pregnant ewes that were administered 20 mg/kg selenium as selenized yeast[24] during the last two months of pregnancy had nearly 30% higher whole blood and 50% higher selenium concentrations in meat than mothers receiving the same concentration of inorganic selenium (Steen *et al.*, 2008). In goats receiving 0.26 mg selenium/head/day from Sel-Plex® for 112 days, there was a greater efficiency of uptake and incorporation of selenium in milk compared to goats receiving a comparable concentration of sodium selenite (Petrera *et al.*, 2009).

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[24] From the information provided in the study it is unknown whether this is mg/kg feed or mg/kg bw.

The effect of supplementation with selenized yeast on selenium status of cows also has been examined. After dietary administration of 0.9 mg selenium/kg dry matter as selenized yeast to cows for 16 weeks, increased concentrations of selenium in hind leg and liver were found, compared to controls receiving diets that were not supplemented with selenium (Lee *et al.*, 2007). Increased concentrations of selenium are also found in heart, liver, kidney and skeletal muscle (psoas major and lumbar multifidus) of cows administered 0.15 or 0.35 mg selenium/kg dry matter from Sel-Plex® for 122 days (Juniper *et al.*, 2008a).

In cows administered Sel-Plex® (approximately 0.25 to 0.5 selenium/kg dry matter) for 5-16 weeks, higher concentrations of SeMet were found in milk compared to cows administered selenium as sodium selenite (Juniper *et al.*, 2006; Guyot *et al.*, 2007; Phipps *et al.*, 2008).

In conclusion, results of recently conducted studies indicate that selenium from Sel-Plex® or selenized yeast is distributed to liver and muscle of rats and; liver, heart, kidney, and muscle of lambs or cows, and milk of cows or goats. In lambs administered Sel-Plex®, SeCys is the predominant form of selenium in the liver and kidney, and SeMet in cardiac and skeletal muscle.

5.3. Metabolism

As mentioned in the previous GRAS dossier, once absorbed, SeMet may be metabolized into H_2Se, which is the starting point for the synthesis of selenoproteins. Oxidation of excess H_2Se leads to production of superoxide and other ROS (Reilly, 1998; Schrauzer, 2000; Combs Jr. and Lu, 2001). Excess H_2Se also undergoes methylation to methylselenol (CH_3SeH), dimethylselenide ($[CH_3]_2Se$) and trimethylselenonium ($[CH_3]_3Se^+$). Dimethylselenide and trimethylselenonium are excreted in the breath and urine, respectively (Daniels, 1996; Schrauzer, 2003). A recent study indicated that methylselenol is an active metabolite, which can induce G1 cell cycle arrest and apoptosis in fibrosarcoma cells (Zeng *et al.*, 2009).

5.4. Elimination

Selenium is excreted from the body either: (1) through the urine, largely in the form of the trimethyl-selenonium ion; (2) in the feces from unabsorbed dietary selenium or biliary, pancreatic, and intestinal secretions; (3) in exhaled air as volatile dimethyl-selenide; or (4) as a small amount lost in hair, nails, and exfoliated skin cells (Reilly, 1998).

5.5. Summary

Results of recently conducted studies indicate that selenium from Sel-Plex® or selenized yeast is well-absorbed and distributes to liver, heart, kidney, muscle and milk. SeMet from Sel-Plex® (or selenized yeast) may be metabolized into H_2Se (the starting point for the synthesis of selenoproteins). Excess H_2Se can be metabolized to an active metabolite (methylselenol) or to dimethylselenide or trimethylselenonium, which are excreted in the breath and urine (respectively).

6. SAFETY EVALUATION

6.1. Acute Studies

No additional information was found regarding the acute toxicity of Sel-Plex® (or selenized yeast) since the original GRAS dossier for Sel-Plex® dated July 5, 2007. Sel-Plex® has an LD_{50} of greater than 2000 mg/kg bw (4 mg selenium /kg bw) the highest dose administered, in rats and mice.[1]

6.2. Subchronic Studies

Results of recent published studies (Table 7) show no adverse effects resulting from continuous feeding of approximately 60 and 7.5 mg/kg bw/day Sel-Plex® (corresponding to 120 and 15 µg selenium/kg bw/day) in rats and mice, respectively (Korniluk *et al.*, 2007; Niedzwiedzka *et al.*, 2007; Czauderna *et al.*, 2007a; Czauderna *et al.*, 2007b; Czauderna *et al.*, 2009; Qin *et al.*, 2009). The concentrations of Sel-Plex® used in these more recent studies are lower than the 13-week oral no observed adverse effect levels (NOAEL) for Sel-Plex® in rats (114 mg Sel-Plex®/kg bw/day or 228 µg selenium/kg bw/day when administered in the diet) and beagle dogs (30 mg Sel-Plex®/kg bw/day or 60 µg selenium/kg bw/day when administered by gavage) (Griffiths *et al.*, 2006a) reported in the original GRAS dossier for Sel-Plex®. The NOAEL of 30 mg Sel-Plex®/kg bw/day in beagle dogs is highly conservative, because the only changes observed at the lowest observable effect level (LOAEL) of 100 mg/kg bw/day were excessive salivation (5/8 treated animals *vs.* 0/8 controls), and increased mean corpuscular hemoglobin concentration (MCHC) and serum cholesterol in females (4.1 mmol/L in treated *vs.* 2.9 mmol/L in control), which may have not been biologically significant (Lortie, 2004). The authors of the study report (Lortie, 2004) considered excessive salivation to be treatment related,

but not adverse, because excessive salivation is commonly observed in dogs treated by gavage. Because (a) no increase in MCHC was noted at 300 mg/kg bw/day, (b) the average MCHC value reported for females treated with 100 mg Sel-Plex®/kg bw/day (34.3 g/dl) is within the normal range of MCHC values reported for beagle dogs (25-38 g/dl) (Field and Jackson, 2007) and, (c) changes in other red blood cell parameters (*i.e.* red blood cell count, hemoglobin concentration, or packed cell volume) were not observed in females treated with 100 mg Sel-Plex®/kg bw/day, it is unlikely that the increase in MCHC in females treated with 100 mg Sel-Plex®/kg bw/day was biologically significant. Furthermore, although the study investigators concluded that the increase in cholesterol in females treated with 100 mg Sel-Plex®/kg bw/day was treatment-related, it was not dose-responsive because (a) a further increase was not noted in females exposed to 300 mg Sel-Plex®/kg bw/day (cholesterol was 3.9 mmol/L in this group) and, (b) the cholesterol concentration of females exposed to 100 mg Sel-Plex®/kg bw/day (4.1 mmol/L) was within the range of historical control values for beagles (3.2 – 8.7 mmol/L) (Field and Jackson, 2007).[25] In conclusion, based on the fact that the changes observed at 100 mg Sel-Plex®/kg bw/day were likely not adverse, but only physiologically adaptive in nature, it could be argued that the NOAEL is actually 100 mg Sel-Plex®/kg bw/day. Based on the facts presented above, we conclude that the original NOAEL that was assigned to the study (30 mg Sel-Plex®/kg bw/day) should be considered a No Observed Effect Level (NOEL) rather than a NOAEL.

In other studies using animals not typically used as models to determine safety in man, no adverse effects were noted. For example cows administered 6.8 mg/kg bw/day Sel-Plex® (corresponding to 13.6 μg selenium/kg bw/day) or 16 mg/kg bw/day selenized yeast containing 1000 ppm selenium (16 μg selenium/kg bw/day) or sheep administered 15.8 mg/kg bw/day Sel-Plex® (corresponding to 31.6 μg selenium/kg bw/day) gained weight normally and did not exhibit any signs of toxicity (Juniper *et al.*, 2006; Lee *et al.*, 2007; Vignola *et al.*, 2009).

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[25] Values reported in Field and Jackson (2007) were converted from mg/dl to mmol/L using a molecular weight of cholesterol of 386.65.

Table 7. Repeated dose studies conducted with Sel-Plex® or selenized yeast since 2007

Material	Method	Species (#/dose group)	Dose[a]	Results	Reference
Sel-Plex®	29 day dietary study	Wistar rat (7-8)	1.2 mg selenium/kg feed as Sel-Plex® (approximately 60 mg/kg bw Sel-Plex®).[1] Control diet contained 0.63 mg .selenium/kg feed(from sodium selenate).	No effect of Sel-Plex® on feed intake or body weight gain. No macroscopic lesions or toxic symptoms were noted.	Czaudema *et al.* (2007a)
Sel-Plex®	29 day dietary study	Wistar rat (7-8)	1.2 mg selenium/kg feed as Sel-Plex® (approximately 60 mg/kg bw Sel-Plex®).[1] Control diet contained 0.63 mg selenium/kg diet (from sodium selenate).	No effect of Sel-Plex® on feed intake or body weight gain. No macroscopic lesions in liver or femoral muscles were noted.	Czaudema *et al.* (2007b)
Sel-Plex®	28 day dietary study	Wistar rat (8)	1.2 mg selenium/kg feed as Sel-Plex® (approximately 60 mg/kg bw Sel-Plex®).[1] Control diet contained 0.63 mg selenium/kg diet (from sodium selenate).	No effect of Sel-Plex® on feed intake, body weight gain or weight of pancreas, liver or spleen. No macroscopic lesions or toxic symptoms were noted.	Korniluk *et al.* (2007)
Sel-Plex®	29 day dietary study	Wistar rat (7-8)	1.2 mg selenium/kg feed as Sel-Plex® (approximately 60 mg/kg bw Sel-Plex®).[1] Control diet contained 0.63 mg selenium/kg diet (from sodium selenate).	No effect of Sel-Plex® on body weight gain or feed conversion efficiency. No macroscopic lesions or toxic symptoms were noted.	Niedzwiedzka *et al.* (2007)
Sel-Plex®	29 day dietary study	Wistar rat (7-8)	1.2 mg selenium/kg feed as Sel-Plex® (approximately 60 mg/kg bw Sel-Plex®).[1] Control diet contained 0.63 mg selenium/kg diet (from sodium selenate)	No effect of Sel-Plex® on body, liver or femoral muscle weight. No macroscopic lesions or toxic symptoms were noted.	Czaudema *et al.* (2009)
Sel-Plex®	30 day dietary study	Kunming mouse (2 replicates of 10/group)	Basal diet or diet supplemented with 0.1 mg selenium /kg as sodium selenite or Sel-Plex® (approximately 7.5 mg/kg bw Sel-Plex®).[2]	No effect of Sel-Plex® on growth performance, body weight, body length, heart, kidney or liver weight.	Qin *et al.* (2009)

Material	Method	Species (#/dose group)	Dose[a]	Results	Reference
Sel-Plex®	5 week dietary study	Holstein cow (20)	0.27, 0.33 or 0.40 mg selenium/kg dry matter as Sel-Plex® (approximately 4.6, 5.6 or 6.8 mg/kg bw Sel-Plex®).[3] Control diet contained 0.15 mg selenium/kg dry matter.	No effect of Sel-Plex® on blood chemistry, hematology, or milk yield.	Juniper *et al.* (2006)
Selenized Yeast (Se-Y, from Alltech)	16 week dietary study	Hanwoo steer (5)	0.9 mg selenium/kg dry matter as Se-Y (approximately 16 mg/kg bw Se-Y).[4] Control diet contained 0.082 mg selenium/kg dry matter.	No effect of Se-Y on body weight gain or dry matter intake.	Lee *et al.* (2007)
Sel-Plex®	63 day dietary study	Apienne lamb (12)	0.30 or 0.45 mg selenium/kg dry matter as Sel-Plex® (approximately 10.6 or 15.8 mg/kg bw Sel-Plex®).[5] Control diet contained 0.13 mg selenium/kg dry matter.	No effect of Sel-Plex® on growth performance or weight.	Vignola *et al.* (2009)

[1] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® selenium content of 2000 mg/kg, feed consumption of 20 g/day and a body weight of 200 g; [2] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® selenium content of 2000 mg/kg, estimated feed consumption of 4.5 g/day (http://research.uiowa.edu/animal/?get=mouse) and a body weight of 30 g; [3] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® selenium content of 2123 mg/kg dry matter, dry matter consumption of 23.4 kg/day and a body weight of 647 kg; [4] Dose of Se-Y in mg/kg bw/day calculated from Se-Y selenium content of 1000 mg/kg, estimated feed consumption of 9.54 kg/day and a body weight of 536 kg. [5] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® selenium content of 2000 mg/kg, average feed consumption of 901 g/day and a body weight of 12.8 kg

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6.3. Studies on Reproduction and Development

As shown in Table 8, the effect of Sel-Plex® on reproduction of sheep and cows has been tested in field studies (Guyot *et al.*, 2007; Munoz *et al.*, 2008; Slavik *et al.*, 2008). The results of these studies show no effect of approximately 12.8 mg Sel-Plex®/kg bw/day (25.6 μg selenium/kg bw/day) or up to 7.54 mg Sel-Plex®/kg bw/day (15.1 μg selenium/kg bw/day) on reproduction or development of sheep or cows (respectively).

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Table 8. Developmental/Reproductive studies with selenized yeast

Species (#/dose group)	Dose[a]	Duration	Results	Reference
Crossbred Ewe (42 control, 40 treated).	Normal diet or diet supplemented with Selplex® for intake of 0.5 mg selenium/ewe/day (approximately 12.8 mg/kg bw/day Selplex®)[1]	14 days prior to 90 days after mating, followed by grass-based diet supplemented with standard mineral and multivitamin mix to lambing (approximately Day 147 of gestation).	No effect of Selplex® on conception or abortion rates, length of gestation, number of lambs born or weaned, or weight at birth. Lambs from supplemented ewes showed faster progression to stand, greater weaning rate and decreased mortality rate at one week than controls.	Munoz *et al.* (2008)
Belgian Blue Cow (20).	0.5 ppm selenium as Sel-Plex® (YS) or sodium selenite (SS) or 0.1 ppm sodium selenite (LSS) (approximately 7.54 mg/kg bw/day Sel-Plex®[2]).	2 months before calving until 2 months after calving.	Diarrhea in 6%, 21% and 35% of 15 –day old calves from YS, SS and LSS groups, respectively. At 75 days the incidences of diarrhea were 19, 29 and 65%, respectively. The sex ratio (M:F) of the calves was different in YS (2.2) than in the SS (0.75) or LSS (0.7) groups.[4] Calves from YS group had higher average daily gains than calves in other groups.	Guyot *et al.* (2007)
Piemontaise, Simmental or Hereford Cow (14/Selplex-50, 30 sodium selenite, 62 control diet).	Diet of cows in late pregnancy supplemented with 1 mg Se/head/day (approximately 1 mg/kg bw/day Selplex®).[3]	6 months	There was no effect of either form of selenium on conception rate or weight gain of calves.. There were fewer cases of retained placenta and mastitis, and lower calf losses.	Slavik *et al.* (2008)

[1] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® dose of 1 g/ewe/day divided by an average body weight of 77.9 kg; [2] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex® selenium content of 2000 mg/kg, estimated feed consumption of 23 kg/day (http://www.ag.ndsu.edu/pubs/ansci/beef/eb74w.htm; site visited April 15, 2010) and a body weight of 775 kg; [3] Dose of Sel-Plex® in mg/kg bw/day calculated from Sel-Plex®-50 selenium content of 1000 mg/kg (http://www.livestocktrail.uiuc.edu/porknet/paperDisplay.cfm?ContentID=47; site visited April 15, 2010) and estimated 1150 lb (522 kg) bw (http://ars.sdstate.edu/AnimalEval/Beef/beefgrade.htm; site visited April 15, 2010); [4] This is an anomaly which cannot be considered to be an effect of Sel-Plex® because Sel-Plex® was administered two months before calving (well after the time when sex is determined).

6.4. Genotoxicity

For this GRAS amendment, no additional information was found on the genotoxicity of Sel-Plex® or selenized yeast. As reported in the GRAS dossier for Sel-Plex® dated July 5, 2007, Sel-Plex® is not mutagenic in *Salmonella typhimurium* bacterial tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence or absence of metabolic activation and does not induce chromosome aberrations *in vivo* or *in vitro* (Griffiths *et al.*, 2006b).

6.5. Carcinogenesis

The ability of Sel-Plex® (1, 4 or 8 ppm selenium in the diet for 29 weeks) to inhibit azoxymethane-induced colon carcinogenicity (two doses of 15 mg/kg subcutaneously, separated by one week) was tested in Sprague Dawley rats (n = 25 *per* group). The doses of 1, 4 or 8 ppm selenium are approximately equal to 25, 100 or 200 mg Sel-Plex®/kg bw/day (50, 200 or 400 μg selenium/kg bw/day) based on an estimated average body weight of 400 g.[26] At 8 ppm (but not 1 or 4 ppm) a significant decrease in body weight was observed (10.5%, $P < 0.05$). At a concentration providing 8 ppm selenium in the diet (but not 1 or 4 ppm), Sel-Plex® protected rats against colon carcinogenicity induced by azoxymethane (McIntosh *et al.*, 2006; McIntosh, 2008). In a similar study performed in mice, administration of Sel-Plex® for 36 weeks at a dose providing 1 or 4 ppm selenium in the diet (approximately 75 or 300 mg Sel-Plex®/kg bw/day or 150 or 600 μg selenium/kg bw/day) had no effect on body weight or azomethane-induced carcinogenesis (Hu *et al.*, 2008).

6.6. Observations in Humans

Results of clinical studies that have been performed with organic forms of selenium that have been published since the original GRAS Determination for Sel-Plex® are shown in Table 9.[27] In general, these recent studies, performed with selenized yeast, support the safety of supplementation with 200 μg selenium/day (approximately 3.3 μg selenium/kg bw/day) (Reid *et*

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[26] Rats were 28 days old at the start and weighed an average of 609 g at study end. The conversion from ppm selenium to ppm Sel-Plex® was based on Sel-Plex® selenium content of 2000 ppm and data obtained from the Priority Based Assessment of Food Additives (PAFA) Database, US Food and Drug Administration, dated 10/19/93.
[27] This table also includes two studies published prior to 2007 (Luoma *et al.*, 1984; Yu *et al.*, 1990) that were not mentioned in the previous GRAS dossier. As shown, no adverse effects were noted in these studies.

al., 2006; Xiaoxia *et al.*, 2006; Hawkes *et al.*, 2008; Reid *et al.*, 2008; Schomburg *et al.*, 2009; Tsavachidou *et al.*, 2009). The relevance of the small, but statistically significant increase ($P < 0.001$) in serum triidothyronine (T3) concentrations in 17 males after 18 months of supplementation with 200 µg SeMet/day is unclear, especially since it was not accompanied by a change in thyrotropin (TSH) concentration. In this study, the authors stated that considering the fairly long period of supplementation, the findings were not clinically significant (Combs Jr. *et al.*, 2009). Hawkes *et al.* (2008) reported that there was no effect of 300 µg selenium/day (5 µg selenium/kg bw/day) as selenized yeast, on clinical chemistry and no signs of selenium toxicity in a 48-week study. In the Hawkes *et al.* (2008) study, the total selenium intake of subjects receiving selenized yeast (from three day dietary intake records) was approximately 435 µg selenium/day (7.25 µg selenium/kg bw/day).

Recently, a phase 3, randomized, placebo-controlled trial of the effect of organic selenium (200 µg selenium/day from L-SeMet[28]) or vitamin E (400 IU/d) supplementation for up to four years on risk of prostate cancer was conducted in a large male study population (n = 35,533) at 427 participating sites in the United States, Canada and Puerto Rico. Results of this study (referred to as the Selenium and Vitamin E Cancer Prevention Trial (SELECT)), were recently published by Lippman *et al.* (2009). In this study, serum selenium concentrations in L-SeMet supplemented males increased from 135.0 µg/L at baseline to 223.4 µg/L at six months (where they remained study for the duration of the study). Supplementation with L-SeMet had no effect on the death rate, or rates of prostate cancer (or other cancers), cardiovascular events, nausea, or fatigue. However, selenium supplementation was associated with increased incidences of alopecia (265 *vs.* 206, $P < 0.01$) and grades 1-2 dermatitis (605 *vs.* 516, $P < 0.01$) compared to placebo (Lippman *et al.*, 2009). There also was a slight increase in the incidence of diabetes mellitus (n = 724 in treated *vs.* 669 in control, relative risk (RR = 1.07)), which was not statistically significant from control (P = 0.16), but was mentioned as a "statistically nonsignificant increased risk of diabetes" by the authors of the study.

Two recent cross-sectional studies reported that increased serum selenium concentrations are associated with increased concentrations of total cholesterol in humans (Bleys, 2008;

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[28] The source of L-SeMet was not provided in the reference that was consulted.

Stranges, 2009). Because these studies were observational, a cause and effect relationship between ingestion of selenium and increased blood lipid concentrations cannot be established. As shown in Table 9, studies that have examined the effect of selenium supplementation on blood lipids show no effect of administration of up to 300 μg organic selenium/day for up to one year on total cholesterol (Luoma *et al.*, 1984; Yu *et al.*, 1990; 2008).

In a recent opinion letter on the safety of L-SeMet as a source of selenium in food supplements, the European Food Safety Authority (EFSA) concluded that selenium-related toxicity may be observed at a supplemental level of 200 μg/day in individuals that have a "high dietary intake of selenium". Because of the purported greater bioavailability of selenium from L-SeMet compared to other sources of selenium and findings of the SELECT study, EFSA determined that the safe level of exposure to L-SeMet was 250 μg/day, corresponding to 100 μg selenium/day.

EFSA's conclusion that supplementation with 200 μg selenium/day from Se-Met (the primary ingredient of selenized yeast) may produce selenium-related toxicity (EFSA, 2009) is not supported by the bulk of clinical evidence. As noted in the GRAS dossier for Sel-Plex® dated July 7, 2007, numerous clinical trials support the safety of selenized yeast supplements when used at doses that provide 200 μg selenium/day (Yu *et al.*, 1991; Clark *et al.*, 1996; Combs Jr. *et al.*, 1997; Peretz *et al.*, 2001; Duffield-Lillico *et al.*, 2002; El-Bayoumy *et al.*, 2002). One study performed on 69 patients with psoriasis indicated that use of up to 600 μg selenium/day (0.01 mg/kg bw/day) as selenized yeast for twelve weeks was not associated with toxicity (Fairris *et al.*, 1989). In a 16-week study in 83 subjects, total daily intake of selenium at up to 800 μg did not result in selenium-related toxicity (Burk *et al.*, 2006). Selenized yeast was administered to 24 biopsy-proven prostate cancer patients at up to 3200 μg/day for approximately twelve months with no identified selenium-associated adverse effects (Reid *et al.*, 2004).

Furthermore, the only statistically significant findings reported in the only study that showed adverse effects of selenium intake of 200 μg selenium/day from selenized yeast (SELECT) were increased incidences of alopecia and grade 1-2 dermatitis (Lippman *et al.*, 2009), which could have been subject to reporting bias due to the unblinded nature of the study.

In the study by Combs *et al.* (1997), no dermatologic signs of selenium toxicity were observed in 653 skin cancer patients receiving 200 μg selenium/day from selenized yeast for up to ten years.

Regarding the slight increase in diabetes reported in male subjects supplemented with 200 μg selenium/day from selenized yeast in the select study (Lippman *et al.*, 2009), the cases of diabetes were not controlled for in the randomization process and the outcome measure for diabetes relied on subject-reported diagnoses and recorded medication (and were not clinically confirmed by analyses of blood glucose or insulin or diabetes risk factors (*e.g.,* BMI, waist circumference or fasting glucose levels)). Furthermore, the increase was not statistically significant from control. Therefore, the slight increase in diabetes in the SeMet-supplemented group in the SELECT study should not be considered to be caused by selenium. Evidence to support a lack of effect of organic selenium on plasma glucose was reported in the study by Hawkes *et al.* (2008), in which administration of 300 μg selenium/day from selenized yeast for 48 weeks to 22 healthy males did not result in plasma glucose levels that were "outside of normal range."

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Table 9. Additional clinical studies that have been performed on selenized yeast

Subjects	Dose	Results	Reference
27 healthy subjects (9 males, 18 females).	96 µg selenium/day as selenized yeast or placebo for two weeks.	No effect of selenium on HDL-C, total cholesterol, triglycerides or HDL-C/ total cholesterol ratio.	Luoma *et al.* (1984)
40 healthy, male subjects with low dietary selenium intake.	300 µg selenium/day in organic form or placebo for one year.	No effect of selenium on hemoglobin, albumin, total cholesterol, or SGPT.	Yu *et al.* (1990)
598 participants of Nutritional Prevention of Cancer Trial[1] undergoing colorectal screening.	200 µg selenium/day as selenized yeast or placebo.	An increased risk of adenomas was not noted in subjects supplemented with selenium when stratified according to age, sex or smoking status. Current smokers and subjects in the lowest tertile of baseline selenium had significant reductions in risk of colorectal adenomas.	Reid *et al.* (2006)
49 Kashin-Beck patients	Selenized yeast (n = 25) or sodium selenate (n = 24) at 200 µg selenium/day for 12 weeks.	Increased selenium content and activity of glutathione peroxidase in erythrocytes in both groups. Increased red blood cell immune adherence (beneficial effect) in both groups.	Xiaoxia *et al.* (2006)
42 healthy men	300 µg selenium/day as selenized yeast[1] (n = 22) or placebo (n = 20) for 48 weeks.	No effect of selenium on serum sodium, potassium, chloride, CO_2, urea nitrogen, creatinine, glucose, calcium, protein, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, triglycerides, or LDL-C, HDL-C or total cholesterol. No signs of selenium toxicity (garlic odor of breath, abnormal growth or loss of hair or nails).	Hawkes *et al.* (2008)
424 subjects in Nutritional Prevention of Cancer Trial[2] receiving high dose of selenium.	400 µg selenium/day as selenized yeast or placebo.	No evidence of an effect of selenium on nonmelanoma skin cancer or total cancer incidence. Compliance was similar in both groups.	Reid *et al.* (2008)
28 healthy adults (17 males, 17 females).	200 µg SeMet/day for 28 months.	No clinically significant changes in T_4 or TSH. Increased T_3 concentration in men after 18 months.	Combs *et al.* (2009)

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35533 male participants of a selenium and vitamin E cancer prevention trial (SELECT)[3]	200 µg selenium/day from L-SeMet (n = 8752), 400 IU vitamin E (n = 8737), selenium plus vitamin E (n = 8703) or placebo (n = 8696).	No effect selenium or vitamin E (either alone or in combination) on prostate cancer incidence, death rate, overall incidence of cardiovascular events, nail changes, fatigue, nausea, or halitosis. Increased incidence of alopecia and dermatitis (grades 1-2) in selenium group.	Lippman *et al.* (2009)
5 children (3 with mutations in SBP2 gene[4] and 2 unaffected siblings)	100, 200 or 400 µg SeMet-enriched yeast or 400 µg sodium selenite for one month each.	None of the treatments corrected the thyroid function abnormalities in SBP2 children. No side effects of treatment were reported.	Schomburg *et al.* (2009)
39 men with prostate cancer	200 µg L-SeMet/day (n = 13), 400 IU vitamin E (n = 14), selenium plus vitamin E (n = 10) or placebo (n = 11) for 3-6 weeks.	No toxic effects attributed to treatment. Expression of p53[5] gene in prostate tumor cells greater in selenium group than control (26.3% *vs.* 5%, P < 0.051).	Tsavachidou *et al.* (2009)

HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; n = number of subjects; SeMet = selenomethionine; SGPT = serum glutamic pyruvic transminase, a biochemical index of liver toxicity; T_3 = triodothyronine; T_4 = thyroxine; TSH = thyrotropin ; [1] The source of selenium was SelenoPrecise™ yeast, which contained 81% of the total selenium as SeMet; [2]A study conducted from 1983 – 1993 in 1312 subjects from 7 dermatology practices. The source of selenium was high selenium baker's yeast from Nutrition 21, which contained 54-62% selenomethinonine (Se Met); [3]Enrollment was between August 22, 2001 and June 24, 2004. The duration was originally planned to be 12 years but the study was discontinued after a median period of 5.46 years (Hatfield and Gladyshev, 2009); [4]SBP2 is essential for normal selenoprotein biosynthesis. The SBP2 children displayed abnormal thyroid metabolism, delayed growth rates and depressed serum selenium and selenoprotein concentrations; [5]p53 gene is a tumor suppressor gene that induces apoptosis.

7. EVALUATION

Sel-Plex® is composed of the intact, dried (non-viable) yeast strain *Saccharomyces cerevisiae* strain CNCM I-3060, which is enriched with selenium and yeast-derived selenoproteins, such as SeMet. Sel-Plex® was determined GRAS for use in yogurts, breads, instant cereals, breakfast and granola-type bars, soups and beverage at a use level of 10 ppm by a panel of experts on July 5, 2007. The original GRAS dossier is being amended to: (1) include use of Sel-Plex® in salty snacks; (2) modify levels of Sel-Plex® in existing foods; and (3) include use of Sel-Plex® in medical foods, either as a sole source of the diet or as part of a balanced diet that includes conventional foods. As a result of these new uses, anticipated 90th percentile consumption of selenium from Sel-Plex® will increase from 31.2 μg/day to 38.4 μg/day. The manufacturing process has not been changed from what was presented in the original GRAS determination.

In the original GRAS dossier, data from studies indicating LD_{50}'s of greater than 2000 mg/kg (4 mg Se/kg) in both rats and mice, 13-week study NOAELs of 114 and 30 mg/kg/day Sel-Plex® in rats and dogs (respectively), and no evidence of genotoxicity *in vitro* or *in vivo* were presented. It was concluded that intake of 300 μg/day yeast-derived selenium (5 μg/kg bw/day) and a total daily intake of selenium of 850 μg/day (14.2 μg/kg bw/day) is safe in humans.

Data reported in this GRAS amendment support the addition of Sel-Plex® to foods listed in APPENDIX 1, resulting in a mean consumption of 0.16 mg Sel-Plex®/kg bw/day (9.6 mg/day Sel-Plex®) and a 90th percentile consumption of 0.32 mg Sel-Plex®/kg/day (19.2 mg/day Sel-Plex®). These consumption levels are equal to a daily consumption of 19.2 and 38.4 μg selenium/day (or 0.32 and 0.64 μg selenium/kg bw/day, respectively). Results of recent studies show no adverse effects of consumption of approximately 60, 7.5, 6.8 or 15.8 mg/kg bw/day Sel-Plex® (corresponding to 120, 15, 13.6 or 31.6 μg selenium/kg bw/day) in rats, mice, cows, or sheep, (respectively) or 16 mg/kg bw/day selenized yeast containing 1000 ppm selenium (16 μg selenium/kg bw/day) in cows. Studies performed to assess the effect of Sel-Plex® on reproduction or development of cows or sheep show no effect of consumption of approximately 12.8 mg Sel-Plex®/kg bw/day (25.6 μg selenium/kg bw/day) or up to 7.54 mg Sel-Plex®/kg bw/day (15.1 μg selenium/kg bw/day) (respectively). These intakes are substantially higher than

the intake of Sel-Plex® that will be consumed by 90th percentile users of Sel-Plex® (0.32 mg/kg bw/day).

The conservative NOAEL for Sel-Plex® in dogs of 30 mg/kg bw/day (60 μg selenium/kg bw/day) on which the safety of Sel-Plex® was established for the original GRAS determination supports the safety of Sel-Plex® for the new uses and use levels defined in this GRAS amendment. Studies that have been performed in humans continue to support the safety of supplementation with 200 μg selenium/day from yeast or other organic sources. It is acknowledged that 90th percentile users of foods containing Sel-Plex® who also consume dietary supplements containing 200 μg/day selenium as selenized yeast may consume a total level of selenium that is higher than recommended ULs by SCF and IOM (300 or 400 μg/day, respectively). Likewise, users of medical foods containing Sel-Plex® could also ingest higher than currently recommended amounts of selenium. However, the likelihood of either of these scenarios occurring is extremely low, because consumers of dietary supplements containing high amounts of selenized yeast typically consume low levels of selenium in the diet and, the diet of users of medical foods will be under supervision of a physician. Furthermore, even in 90th percentile consumers Sel-Plex® in the diet who also ingest the highest available concentration of selenium in dietary supplements (200 μg selenium/day), the total amount of selenium that could be consumed (449.8 μg selenium/day) is considerably lower than the NOAEL for clinical selenosis (approximately 800 μg/day), upon which safety factors of 2-3 were applied to derive the SCF and IOM ULs. Therefore, the likelihood of selenosis arising from use of Sel-Plex® is extremely low.

In conclusion, information contained in the original GRAS dossier and this amendment indicates that the use of Sel-Plex® in the foods specified in APPENDIX 1 and in medical foods at the levels specified in this amendment is safe according to the standard of a reasonable certainty of no harm.

8. CERTIFICATION

The undersigned authors of this document—an amendment to the dossier in support of GRAS status determination for use of Sel-Plex®—hereby certify that, to the best of their knowledge and belief, this document is a complete and balanced representation of all available information, favorable as well as unfavorable, known by the authors to be relevant to evaluation of the substance described herein.

(b) (6)

July 2, 2010

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Toxicologist, Burdock Group

Date

(b) (6)

July 2, 2010

Ray A. Matulka, Ph.D.
Director of Toxicology, Burdock Group

Date

9. CONCLUSION

We, the members of the Expert Panel, have independently and collectively critically evaluated the information summarized above (amendment to the dossier in support of the generally recognized as safe (GRAS) status of Sel-Plex® as a food ingredient) and conclude that Sel-Plex®, produced in accordance with current Good Manufacturing Practice (cGMP) and meeting the specifications described herein, is safe for use in foods up to and including the mean and 90th percentile levels of Sel-Plex® consumption of 0.16 mg Sel-Plex®/kg bw/day (9.6 mg/day Sel-Plex® for a 60 kg individual) and 0.32 mg Sel-Plex®/kg bw/day (19.2 mg/day), respectively (based on a selenium content of 2000 mg Se/kg Sel-Plex®, these consumption levels are equal to daily consumption of selenium of 19.2 µg/day and 38.4 µg/day, respectively; for specific foods and levels of use, refer to Appendix 1). Medical food products may contain Sel-Plex® such that the aggregate amount of selenium consumed in the daily diet will not exceed 38.4 µg/day. We further conclude that these uses of Sel-Plex® are Generally Recognized As Safe by scientific procedures. It is our opinion that other experts qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

10. SIGNATURES

(b) (6)

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2 July 2010
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12. APPENDIX 1

Foods selected for the addition of Sel-Plex®

Food description	Sel-Plex (mg/g)
YOGURT, NS AS TO TYPE OF MILK/FLAVOR	0.01
YOGURT, PLAIN, NS AS TO TYPE OF MILK	0.01
YOGURT, PLAIN, WHOLE MILK	0.01
YOGURT, PLAIN, LOWFAT MILK	0.01
YOGURT, PLAIN, NONFAT MILK	0.01
YOGURT, VANILLA, LEMON, COFFEE, NS AS TO MILK TYPE	0.01
YOGURT, VANILLA, LEMON, COFFEE, WHOLE MILK	0.01
YOGURT, VANILLA, LEMON, COFFEE, LOWFAT MILK	0.01
YOGURT, VANILLA, LEMON, COFFEE, NONFAT MILK	0.01
YOGURT, VANILLA, LEMON, COFFEE, NONFAT MILK, LOW CAL SWEET	0.01
YOGURT, CHOCOLATE, NS AS TO TYPE OF MILK	0.01
YOGURT, CHOCOLATE, NONFAT MILK	0.01
YOGURT, FRUIT VARIETY, NS AS TO MILK TYPE	0.01
YOGURT, FRUIT VARIETY, WHOLE MILK	0.01
YOGURT, FRUIT VARIETY, LOWFAT MILK	0.01
YOGURT, FRUIT VARIETY, NONFAT MILK	0.01
YOGURT, FRUITED, NONFAT MILK, LOW CAL SWEETENER	0.01
YOGURT, FRUIT & NUTS, LOWFAT MILK	0.01
CHEDDAR CHEESE SOUP	0.005
BEEF, POT, & VEG (INCL CAR/DK GRN), (MUSHROOM) SOUP	0.005
BEEF, POT, & VEG (NO CAR/DK GREEN), (MUSHROOM) SOUP	0.005
OXTAIL SOUP	0.005
MEATBALL SOUP, MEXICAN STYLE (SOPA DE ALBONDIGAS)	0.005
BEEF NOODLE SOUP, P.R. (SOPA DE CARNE Y FIDEOS)	0.005
BEEF & NOODLE SOUP, ORIENTAL (VIETNAMESE PHO BO)	0.005
PEPPERPOT (TRIPE) SOUP (INCL MENUDO/MONDONGO SOUP)	0.005
BEEF VEG SOUP W/POTATO, STEW TYPE (INCL CHUNKY STY)	0.005
BEEF VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYLE	0.005
BEEF VEG SOUP W/ RICE, STEW TYPE, CHUNKY STYLE	0.005
BEEF VEGETABLE SOUP,MEXICAN STYLE (SOPA / CALDO DE RES)	0.005
MEAT & CORN HOMINY SOUP, MEXICAN STYLE (POZOLE)	0.005
PORK & RICE SOUP, STEW TYPE, CHUNKY STYLE	0.005
PORK VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYLE	0.005
PORK, VEGETABLE SOUP W/ POTATOES, STEW TYPE	0.005
PORK W/VEG (NO CAR,BROC,&/OR DK GREEN)SOUP,ORIENTAL	0.005
LAMB, PASTA & VEGETABLE SOUP, P.R.	0.005
MEXICAN STYLE CHICKEN BROTH SOUP STOCK	0.005
CHICKEN RICE SOUP, P.R. (SOPA DE POLLO CON ARROZ)	0.005
CHICKEN SOUP W/ NOODLES & POTATOES, P.R.	0.005
CHICKEN GUMBO SOUP	0.005
CHICKEN NOODLE SOUP, CHUNKY	0.005
CHICKEN SOUP, CANNED, UNDILUTED	0.005
CHICKEN SOUP	0.005
CHICKEN SOUP,W/VEGS(BROC,CRT,CELERY,POTS)ORIENTAL	0.005
CHICKEN VEGETABLE SOUP, STEW TYPE (INCL CHUNKY)	0.005

CHICKEN VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYL	0.005
CHICKEN OR TURKEY VEGETABLE SOUP, HOME RECIPE	0.005
CHICKEN VEGETABLE SOUP,W/RICE,MEXICAN(SOPA / CALDO DE POLLO)	0.005
HOT & SOUR SOUP (INCLUDE HOT & SPICY CHINESE SOUP)	0.005
CHICKEN SOUP W/ VEGETABLES & FRUIT, ORIENTAL STYLE	0.005
CHICKEN SOUP, CREAM OF, NS AS TO MILK OR WATER	0.005
CHICKEN/TURKEY SOUP,CREAM OF, W/ MILK	0.005
CHICKEN SOUP, CREAM OF, PREPARED W/ WATER	0.005
CHICKEN SOUP, CREAM OF, CANNED, UNDILUTED	0.005
FISH CHOWDER (INCL FISHERMAN'S SOUP, SEAFOOD CHOWD)	0.005
CRAB SOUP, NS AS TO TOMATO-BASE OR CREAM	0.005
FISH & VEGETABLE SOUP,NO POTATOES (SOPA DE PESCADO)	0.005
FISH SOUP, W/ POTATOES (SOPA DE PESCADO)	0.005
CRAB SOUP, CREAM OF, W/ MILK	0.005
SHRIMP SOUP, CREAM OF, NS AS TO MILK/WATER ADDED	0.005
SHRIMP SOUP, CREAM OF, W/ MILK	0.005
SEAFOOD SOUP W/ POTATOES & VEGETABLES (INCL DK GREEN LEAF)	0.005
SEAFOOD SOUP W/ POTATOES & VEGETABLES (EXCL DK GREEN LEAF)	0.005
SEAFOOD SOUP W/ VEGETABLES (INCL DK GREEN LEAFY)	0.005
SEAFOOD SOUP W/ VEGETABLES (EXCL DK GREEN LEAFY)	0.005
EGG DROP SOUP	0.005
GARLIC EGG SOUP, P.R. (SOPA DE AJO)	0.005
HIGH PROTEIN BAR, CANDY-LIKE, SOY & MILK BASE	0.005
BEAN SOUP, NFS	0.005
BEAN W/ BACON OR PORK SOUP	0.005
BLACK BEAN SOUP	0.005
SOYBEAN SOUP, MISO BROTH	0.005
PINTO BEAN SOUP	0.005
BEAN SOUP W/ MACARONI (INCL PASTA E FAGIOLI)	0.005
PORTUGUESE BEAN SOUP	0.005
BEAN SOUP, HOME RECIPE	0.005
BEAN & RICE SOUP	0.005
BEAN & HAM SOUP, HOME RECIPE	0.005
CHUNKY PEA & HAM SOUP	0.005
GARBANZO OR CHICKPEA SOUP	0.005
SPLIT PEA & HAM SOUP	0.005
SPLIT PEA SOUP	0.005
SPLIT PEA SOUP, CAN, REDUCED SODIUM, W/ WATER/RTS	0.005
LENTIL SOUP	0.005
BREAD, NS AS TO MAJOR FLOUR	0.06
BREAD, NS AS TO MAJOR FLOUR, TOASTED	0.06
BREAD, HOMEMADE/PURCH AT A BAKERY, NS AS TO FLOUR	0.06
BREAD, WHITE	0.06
BREAD, WHITE, TOASTED	0.06
BREAD, WHITE, HOMEMADE OR PURCHASED AT A BAKERY	0.06
BREAD, WHITE, HOMEMADE OR PURCH AT A BAKERY TOASTED	0.06
BREAD, FRENCH OR VIENNA	0.06
BREAD, FRENCH OR VIENNA, TOASTED	0.06

FOCACCIA, ITALIAN FLATBREAD, PLAIN	0.06
BREAD, ITALIAN, GRECIAN, ARMENIAN	0.06
BREAD, ITALIAN, GRECIAN, ARMENIAN, TOASTED	0.06
BREAD, PITA	0.06
BREAD, PITA, TOASTED	0.06
BREAD, CHEESE (INCLUDE ONION CHEESE)	0.06
BREAD, CHEESE, TOASTED (INCLUDE ONION CHEESE)	0.06
BREAD, CINNAMON	0.06
BREAD, CINNAMON, TOASTED	0.06
BREAD, GARLIC	0.06
BREAD, GARLIC, TOASTED (INCLUDE TEXAS TOAST)	0.06
BREAD, ONION	0.06
BREAD, REDUCED CALORIE/HIGH FIBER	0.06
BREAD, REDUCED CALORIE/HIGH FIBER, ITALIAN	0.06
BREAD, REDUCED CALORIE/ HIGH FIBER, W/ FRUIT/NUTS	0.06
BREAD, HIGH PROTEIN	0.06
BREAD, RAISIN	0.06
BREAD, RAISIN, TOASTED	0.06
BREAD, SOUR DOUGH	0.06
BREAD, SOUR DOUGH, TOASTED	0.06
BREAD STICK, HARD	0.06
BREAD STICK, SOFT	0.06
BREAD STICK, NS AS TO HARD OR SOFT	0.06
BREAD STICK, SOFT, PREP W/ GARLIC & PARMESAN CHEESE	0.06
BREAD STICK, HARD, LOW SODIUM	0.06
BREAD, 100% WHOLE WHEAT	0.06
BREAD, 100% WHOLE WHEAT, TOASTED	0.06
BREAD, 100% WHOLE WHEAT, HOME-MADE	0.06
BREAD, 100% WHOLE WHEAT, HOME-MADE, TOASTED	0.06
BREAD, PITA, 100% WHOLE WHEAT	0.06
BREAD, SPROUTED WHEAT	0.06
BREAD, WHOLE WHEAT, OTHER THAN 100%/NS AS TO 100%	0.06
BREAD, WHOLE WHEAT, OTHER THAN 100%/NS 100%, TOAST	0.06
BREAD, "WHOLE" WHEAT, HOME RECIPE/BAKERY	0.06
BREAD, "WHOLE" WHEAT, HOME RECIPE/BAKERY, TOASTED	0.06
BREAD, WHOLE WHEAT, NS AS TO 100%, W/ RAISINS	0.06
BREAD, WHOLE WHEAT,NS AS TO 100%,W/ RAISINS,TOASTED	0.06
BREAD, WHEAT OR CRACKED WHEAT	0.06
BREAD, WHEAT OR CRACKED WHEAT, TOASTED	0.06
BREAD, CRACKED WHEAT, HOME RECIPE/BAKERY	0.06
BREAD, CRACKED WHEAT, HOME RECIPE/BAKERY, TOASTED	0.06
BREAD, WHEAT OR CRACKED WHEAT, W/ RAISINS	0.06
BREAD, CRACKED WHEAT, REDUCED CALORIE/ HIGH FIBER	0.06
BREAD, CRACKED WHEAT, RED CALORIE/ HI FIBER, TOAST	0.06
BREAD, FRENCH, "WHOLE" WHEAT, HOMEMADE	0.06
BREAD, PITA, "WHOLE" WHEAT	0.06
BREAD, PITA, CRACKED WHEAT	0.06
BREAD, WHEAT BRAN, TOASTED	0.06

BREAD, RYE	0.06
BREAD, RYE, TOASTED	0.06
BREAD, MARBLE RYE & PUMPERNICKEL	0.06
BREAD, PUMPERNICKEL	0.06
BREAD, PUMPERNICKEL, TOASTED	0.06
BREAD, BLACK	0.06
BREAD, OATMEAL	0.06
BREAD, OATMEAL, TOASTED	0.06
BREAD, OAT BRAN	0.06
BREAD, OAT BRAN, TOASTED	0.06
BREAD, MULTIGRAIN, TOASTED	0.06
BREAD, MULTIGRAIN	0.06
BREAD, MULTIGRAIN, W/ RAISINS, TOASTED	0.06
BREAD, MULTIGRAIN, REDUCED CALORIE/ HIGH FIBER	0.06
BREAD, SOY, TOASTED	0.06
BREAD, SUNFLOWER MEAL	0.06
BREAD, SUNFLOWER MEAL, TOASTED	0.06
BREAD, RICE	0.06
CORNBREAD, PREPARED FROM MIX	0.06
CORNBREAD, HOMEMADE	0.06
CORNBREAD MUFFIN, STICK, ROUND	0.06
CORNBREAD MUFFIN, STICK, ROUND, HOMEMADE	0.06
BREAD, NUT	0.06
BREAD, PUMPKIN (INCLUDE W/ RAISINS)	0.06
BREAD, FRUIT, W/O NUTS	0.06
BREAD, FRUIT & NUT	0.06
BREAD, ZUCCHINI (INCL SQUASH BREAD; W/ NUTS)	0.06
BREAD, IRISH SODA	0.06
BREAKFAST BAR, NFS	0.06
BREAKFAST BAR, CEREAL CRUST W/ FRUIT FILLING, LOWFAT	0.06
BREAKFAST BAR, CEREAL CRUST W/ FRUIT FILLING, FAT FREE	0.06
BREAKFAST BAR, DATE, W/ YOGURT COATING	0.06
MEAL REPLACEMENT BAR (INCL SLIM FAST BAR)	0.06
GRANOLA BAR W/ OATS, SUGAR, RAISINS, COCONUT	0.06
GRANOLA BAR, OATS, FRUIT, NUTS, LOWFAT	0.06
GRANOLA BAR, NONFAT	0.06
GRANOLA BAR, CHOCOLATE-COATED	0.06
GRANOLA BAR, W/ COCONUT, CHOCOLATE-COATED	0.06
GRANOLA BAR W/ NUTS, CHOCOLATE-COATED	0.06
GRANOLA BAR, COATED W/ NONCHOCOLATE COATING	0.06
GRANOLA BAR, HIGH FIBER, YOGURT COATING, NOT CHOC	0.06
GRANOLA BARS, W/ RICE CEREAL	0.06
POWERBAR (FORTIFIED HIGH ENERGY BAR)	0.06
CRISPBREAD, WHEAT, NO ADDED FAT	0.06
CRISPBREAD,WHEAT / RYE, EXTRA CRISPY	0.06
CRISPBREAD, RYE, NO ADDED FAT	0.06
MULTIGRAIN MIXTURE, PRETZELS, CEREAL &/ CRACKERS,NUTS	0.06
MULTIGRAIN MIX, BREAD STICKS, SESAME NUGGETS, PRETZ	0.06

CEREAL, COOKED, INSTANT, NS AS TO GRAIN	0.06
WHOLE WHEAT CEREAL, COOKED, NO FAT ADDED	0.06
WHOLE WHEAT CEREAL, W/ BARLEY, COOKED, NO FAT ADDED	0.06
WHOLE WHEAT CEREAL, WHEAT & BARLEY, FAT ADDED	0.06
WHEAT CEREAL, CHOC FLAVORED, COOKED, NO FAT ADDED	0.06
WHEAT CEREAL, CHOC FLAV,COOKED,NS AS TO ADDED FAT	0.06
OAT BRAN CEREAL, COOKED, NO FAT ADDED	0.06
NESTUM, CEREAL	0.06
CEREAL, NFS	0.06
KASHI CEREAL, NS AS TO READY-TO-EAT OR COOKED	0.06
OAT CEREAL, NFS	0.06
CEREAL, READY-TO-EAT, NFS	0.06
ALL-BRAN CEREAL	0.06
ALL BRAN CEREAL W/ EXTRA FIBER	0.06
ALPHA-BITS CEREAL	0.06
APPLE CINNAMON SQUARES MINI-WHEATS CEREAL, KELLOGG'S	0.06
APPLE JACKS CEREAL	0.06
BANANA NUT CRUNCH CEREAL (POST)	0.06
BASIC 4 (RTE CEREAL)	0.06
BOOBERRY CEREAL	0.06
ALL-BRAN BRAN BUDS CEREAL, KELLOGG'S (FORMERLY BRAN BUDS)	0.06
BRAN CHEX CEREAL	0.06
CAP'N CRUNCH CEREAL	0.06
CAP'N CRUNCH'S CRUNCH BERRIES CEREAL	0.06
CAP'N CRUNCH'S PEANUT BUTTER CRUNCH CEREAL	0.06
CHEX CEREAL, NFS	0.06
CHOCOLATE FLAVORED FROSTED PUFFED CORN CEREAL	0.06
CINNAMON TOAST CRUNCH CEREAL	0.06
HONEY NUT CLUSTERS CEREAL	0.06
COCOA KRISPIES CEREAL	0.06
COCOA PEBBLES CEREAL	0.06
COCOA PUFFS CEREAL	0.06
COOKIE-CRISP CEREAL (INCLUDE ALL FLAVORS)	0.06
CRUNCHY CORN BRAN CEREAL, QUAKER	0.06
CORN CHEX CEREAL	0.06
CORN PUFFS CEREAL	0.06
COUNT CHOCULA CEREAL	0.06
CRACKLIN' OAT BRAN CEREAL	0.06
CRISP CRUNCH CEREAL	0.06
CRISPIX CEREAL	0.06
CRISPY RICE CEREAL	0.06
CRISPY WHEATS'N RAISINS CEREAL	0.06
DISNEY CEREALS, KELLOGG'S	0.06
FAMILIA CEREAL	0.06
FIBER ONE CEREAL	0.06
BRAN FLAKES CEREAL, NFS (FORMERLY 40% BRAN FLAKES, NFS)	0.06
NATURAL BRAN FLAKES CEREAL, POST	0.06
FRANKENBERRY CEREAL	0.06

FROOT LOOPS CEREAL	0.06
FROSTED CHEERIOS CEREAL	0.06
FROSTED MINI-WHEATS CEREAL (INCL ALL FLAVORS)	0.06
FROSTY O'S CEREAL	0.06
FROSTED RICE KRISPIES CEREAL	0.06
FRUIT & FIBRE CEREAL, W/ DATES, RAISINS, & WALNUTS	0.06
FRUITY PEBBLES CEREAL	0.06
GOLDEN GRAHAMS CEREAL	0.06
GRAPE-NUTS CEREAL	0.06
GREAT GRAINS, RAISIN, DATE, & PECAN,WHOLE GRAIN CEREAL, POST	0.06
GREAT GRAINS DOUBLE PECAN WHOLE GRAIN CEREAL, POST	0.06
HEALTHY CHOICE ALMOND CRUNCH CEREAL W/ RAISINS	0.06
HONEY BUNCHES OF OATS CEREAL	0.06
HONEYCOMB CEREAL, PLAIN	0.06
HONEYCOMB CEREAL, STRAWBERRY	0.06
HONEY CRUNCH CORN FLAKES CEREAL, KELLOGG'S	0.06
HONEY NUT CHEX CEREAL	0.06
HONEY NUT SHREDDED WHEAT CEREAL, POST	0.06
KABOOM CEREAL	0.06
KING VITAMAN CEREAL	0.06
KIX CEREAL	0.06
LIFE CEREAL (PLAIN & CINNAMON)	0.06
LUCKY CHARMS CEREAL	0.06
FROSTED OAT CEREAL W/ MARSHMALLOWS	0.06
MALT-O-MEAL COCO-ROOS CEREAL	0.06
MALT-O-MEAL CORN BURSTS CEREAL	0.06
MALT-O-MEAL HONEY & NUT TOASTY O'S CEREAL	0.06
MALT-O-MEAL MARSHMALLOW MATEYS CEREAL	0.06
MALTO-O-MEAL PUFFED WHEAT CEREAL	0.06
MALT-O-MEAL GOLDEN PUFFS CEREAL (FORMERLY SUGAR PUFFS)	0.06
MALT-O-MEAL TOASTED OAT CEREAL	0.06
MALT-O-MEAL TOOTIE FRUITIES (RTE CEREAL)	0.06
MARSHMALLOW SAFARI CEREAL, QUAKER	0.06
MILLET, PUFFED (CEREAL)	0.06
MUESLIX CEREAL, NFS	0.06
APPLE CINNAMON OATMEAL CRISP CEREAL (OATMEAL CRISP W/ APPLES	0.06
OATMEAL CRISP W/ ALMONDS CEREAL	0.06
OATMEAL RAISIN CRISP CEREAL	0.06
OH'S, HONEY GRAHAM CEREAL	0.06
OH'S, FRUITANGY CEREAL	0.06
100% BRAN CEREAL	0.06
100 % NATURAL CEREAL, W/ OATS,HONEY & RAISINS,QUAKER	0.06
OREO O'S CEREAL, POST	0.06
SWEET CRUNCH CEREAL, QUAKER (FORMERLY POPEYE)	0.06
SWEET PUFFS CEREAL, QUAKER	0.06
QUAKER OAT BRAN CEREAL	0.06
QUAKER OATMEAL SQUARES CEREAL (FORMERLY QUAKER OAT SQUARES)	0.06
RAISIN BRAN CEREAL, NFS	0.06

RAISIN BRAN CEREAL, KELLOGG	0.06
RAISIN BRAN CEREAL, POST	0.06
RAISIN NUT BRAN CEREAL	0.06
REESE'S PEANUT BUTTER PUFFS CEREAL	0.06
RICE CHEX CEREAL	0.06
RICE KRISPIES CEREAL	0.06
RICE KRISPIES TREATS CEREAL (KELLOGG'S)	0.06
PUFFED RICE CEREAL	0.06
SHREDDED WHEAT 'N BRAN CEREAL	0.06
SPECIAL K CEREAL	0.06
CORN POPS CEREAL	0.06
GOLDEN CRISP CEREAL	0.06
TOASTED OAT CEREAL	0.06
MALT-O-MEAL TOASTY O'S CEREAL	0.06
TOTAL CEREAL	0.06
TRIX CEREAL	0.06
UNCLE SAM'S HI FIBER CEREAL	0.06
WAFFLE CRISP CEREAL, POST	0.06
WEETABIX WHOLE WHEAT CEREAL	0.06
WHEAT CHEX CEREAL	0.06
WHEAT GERM CEREAL, PLAIN	0.06
PUFFED WHEAT CEREAL, PLAIN	0.06
WHEATIES CEREAL	0.06
PASTA, W/ TOMATO SAUCE & CHEESE, CANNED	0.005
PASTA W/ TOMATO SAUCE & MEAT/MEATBALLS, CANNED	0.005
PASTA W/ TOMATO SAUCE & FRANKFURTERS/HOT DOGS, CANNED	0.005
PASTA W/ TOMATO SAUCE, MEATLESS	0.005
PASTA W/ MEAT SAUCE (INCLUDE AMER CHOP SUEY)	0.005
PASTA W/ CHEESE & MEAT SAUCE	0.005
PASTA W/ CARBONARA SAUCE	0.005
PASTA W/ CHEESE & TOMATO SAUCE, MEATLESS	0.005
PASTA, MEAT-FILLED, W/ GRAVY, CANNED	0.005
PASTA, WHOLE WHEAT, W/ TOMATO SAUCE, MEATLESS	0.005
PASTA W/ PESTO SAUCE	0.005
FLAVORED PASTA (INCL LIPTON BEEF, CHICKEN FLAVORS)	0.005
MACARONI OR PASTA SALAD	0.005
MACARONI OR PASTA SALAD WITH EGG	0.005
MACARONI OR PASTA SALAD WITH TUNA	0.005
MACARONI OR PASTA SALAD WITH CRAB MEAT	0.005
MACARONI OR PASTA SALAD WITH SHRIMP	0.005
MACARONI OR PASTA SALAD WITH TUNA AND EGG	0.005
MACARONI OR PASTA SALAD WITH CHICKEN	0.005
MACARONI OR PASTA SALAD WITH CHEESE	0.005
PASTA OR MACARONI SALAD W/ OIL & VINEGAR-TYPE DRESSING	0.005
PASTA OR MACARONI SALAD W/ MEAT & OIL & VINEGAR DRESSING	0.005
PASTA,W/ VEGETABLES & CHEESE SAUCE (DIET FROZ MEAL)	0.005
SOUP, NFS	0.005
NOODLE SOUP, NFS	0.005

RICE SOUP, NFS	0.005
BARLEY SOUP (INCLUDE BEEF/CHICKEN/MUSHROOM BARLEY)	0.005
BEEF NOODLE SOUP	0.005
BEEF RICE SOUP	0.005
BEEF NOODLE SOUP, HOME RECIPE	0.005
CHICKEN NOODLE SOUP (INCLUDE CHICKEN & STARS SOUP)	0.005
CHICKEN NOODLE SOUP, CANNED, UNDILUTED	0.005
CHICKEN NOODLE SOUP, CANNED, LOW SODIUM	0.005
CHICKEN NOODLE SOUP, HOME RECIPE	0.005
CHICKEN NOODLE SOUP, CREAM OF	0.005
CHICKEN NOODLE SOUP,CAN,RED SODIUM,READY-TO-SERVE	0.005
CHICKEN RICE SOUP (INCL TURKEY RICE SOUP)	0.005
CHICKEN OR TURKEY RICE SOUP, HOME RECIPE	0.005
CHICKEN RICE SOUP, CAN, RED SODIUM, PREP W/ WATER/RTS	0.005
MATZO BALL SOUP	0.005
CHICKEN SOUP W/ DUMPLINGS, POTATOES	0.005
CHICKEN SOUP W/ DUMPLINGS	0.005
TURKEY NOODLE SOUP	0.005
TURKEY NOODLE SOUP, HOME RECIPE	0.005
INSTANT SOUP, NFS	0.005
INSTANT SOUP, NOODLE (INCLUDE MEAT & VEG FLAVORS)	0.005
SOUP, MOSTLY NOODLES(INCL SPAGHETTI SOUP,TOP RAMEN)	0.005
INSTANT SOUP, RICE (INCLUDE MEAT/CHICKEN FLAVOR)	0.005
INSTANT SOUP, NOODLE W/ EGG, SHRIMP OR CHICKEN	0.005
WON TON (WONTON) SOUP	0.005
NOODLE SOUP W/ VEGETABLES,ORIENTAL STYLE	0.005
NOODLE SOUP,W/ FISH BALL,SHRIMP,&DK GREEN LEAFY VEG	0.005
SOPA SECA (DRY SOUP), Mexican style, NFS	0.005
SOPA DE FIDEO AGUADA, MEXICAN STYLE NOODLE SOUP	0.005
SOPA SECA DE ARROZ (DRY RICE SOUP), MEXICAN STYLE	0.005
SOPA DE TORTILLA, MEXICAN STYLE TORTILLA SOUP	0.005
POTATO SOUP, NS AS TO MADE W/MILK OR WATER	0.005
POTATO SOUP, CREAM OF, W/ MILK	0.005
POTATO SOUP, PREPARED W/ WATER	0.005
POTATO SOUP, INSTANT, MADE FROM DRY MIX	0.005
POTATO & CHEESE SOUP	0.005
MACARONI & POTATO SOUP	0.005
BROCCOLI SOUP (INCLUDE CREAM OF BROCCOLI SOUP)	0.005
BROCCOLI CHEESE SOUP, PREP W/ MILK	0.005
SPINACH SOUP	0.005
DARK-GREEN LEAFY VEGETABLE SOUP,W/MEAT,ORIENTAL	0.005
DARK-GREEN LEAFY VEGETABLE SOUP,MEATLESS,ORIENTAL	0.005
CARROT SOUP, CREAM OF, W/ MILK	0.005
TOMATO SOUP, NFS	0.005
TOMATO SOUP, CREAM OF,PREP W/ MILK	0.005
TOMATO SOUP, PREPARED W/ WATER	0.005
TOMATO SOUP, CANNED, UNDILUTED	0.005
TOMATO SOUP, CANNED, LOW SODIUM, READY-TO-SERVE	0.005

TOMATO SOUP, CAN, RED. SODIUM, PREP. W/ WATER	0.005
TOMATO SOUP, CAN, RED. SODIUM, PREP W/ MILK	0.005
TOMATO BEEF NOODLE SOUP, PREPARED W/ WATER	0.005
TOMATO BEEF RICE SOUP, PREPARED W/ WATER	0.005
TOMATO NOODLE SOUP, PREPARED W/ WATER	0.005
TOMATO NOODLE SOUP, CREAM OF	0.005
TOMATO RICE SOUP, PREPARED W/ WATER	0.005
TOMATO VEGETABLE SOUP, PREP W/ WATER	0.005
TOMATO VEGETABLE SOUP W/NOODLES, PREPARED W/ WATER	0.005
BEET SOUP (BORSCHT)	0.005
CABBAGE SOUP	0.005
CABBAGE W/ MEAT SOUP	0.005
CAULIFLOWER SOUP, CREAM OF, W/ MILK	0.005
CELERY SOUP, CREAM OF, NS AS TO MILK OR WATER ADDED	0.005
CELERY SOUP, CREAM OF, W/ MILK	0.005
CORN SOUP, CREAM OF, W/ MILK	0.005
CORN SOUP, CREAM OF, PREPARED W/ WATER	0.005
MUSHROOM SOUP, CREAM OF, PREP W/ MILK	0.005
MUSHROOM SOUP, CREAM OF, PREPARED W/ WATER	0.005
MUSHROOM SOUP, CANNED, UNDILUTED (INCL CREAM OF)	0.005
MUSHROOM SOUP, W/ MEAT BROTH, PREPARED W/ WATER	0.005
MUSHROOM SOUP, CM OF, LOW SOD, PREP W/ WATER	0.005
MUSHROOM SOUP, CREAM OF, NS AS TO W/ MILK OR WATER	0.005
MUSHROOM SOUP, CM OF, CAN, RED SOD, PREP W/ WATER	0.005
ONION SOUP, CREAM OF, PREP W/ MILK	0.005
ONION SOUP, CREAM OF, CANNED, UNDILUTED	0.005
ONION SOUP, FRENCH	0.005
ONION SOUP, MADE FROM DRY MIX	0.005
PEA SOUP, NFS	0.005
PEA SOUP, PREPARED W/ WATER	0.005
PEA SOUP, CAN, LOW SOD, PREP W/ WATER	0.005
VEGETABLE SOUP, CREAM OF, PREP W/ MILK	0.005
ZUCCHINI SOUP, CREAM OF, PREP W/ MILK	0.005
VEGETABLE SOUP, PREP W/ WATER OR READY-TO-SERVE	0.005
VEGETABLE SOUP, CANNED, LOW SODIUM	0.005
VEGETABLE SOUP, MADE FROM DRY MIX	0.005
VEGETABLE SOUP, HOME RECIPE	0.005
VEGETABLE NOODLE SOUP, HOME RECIPE	0.005
MINESTRONE SOUP, HOME RECIPE	0.005
VEGETABLE BEAN SOUP, PREPARED W/ WATER	0.005
VEGETABLE BEEF SOUP, PREPARED W/ WATER	0.005
VEGETABLE NOODLE SOUP, PREPARED W/ WATER	0.005
VEGETABLE CHICKEN SOUP, W/ WATER OR READY-TO-SERVE	0.005
VEGETABLE RICE SOUP, PREPARED W/ WATER	0.005
VEG CHICKEN RICE SOUP, PREPARED W/ WATER / READY TO	0.005
VEG CHICKEN NOODLE SOUP,PREP W/WATER,READY-TO-SERVE	0.005
VEG SOUP W/ CHICKEN BROTH, MEXICAN STYLE (SOPA RANCHERA)	0.005
VEGETABLE NOODLE SOUP, CAN, RED SODIUM, PREP W/ WATER/RTS	0.005

VEGETABLE BEEF SOUP, HOME RECIPE	0.005
VEG BEEF SOUP W/ NOODLES, HOME RECIPE	0.005
VEG BEEF SOUP W/ RICE, HOME RECIPE	0.005
VEGETARIAN VEGETABLE SOUP, PREPARED W/ WATER	0.005
VEGETABLE SOUP, SPANISH, STEW TYPE	0.005
VEGETABLE SOUP, CHUNKY STYLE	0.005
VEG BEEF SOUP, CHUNKY STYLE (INCL VEG W/ MEAT SOUPS	0.005
SOFT DRINK, NFS	0.01
SOFT DRINK, COLA-TYPE	0.01
SOFT DRINK, COLA-TYPE, SUGAR-FREE	0.01
SOFT DRINK, COLA-TYPE, DECAFFEINATED	0.01
SOFT DRINK, COLA-TYPE, DECAFFEINATED, SUGAR-FREE	0.01
SOFT DRINK, PEPPER-TYPE (INCL DR. PEPPER, MR. PIBB)	0.01
SOFT DRINK, PEPPER-TYPE, SUGAR-FREE	0.01
SOFT DRINK, PEPPER-TYPE, DECAFFEINATED	0.01
SOFT DRINK, PEPPER-TYPE, DECAFFEINATED, SUGAR-FREE	0.01
CREAM SODA	0.01
CREAM SODA, SUGAR-FREE	0.01
SOFT DRINK, FRUIT-FLAVORED, CAFFEINE FREE	0.01
SOFT DRINK, FRUIT-FLAV, SUGAR-FREE, CAFFEINE FREE	0.01
SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE	0.01
SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE, SUGAR-FREE	0.01
GINGER ALE	0.01
GINGERALE, SUGAR-FREE	0.01
ROOT BEER	0.01
ROOT BEER, SUGAR-FREE	0.01
CHOCOLATE-FLAVORED SODA, SUGAR-FREE	0.01
COLA W/ FRUIT OR VANILLA FLAVOR	0.01
COLA W/ FRUIT OR VANILLA FLAVOR, SUGAR-FREE	0.01
CARBONATED JUICE DRINK, NS AS TO TYPE OF JUICE	0.01
CARBONATED NONCITRUS JUICE DRINK	0.01
APPLE-CHERRY DRINK	0.01
APPLE JUICE DRINK	0.01
APPLE-CRANBERRY-GRAPE JUICE DRINK	0.01
APPLE-ORANGE-PINEAPPLE JUICE DRINK	0.01
BANANA-ORANGE DRINK	0.01
BLACK CHERRY DRINK	0.01
FRUIT DRINK (INCLUDE FRUIT PUNCH & FRUIT ADE)	0.01
FRUIT JUICE DRINK, NFS	0.01
TAMARIND DRINK, P.R. (REFRESCO DE TAMARINDO)	0.01
FRUIT PUNCH, MADE W/ FRUIT JUICE & SODA	0.01
FRUIT PUNCH, MADE W/ SODA, FRUIT JUICE & SHERBET	0.01
GRAPEADE & GRAPE DRINK	0.01
GRAPE JUICE DRINK	0.01
GRAPEFRUIT JUICE DRINK	0.01
GUAVA JUICE DRINK	0.01
LEMONADE, FROZEN CONCENTRATE, NOT RECONSTITUTED	0.01
LEMONADE	0.01

LEMON-LIMEADE	0.01
LIMEADE	0.01
ORANGE-MANGO JUICE DRINK	0.01
ORANGE DRINK (INCLUDE ORANGE ADE, YABA DABA DEW)	0.01
CITRUS FRUIT JUICE DRINK (INCL 5-ALIVE)	0.01
ORANGE-CRANBERRY JUICE DRINK	0.01
ORANGE-PEACH JUICE DRINK	0.01
ORANGE-GRAPE-BANANA JUICE DRINK	0.01
PAPAYA JUICE DRINK	0.01
PINEAPPLE-GRAPEFRUIT JUICE DRINK	0.01
PINEAPPLE-ORANGE JUICE DRINK	0.01
RASPBERRY-FLAVORED DRINK	0.01
STRAWBERRY-FLAVORED DRINK	0.01
FRUIT DRINK, LOW CALORIE	0.01
LEMONADE, LOW CALORIE	0.01
CHERRY DRINK W/ VITAMIN C ADDED	0.01
CITRUS DRINK W/ VITAMIN C ADDED	0.01
CRANBERRY JUICE DRINK W/VIT C ADDED(INCL COCKTAIL)	0.01
CRANBERRY-APPLE JUICE DRINK W/ VITAMIN C ADDED	0.01
FRUIT PUNCH/DRINK/ADE W/ VIT C ADDED (INCL HI-C)	0.01
GRAPEFRUIT JUICE DRINK W/ VITAMIN C ADDED	0.01
GUAVA JUICE DRINK W/ VIT C ADDED	0.01
LEMONADE W/ VITAMIN C ADDED	0.01
VEGETABLE & FRUIT JUICE DRINK, W/ VIT C	0.01
ORANGE DRINK & ORANGEADE W/ VITAMIN C ADDED	0.01
ORANGE BREAKFAST DRINK, FROM FROZEN CONCENTRATE	0.01
ORANGE BREAKFAST DRINK	0.01
FRUIT-FLAVORED DRINK, FROM SWEETENED PWDR,FORTIFIED W/ VIT C	0.01
LEMONADE-FLAV DRINK, FROM POWDER, W/ SUGAR & VIT C	0.01
LEMONADE-FLAV DRINK, FROM POWDER, LO CAL, W/ VIT C	0.01
APPLE CIDER DRINK, FROM MIX, SUGAR & VIT C ADDED	0.01
FRUIT-FLAVORED DRINK, FROM POWDER, W/HI VIT C(TANG)	0.01
FRUIT-FLAVOR DRINK, FROM UNSWEET PWDR,W/ VIT C,W/ SUGAR	0.01
APPLE-WHITE GRAPE JUICE DRINK,LOW CAL,W/VIT C ADDED	0.01
CRANBERRY JUICE COCKTAIL, LO CAL, W/ VIT C ADDED	0.01
CRANBERRY-APPLE JUICE DRINK, LO CAL, VIT C ADDED	0.01
GRAPEFRUIT JUICE DRINK,LOW CALORIE,W/ VITAMIN C	0.01
FRUIT-FLAVORED DRINK, LOW CAL, W/ VITAMIN C ADDED	0.01
JUICE DRINK, LOW CALORIE	0.01
FRUIT-FLAV DRINK, FROM MIX, HI VIT C ADDED, LOW CAL	0.01
ORANGE-CRANBERRY JUICE DRINK,LOW CAL,W/ VIT C ADDED	0.01
FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL	0.01
FRUIT-FLAVORED THIRST QUENCHER BEVERAGE	0.01
FLUID REPLACEMNT,ELECTROLYTE SOLUTN(INCL PEDIALYTE)	0.01
FLUID REPLACEMENT, 5% GLUCOSE IN WATER	0.01
ORANGE BREAKFAST DRINK, CALCIUM FORTIFIED	0.01
OATMEAL BEVERAGE W/ MILK	0.01
RICE BEVERAGE, MEXICAN (HORCHATA)	0.01

ATOLE (CORNMEAL BEVERAGE)	0.01
CORN BEV W/ CHOC & MILK(CHAMPURRADO,ATOLE DE CHOC)	0.01
RED BULL ENERGY DRINK	0.01
FRUIT-FLAVORED DRINK,NON-CARB,FROM POWDER, W/ SUGAR	0.01
FRUIT-FLAVORED DRINK, NON-CARB, FROM LO CAL POWDER	0.01
NONALCOHOLIC MALT BEVERAGE	0.01
CRACKER, NS AS TO SWEET/NONSWEET (INCL CRACKER,NFS)	0.06
CRACKERS, SALTINE, LOW SODIUM	0.06
CRACKERS, SALTINE, FAT FREE, LOW SODIUM	0.06
CRACKERS, TOAST THINS (RYE/WHEAT/WHITE), LOW SODIUM	0.06
CRACKER, 100% WHOLE WHEAT,LO SODIUM	0.06
CRACKER, SNACK, LOW SODIUM	0.06
CRACKER, CHEESE, LOW SODIUM	0.06
CRACKER, SNACK, LOWFAT, LOW SODIUM	0.06
CRACKER, SNACK	0.06
CRACKER, SNACK, REDUCED FAT	0.06
CRACKER, SNACK, FAT FREE	0.06
CRACKERS, CHEESE	0.06
CRACKER, CHEESE, REDUCED FAT	0.06
CRACKER, HIGH FIBER, NO ADDED FAT	0.06
CRACKERS, SALTINES	0.06
CRACKERS, SALTINE, WHOLE WHEAT	0.06
CRACKERS, CYLINDRICAL, PEANUT BUTTER-FILLED	0.06
CRACKER, SANDWICH-TYPE, NFS	0.06
CRACKER,SANDWICH-TYPE,PEANUT BUTTER FILLED	0.06
CRACKER,SANDWICH-TYPE, CHEESE-FILLED	0.06
CRACKERS, TOAST THINS	0.06
CRACKER, WATER BISCUIT	0.06
CRACKER, 100% WHOLE WHEAT	0.06
CRACKER, 100% WHOLE WHEAT, REDUCED FAT	0.06
CRACKER,WHOLE WHEAT & BRAN (INCL WH & BRAN TRISCUIT	0.06
CRACKERS, WHEAT	0.06
CRACKERS, WHEAT, REDUCED FAT	0.06
CRACKER CORN (INCL STONED CORN CRACKER)	0.06
SALTY SNACKS, CORN / CORNMEAL BASE, NUT /NUG, TSTD	0.06
SALTY SNACKS, CORN OR CORNMEAL, CORN CHIPS, CHEESE	0.06
SALTY SNACKS, CORN OR CORNMEAL, CORN PUFFS, TWISTS	0.06
SALTY SNACKS, CORN OR CORNMEAL, TORTILLA CHIPS	0.06
SALTY SNACKS, CORN/CORN-CHEESE CHIPS, UNSALTED	0.06
SALTY SNACKS,CORN / CORNMEAL BASE,TORTILLA CHIPS LT	0.06
SALTY SNACKS, TORTILLA CHIPS, FAT FREE, W/ OLEAN	0.06
SALTY SNACKS,CORN/CORNMEAL BASE,TORTILLA,LOWFAT,BKD	0.06
SALTY SNACKS,CORN/CORNMEAL,TORTILLA,LOWFAT,BKD,NO SALT	0.06
SALTY SNACKS, CORN/CORNML BASE,W/OAT BRAN,TORT CHPS	0.06
SALTY SNACKS, CORN BASED/CHEESE PUFFS & TWISTS, LOWFAT	0.06
SALTY SNACK MIXTURE,MOSTLY CORN,W/PRETZELS,W/O NUTS	0.06
SALTY SNACKS, WHEAT-BASE, HIGH FIBER	0.06
SALTY SNACKS, WHEAT-AND CORN-BASED CHIPS	0.06

SALTY SNACKS, MULTIGRAIN CHIPS	0.06
PRETZELS, NFS	0.06
PRETZELS, HARD	0.06
PRETZELS, SOFT	0.06
PRETZEL, OAT BRAN, HARD	0.06
PRETZEL, HARD, MULTIGRAIN	0.06
PRETZEL, BABY FOOD	0.06
PRETZEL, HARD, CHOCOLATE COATED	0.06
PRETZEL, YOGURT COVERED	0.06
PRETZELS, CHEESE-FILLED (INCL COMBOS)	0.06
WHEAT STICKS, 100% WHOLE WHEAT	0.06
MULTIGRAIN MIXTURE, PRETZELS, CEREAL &/ CRACKERS,NUTS	0.06
ORIENTAL PARTY MIX, W/ PEANUTS, SESAME STICKS, ETC	0.06
MULTIGRAIN MIX, BREAD STICKS, SESAME NUGGETS, PRETZ	0.06
YOGURT CHIPS	0.06
BAGEL CHIP	0.06
POPCORN, POPPED IN OIL, UNBUTTERED	0.06
POPCORN, AIR-POPPED (NO BUTTER OR OIL ADDED)	0.06
POPCORN, POPPED IN OIL, BUTTERED	0.06
POPCORN, AIR-POPPED, BUTTERED	0.06
POPCORN, FLAVORED (CHEESE, BBQ, SOUR CREAM, ONION)	0.06
POPCORN, POPPED IN OIL, LOWFAT, LOW SODIUM	0.06
POPCORN, POPPED IN OIL, LOWFAT	0.06
POPCORN, SUGAR SYRUP OR CARAMEL COATED	0.06
POPCORN, SUGAR SYRUP OR CARAMEL COATED, W/ NUTS	0.06
POPCORN, SUGAR SYRUP/CARAMEL COATED, FAT FREE	0.06
ONION-FLAVORED RINGS (INCL FUNYUNS)	0.06

DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

July 5, 2007

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

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DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

1. EXECUTIVE SUMMARY

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Expert Panel)[1], qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was requested by Alltech® to determine the Generally Recognized As Safe (GRAS) status of Sel-Plex® (a selenium-enriched yeast preparation by Alltech®) based on scientific procedures. Sel-Plex® is to be used as an ingredient for increased selenium intake, such that addition of Sel-Plex® to food resulting in a mean consumption of 0.3 mg/kg/day or 18 mg/day Sel-Plex® for a 60 kg individual and a 90th percentile consumption at 0.6 mg/kg/day or 36 mg/day is safe. In particular, the Expert Panel has evaluated the proposed use of Sel-Plex® at specified levels in the foods listed in Table 8 of this document. A comprehensive search of the scientific literature was conducted by Burdock Group for safety and toxicity information on Sel-Plex® and related compounds and, along with supporting documentation, was made available to the Expert Panel. Alltech® assures that all relevant, unpublished information in its possession has been supplied to Burdock Group and has been summarized in this monograph. The Expert Panel independently evaluated materials submitted by Burdock Group and Alltech® and any other materials deemed appropriate and necessary. Following an independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

2. INTRODUCTION

Selenium (atomic number of 34) is a nonmetallic element with three valence states and chemical properties similar to sulfur, both containing two electrons less than the maximum of eight in the outer shell, and an atomic weight of 78.96 g/mole. Selenium is a trace mineral unevenly distributed throughout the Earth's crust, found at high concentrations in sedimentary

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[1] Modeled after that described in Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as amended. See also attachments (*curriculum vitae*) documenting the expertise of the Panel members.

rocks such as shale, sandstone, limestone, phosphorite, and copper sulfide ores. Selenium enters the food chain *via* plant and microorganism conversion of inorganic selenium to organically bound forms (Sors *et al.*, 2005). Several areas of the world contain very little selenium in the soil; this leads to insufficient incorporation by plants, ultimately resulting in human selenium-deficiency diseases, such as Keshan disease that occurs in northeastern China.[2] The mechanism of action by which selenium deficiency results in the development of Keshan disease is unknown. Selenium supplementation has significantly reduced the incidence of Keshan disease in China (Cheng and Qian, 1990), but people living in many other areas of the world may also have insufficient selenium intake resulting in less-than-optimal cellular vitality (Combs Jr., 2001).

Selenium is a component of several selenoproteins and selenoenzymes required for various functions, including antioxidant defense, DNA synthesis, fertility and reproduction, reduction of inflammation, and thyroid hormone production (Buettner *et al.*, 2000; Brown and Arthur, 2001; Curcio *et al.*, 2001; Hawkes *et al.*, 2001; Combs Jr. *et al.*, 2001; Foresta *et al.*, 2002; Cunningham-Rundles *et al.*, 2005). Decreased plasma selenium levels have been associated with significantly increased mortality rates and an increased risk of developing mycobacterial disease (*e.g.*, tuberculosis, atypical mycobacterium disease) in Human Immunodeficiency Virus (HIV)-infected patients. Selenium may have an important role in immune function, as well as in the clearance of mycobacteria (Shor-Posner,G. *et al.*, 2002). Supplementation with 200 μg/day selenium resulted in a significant decrease in total hospital admission rates among HIV-infected participants ($P = 0.002$) (Fawzi *et al.*, 2005). Increased serum selenium levels may reduce the risk of developing advanced colorectal adenoma in recent smokers (Peters *et al.*, 2006). Selenium is also known to decrease the toxicity of methyl mercury as well as heavy metals such as arsenic, copper, silver, and cadmium, *via* formation of insoluble complexes (Levander, 1977; Kenyon *et al.*, 1997; Patrick, 2003).

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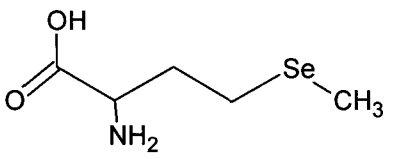
[2] Keshan disease is characterized by myocardial degeneration, necrosis, and scar formation, accompanied by various degrees of cardiac dilation and decompensation[2] and manifests itself in four major clinical signs: heart failure, cardiogenic shock, lung edema, and cardiac arrhythmias (Kanekura *et al.*, 2005).

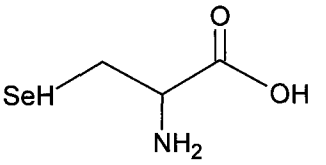
Several strains of baker's yeast (*i.e., Saccharomyces cerevisiae*) are able to incorporate carbon, nitrogen, phosphorus, sulfur, and additional minerals and trace elements (including selenium), into chemical complexes or amino acids, which are distributed into cellular organelles, although it is also becoming apparent that different yeast strains vary greatly in the way they process and compartmentalize selenium within the cell (Larsen *et al.*, 2003; McSheehy *et al.*, 2005). Growth of commercial *S. cerevisiae* in selenium-enriched media results in the incorporation of selenium into several proteins, the majority being selenomethionine (SeMet), with lesser amounts of selenocysteine (SeCys), in place of the analogous sulfur-containing proteins (Korhola *et al.*, 1986). The structures of SeMet and SeCys are presented in Figure 1. Selenium may be accumulated at up to 3000 µg Se/g yeast, with the major product being SeMet, which is incorporated into yeast proteins or physically associated with cell-wall macromolecules (Demirci *et al.*, 1999).

Sel-Plex® is a preparation of the selenium-enriched (*i.e.*, selenized) yeast *S. cerevisiae* strain CNCM I-3060, composed of the intact, dried (non-viable) yeast enriched for selenium content, and other yeast-derived selenoproteins (*i.e.*, proteins containing SeMet and SeCys). As a cell preparation, no formula or molecular structure for Sel-Plex® exists. The cell preparation will be termed "Sel-Plex®" throughout the remainder of this dossier.

This dossier is a summary of the scientific evidence that supports the general recognition that Sel-Plex® is safe for human consumption as a food ingredient when used at the concentrations stated below. Selenoproteins are increasingly the subject of intense study because of selenium's potential bioactivity (Brown and Arthur, 2001). Sel-Plex® will be used as an ingredient to provide consumers with a supplementary source of selenium in their diets.



Selenomethionine



Selenocysteine

Figure 1. Selenomethionine and selenocysteine chemical structures (ChemIDplus Advanced, 2004a; 2004b)

2.1. Description

Sel-Plex® consists of a dried (non-viable) baker's yeast (*Saccharomyces cerevisiae* strain CNCM I-3060) enriched with selenium during its cultivation in a fermentation medium prior to harvesting and drying. The product is a food ingredient (*i.e.*, yeast that contains selenoproteins) and as such, has no specific formula. The preparation is composed of dried yeast containing SeMet, SeCys and selenoproteins, as well as food-grade fermentation medium.

2.2. History of use

Selenium was discovered by Berzelius and Gahn in 1817 while examining the sediment from a sulfuric acid plant at Gripsholm, Sweden (Whanger, 2002). In the United States, it was initially believed that exaggerated consumption of selenium from natural sources induced toxicity in cattle and horses. This belief has been replaced with the hypothesis that cellular and organ toxicity occurs when certain chemical forms of selenium react with tissue thiols to produce reactive oxygen species (ROS), which damage cellular structures critical for cell viability (Raisbeck, 2000).

Trace levels of selenium (as little as 4 μg *per* 100 g diet), supplied either by inorganic sources, such as selenite (Na_2SeO_3) or through organic selenium sources (*e.g.*, selenized yeast, selenomethionine), were found to protect against dietary liver necrosis in rats and pigs (Schwarz and Foltz, 1957). Clinically, selenium supplementation (*i.e.*, sodium selenite-fortified salt) decreased the incidence and improved the prognosis of Keshan disease (Cheng and Qian, 1990).

2.3. Current uses

Selenized yeast is currently sold as a dietary supplement[3] and as an animal feed additive, approved by the U.S. Food and Drug Administration (FDA) for use in poultry, pig and ruminant diets to provide supplemental sources of selenium (Mahan and Parrett, 1996; Mahan and Kim, 1996; Choct *et al.*, 2004).[4] The Institute of Medicine (IOM) has indicated a recommended dietary allowance (RDA) of selenium at 55 μg/day for men and women greater than 19 years of age, 60 μg/day during pregnancy, and 70 μg/day selenium for lactating women. The RDA of selenium for children progressively increases from 20 μg/day for children 1-3 years old, to 55 μg/day for both boys and girls 14-18 years of age (Institute of Medicine, 2006).

2.4. Mechanism of action

Sel-Plex® contains a high level of selenomethionine, and several experimental studies have established that selenomethionine and selenized yeast increase selenium levels in humans (Clark *et al.*, 1996; Reid *et al.*, 2004; Burk *et al.*, 2006). Cereal and forage plants convert selenium mainly into selenomethionine and incorporate it into protein in place of methionine, as tRNA-Met incorporates methionine or selenomethionine indiscriminately. Selenomethionine is not required for plant growth, but is produced in quantities dependent on the amount of available selenium (Schrauzer, 2000).

In mammals, ingested selenomethionine is absorbed in the small intestine *via* a sodium-dependent neutral amino acid transport system (Vendeland *et al.*, 1994). Selenomethionine may be directly metabolized and excreted, or incorporated into organs that have high rates of protein synthesis, such as skeletal muscle, erythrocytes, pancreatic tissue, liver, kidney, stomach, and the gastrointestinal mucosa (Figure 2). Selenomethionine is metabolized by adenosylation and demethylation and, may be converted to selenocysteine *via* selenohomocysteine and selenocystathionine intermediates in pathways analogous to those used in the metabolism of methionine (Esaki *et al.*, 1982; Schrauzer, 2000; Combs Jr., 2001). Selenomethionine

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[3] http://www.drugstore.com/products/prod.asp?pid=41590&catid=36818&aid=335933&aparam=gnc_selenium_200_mcg_tab; GNC 200 μg selenium tablets; site visited February 13, 2007.

[4] http://www.epa.gov/fedrgstr/EPA-IMPACT/2003/September/Day-03/i22358.htm; 21 CFR part 573. Food additives permitted in feed and drinking water of animals; Selenium yeast; site visited February 13, 2007.

metabolism is dependent on vitamin B6 status *via* vitamin B6-dependent enzymes, while tissue deposition of selenomethionine and the utilization in glutathione peroxidase (GSH-PX) is directly correlated with methionine status, as dietary methionine enhances the conversion of selenomethionine into selenocysteine for glutathione peroxidase (Yasumoto *et al.*, 1979; Sunde *et al.*, 1981; Beilstein and Whanger, 1989; Butler *et al.*, 1989).

In contrast to selenomethionine metabolism, inorganic selenium, such as selenate (Na_2SeO_4) and selenite (Na_2SeO_3), undergo reductive metabolism, resulting in hydrogen selenide (H_2Se) that is incorporated into such selenoproteins as GSH-PX, iodothyronine 5'-deiodinases (TDI), thioredoxin reductases (TR), selenophosphate synthetase (SePsyn), plasma selenoprotein P (Se-P), and muscle selenoprotein W (Se-W), although the metabolic functions of many of the selenoproteins remains unclear (Figure 2) (Combs Jr., 2001). Hydrogen selenide is incorporated co-translationally through modification of tRNA-bound serinyl residues at certain loci encoded by specific UGA codons. Methylation of H_2Se detoxifies excess selenium, yielding methylselenol (CH_3SeH), dimethylselenide ($[CH_3]_2Se$) and trimethylselenonium ($[CH_3]_3Se^+$). Dimethylselenide and trimethylselenonium are excreted in the breath and urine, respectively, and is therefore regulated by the kidney glomerular filtration rate, although the exact mechanism of production of the excretory metabolites has not been elucidated (Daniels, 1996; Schrauzer, 2003). Respiratory excretion of selenium is minor, except with toxic intakes when respiratory excretion of selenide gives the characteristic garlic odor to the breath (approximately 3 – 5 mg Se/day). SeMet contained in food can be incorporated non-specifically into proteins in place of methionine, while SeCys is a product of SeMet catabolism and is catabolized into the H_2Se pool by a β-lyase enzyme. Another lyase releases CH_3SeH from selenium-methylselenocysteine (CH_3SeCys) present in some foods (*e.g.*, onions, leaks, garlic). Oxidation of excess H_2Se leads to production of superoxide and other ROS (Reilly, 1998; Schrauzer, 2000; Combs Jr., 2001).

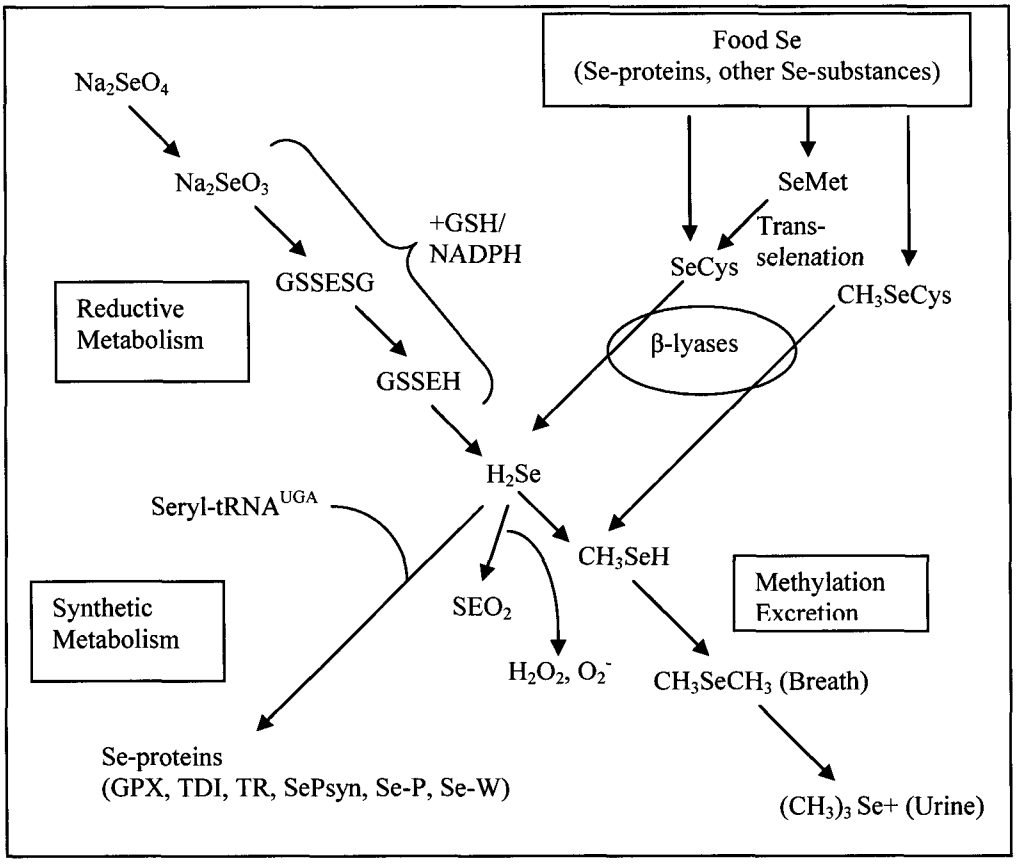

Figure 2. Pathways of selenium (Se) metabolism (see text for definitions) (Combs Jr., 2001; Schrauzer, 2003)

Selenium is incorporated into many different enzyme systems, several of which are related to antioxidant functions (Xia *et al.*, 1989; Diwadkar-Navsariwala and Diamond, 2004; Ebert *et al.*, 2006). Selenium is an essential constituent of glutathione peroxidase and thioredoxin reductase (Diwadkar-Navsariwala and Diamond, 2004; Kim *et al.*, 2004). Glutathione peroxidase is important in scavenging ROS, potentially catalyzing the oxidation of glutathione and reduction of organic hydroperoxides or hydrogen peroxide (protecting membrane lipids and other macromolecules from oxidative damage), and has been hypothesized as the mechanism of selenium-mediated inhibition of tumorigenesis (Munz *et al.*, 1997; Bansal and Kaur, 2005; Goel *et al.*, 2006). The antioxidant property of selenium *in vitro* is concentration-dependent, but the relation to *in vivo* exposure is under continued research. Kim *et al.* (2004) reported that selenium administration *in vitro* attenuated lipopolysaccharide (LPS)-induced ROS and nitric oxide (NO) production in murine macrophage cultures. Macrophage activation is critical for initiation and

maintenance of inflammation and endotoxemia. Stimulation of macrophages by LPS and cytokines results in the expression of inducible NO synthase, catalyzing the production of NO, which regulates macrophage-induced vasorelaxation and inflammation. However, the release of excess NO promotes its oxidization to reactive nitrogen species, resulting in cell signal disruption, systemic inflammation, and septic shock. Ebert *et al.* (2006) found that *in vitro* supplementation of bone marrow stromal cells (BMSC) with selenium (100 nM) restored basal glutathione peroxidase and thioredoxin reductase activity, rescued basal and ROS-stimulated superoxide dismutase mRNA expression and activity, reduced ROS accumulation in telomerase-immortalized human mesenchymal stem cells, and reduced micronuclei generation in BMSC. Selenium supplementation (100 nM as selenite) enhanced selenium dependent and independent ROS scavenging, restored antioxidative capacity, and reduced micronucleus formation (Ebert *et al.*, 2006). Karunasinghe *et al.* (2004) reported that low selenium ingestion in New Zealand individuals that had average serum selenium levels below the mean value of 97.8±16.6 ng/ml had a statistically significant inverse relationship (P=0.02) between lower serum selenium levels and overall accumulated DNA damage. The authors suggest that a subset of the population that consumes low levels of selenium maintains a marginal ability for adequate repair of DNA damage.

2.5. Regulatory status

Dried yeasts (*Saccharomyces cerevisiae* and *S. fragilis*) and dried torula yeast (*Candida utilis*) are regulated by the FDA for safe use in food, provided the total folic acid content of the yeast does not exceed 0.04 milligrams *per* gram of yeast.[5] An extract of baker's yeast has been determined GRAS as a flavoring agent and adjuvant, not to exceed five *percent* in food.[6] The FDA also regulates selenized yeast for addition to complete feed for chickens, turkeys, swine, beef cattle, and dairy cattle at a level not to exceed 0.3 parts *per* million (Table 1).[7] For purposes of this latter animal feed regulation, selenium yeast is defined as:

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[5] Title 21 of the US Code of Federal Regulations (CFR), section 172.896, 2006.
[6] Title 21 of the US Code of Federal Regulations (CFR), section 184.1983, 2006.
[7] Title 21 of the US Code of Federal Regulations (CFR), section 573.920, 2006.

> "...a dried, nonviable yeast (*Saccharomyces cerevisiae*) cultivated in a fed-batch fermentation which provides incremental amounts of cane molasses and selenium salts in a manner which minimizes the detrimental effects of selenium salts on the growth rate of the yeast and allows for optimal incorporation of inorganic selenium into cellular organic material. Residual inorganic selenium is eliminated in a rigorous washing process and must not exceed two *percent* of the total selenium content in the final selenium yeast product."

The same regulation states that the guaranteed organic selenium content from selenium yeast for animal feeds must be declared on the selenium yeast product label. The European Union (EU) has adopted the addition of Sel-Plex® intended to be used in poultry, pigs, and bovines as a nutritional supplement (up to a maximum of 0.5 mg of selenium (total from all sources) *per* kg of complete feedstuffs) (EFSA, 2006). The European Panel on additives and products or substances used in animal feed (FEEDAP) concluded that Sel-Plex® may be used in animal feed at a maximum selenium content of 0.5 mg/kg complete feedstuffs (Ullrey, 1992; EFSA, 2006). The FEEDAP Panel also concluded that excessive selenium intake at ten times greater than 0.5 mg/kg complete feedstuffs produced a reduction on performance parameters of poultry, pigs, and bovines, as indicated by various animal feeding studies. The Panel did not establish an Acceptable Daily Intake (ADI) for Sel-Plex® in humans.

The U.S. Environmental Protection Agency (EPA) proposed an oral selenium reference dose (RfD) in humans of 5 μg/kg bw/day,[8] or 275 μg/day, based on an average adult bodyweight of 55 kg.[9]

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[8] bw = Bodyweight

[9] The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects. The RfD is an estimate (with uncertainty factors) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Selenium and compounds (CASRN 7782-49-2); http://www.epa.gov/iris/subst/0472.htm; site visited June 19, 2006.

Table 1. Regulatory status of yeast and selenized yeast products

Agency	Identification	Permitted functionality	Use limits	Reference
FDA	Direct food substances affirmed as GRAS. Bakers yeast extract	Flavoring agent and adjuvant	Not to exceed 5% in food	21 CFR § 184.1983[10]
FDA	Food additives permitted for direct addition to food for human consumption. Subpart I - Multipurpose additives. Dried yeast	Multipurpose additive	Total folic acid content of the yeast does not exceed 0.04 mg/g yeast	21 CFR § 172.896[6]
FDA	Food additives permitted in feed and drinking water of animals	Selenium additive	The additive selenium yeast is added to complete feed for chickens, turkeys, swine, beef cattle and dairy cattle at a level not to exceed 0.3 parts *per* million	21 CFR § 573.920 (h)[7]

CFR = Code of Federal Regulations; FDA = US Food and Drug Administration; GRAS = Generally Recognized As Safe

2.6. Proposed use or uses

Sel-Plex® is proposed for addition to the foods identified in APPENDIX I at 10 parts *per* million (ppm) for the purpose of increasing dietary organic selenium.

3. DESCRIPTION, SPECIFICATIONS AND MANUFACTURING PROCESS

3.1. Description and specifications

Sel-Plex® is a dried (non-viable) baker's yeast, *Saccharomyces cerevisiae* strain CNCM I-3060, which is cultivated in a fermentation medium that is enriched with selenium prior to harvesting and drying. The product is composed of yeast-derived selenoproteins (the major seleno amino acid being selenomethionine) and other organic proteins; there is no formula or molecular structure for the product as a whole. The physical and chemical properties and specifications for Sel-Plex®, as established by Alltech®, are provided in Table 2 .

[10] Title 21 of the US Code of Federal Regulations (CFR), section 184.1983, 2006.

Table 2. Specifications of Sel-Plex® (Alltech®, personal communication)

Analysis	Method	Specification	Average Batch analysis results ($n = 5$)
Physical aspect	N/A	Light to dark brown free-flowing powder with a slight yeast aroma	
Yeast strain	N/A	*Saccharomyces cerevisiae* CNCM I-3060	
Loss on drying	2nd Directive 71/393/EC	Not more than 7.0%	5.53±0.35
pH	-	-	6.39±0.18
Ash (total %)	NF V 18-101	Maximum of 8%	6.55±0.9
Crude protein	NF V 18-100	Minimum of 45%	46.66±0.93
Mesophilic aerobic germs	NF V 08-051	Less than 5.0 x 10^4 CFU/g	2.5 x 10^4 CFU/g
Coliforms	NF V 08-050	Less than 10 CFU/g	<5 CFU/g
Salmonella (search on 25 g)	NF V 08-052	Negative	Negative
Heavy metals (mg/kg)			
Arsenic	AAS	<3 ppm	0.79 ±0.08
Lead	AAS	<1 ppm	0.07 ±0.03
Cadmium	AAS	<3 ppm	0.022 ±0.005
Mercury	AAS	<0.5 ppm	< 0.005
Total Selenium (mg/kg)	ICP-MS	Not less than 2000 mg/kg	2,275±148.5
Total organic selenium	ICP-MS	≥ 98%	99.6 – 99.63%
Selenomethionine	ICP-MS	65% (62 – 68%)	63.4 – 66.6%
Other organic selenium compounds	ICP-MS	33% (32 – 38%)	33 – 36.2%
Inorganic selenium as Se(IV)	ICP-MS	≤ 2%	0.37 – 0.4%
Inorganic selenium as Se(VI)	ICP-MS	≤ 2% (combined with Se(IV))	Below detection limit

AAS = atomic absorption spectrometry; CFU = colony forming units; ICS-MS = inductively coupled plasma mass spectrometry; N/A = not applicable; ppm = parts *per* million; *Vomitoxin

S. cerevisiae Strain CNCM-I-3060 was selected from a screening program for its ability to accumulate selenium in large quantities and in organic form; this strain is deposited in the Pasteur Institute[11] and its identity and purity are guaranteed by a number of methods, including DNA fingerprinting techniques, such as Polymerase Chain Reaction (PCR) and Pulsed-Field Gel Electrophoresis (PFGE) (Ness *et al.*, 1993). Evidence generated in the literature indicates that not all selenized yeast preparations are the same, and that even closely related yeast strains have their

[11] An internationally known yeast, bacteria, and mammalian cell depository; http://www.pasteur.fr/english.html; site visited December 27, 2006.

own unique biochemical and genetic characteristics. It is also becoming apparent that different yeast strains vary greatly in the way they process and compartmentalize selenium within the cell (Larsen *et al.*, 2003; McSheehy *et al.*, 2005).

Encinar *et al.* (2003) examined three commercial selenized yeast preparations *via* water extraction and enzymatic digestion techniques, which were designed to liberate selenocompounds associated with various polysaccharide and protein fractions within the cell. The selenocompounds were then separated and speciated by Size Exclusion Chromatography-ICP-MS (SEC-ICP-MS) and the recoveries in the various fractions from each yeast product were compared (Figure 3). Different selenoprotein fractions were separated according to solubility and hydrolysable characteristics, indicating that different selenocompounds in selenized yeast can be quantified, resulting in a specific "fingerprint" of the selenized yeast. The aqueous extraction allows the recovery of 15-25% of selenium, of which approximately 30% is protein-bound. Increasing levels of selenium is recovered following each of the fractionation steps for three samples of different commercial yeast food supplements analyzed. The study of recovery of the different classes of selenium species for the three different yeast preparations showed significant differences for selenized yeast samples from different sources. Larson *et al.* (2003) conducted speciation experiments in a different selenized yeast preparation (SelenoPrecise®)[12] using enzymatic extraction coupled with HPLC-ICP-MS, and found that selenomethionine constituted 53% of the total selenium in this yeast. This is in contrast to the 65% selenomethionine found in Sel-Plex® (Table 2). McSheehy *et al.* (2005) also identified the major selenomethionine-containing peptides present in a commercial selenized yeast preparation,[13] and found that the peptides identified showed no overlap with selenopeptides found in Sel-Plex® (Giusti *et al.*, 2006). These data indicate that the subcellular localizations of selenocompounds within several commercial selenium-enriched yeast preparations are very different. This variation may also influence the release of selenium in the gastrointestinal environment, and have a direct effect on the bioavailability, stability, and safety of each selenium product. As an example, Jang *et al.* (2006) evaluated the selenium bioavailability of five unidentified organic selenium sources in the

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[12] Pharma Nord, Denmark http://www.pharmanord.com/; site visited December 27, 2006.
[13] Institute Rosell-Lallemand (Montreal, QC, Canada) provided the yeast sample.

diet of grow-finish pigs, and found significant differences in serum and tissue bioavailability between them and concluded that each organic source should be precisely evaluated for effects and composition prior to the addition to animal feed. In summary, due to differences in selenoprotein speciation in different *S. cerevisiae* strains, diverse commercial selenized yeast products that utilize different strains of *S. cerevisiae* should each be viewed as distinct selenium preparations, each requiring their own data set including composition, stability, and toxicity.

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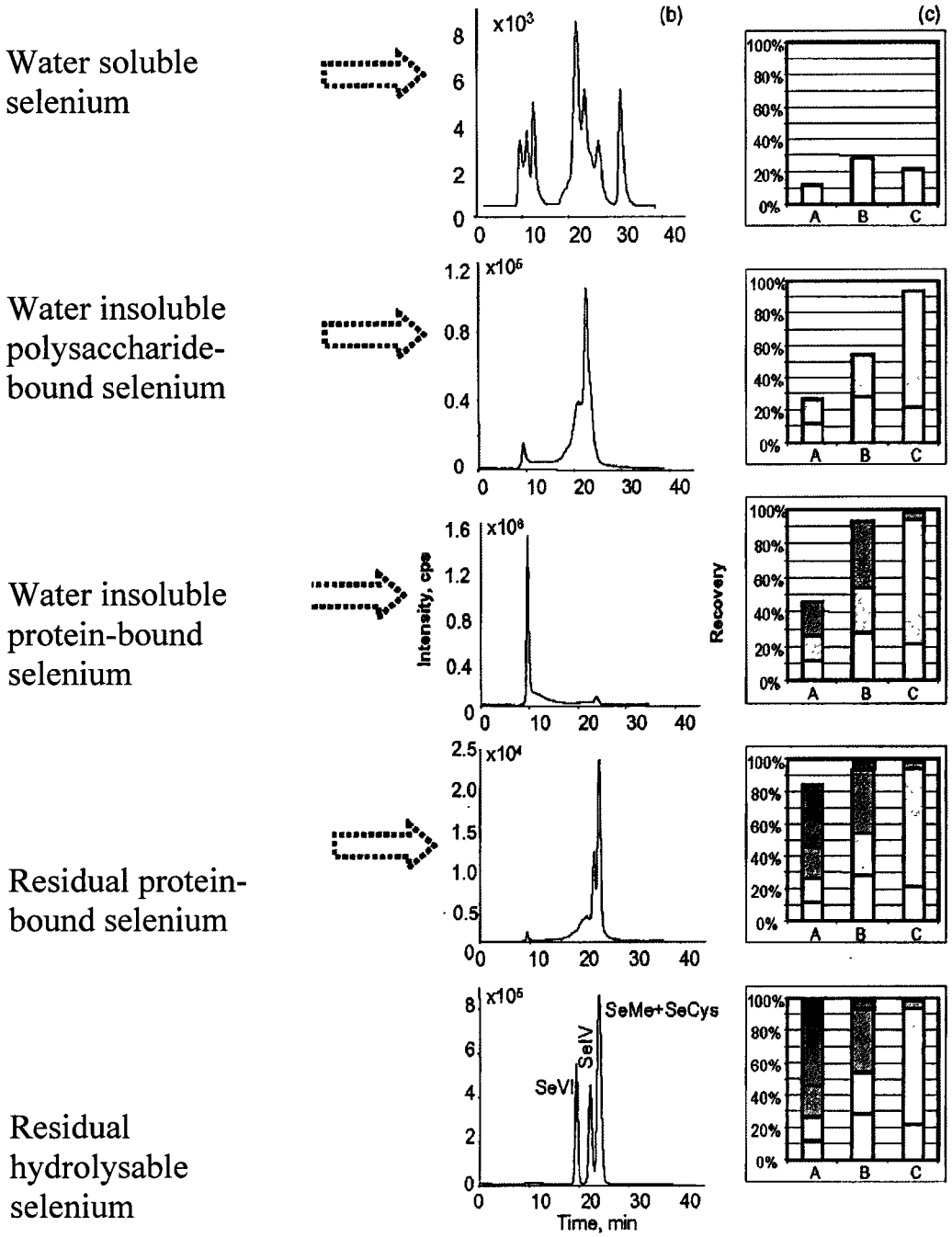

Figure 3. Overview of the sequential extraction of selenium species from selenized yeast preparations for the three (A, B, C) samples of commercial selenized yeast products studied. Different shades correspond to individual fractionation steps (Encinar *et al.*, 2003).

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Based on this information, it is important to define the unique composition for Sel-Plex®, describing the subcellular distribution of selenium within its protein fractions; this selenium "fingerprint" may be tied to the distinctive physicochemical and biological effects of Sel-Plex®. A sequential extraction has been conducted on five non-consecutive production batches of Sel-Plex®, using water, driselase,[14] sodium dodecyl sulfate (SDS), proteolytic extraction, and alkaline hydrolysis using tetramethylammonium hydroxide (TMAH).[15] This sequential extraction allows the recovery of different families of selenium substances as follows:

1) Water soluble selenium species are recovered by hot water extraction;

2) Water insoluble polysaccharide-bound selenium species are recovered by driselase extraction;

3) Water insoluble protein-bound selenium is recovered by SDS extraction;

4) Residual protein-bound selenium is recovered by proteolytic extraction;

5) Residual hydrolysable selenium is recovered by TMAH dissolution.

Total selenium was measured in each extract and compared with the total selenium obtained after wet washing with nitric acid and hydrogen peroxide. Each yeast sample extract from five nonconsecutive batches (analyzed in triplicate) was analyzed by HPLC-ICP-MS using ^{78}Se-specific detection by ICP-MS. A histogram of the total selenium extracted at each step was established and the chromatographic profiles of the extracts were compared (Table 3).

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[14] A cocktail of polysaccharide-degrading enzymes from snail gut.
[15] TMAH is a surface-active agent which is an excellent solubilizer of biological tissues.

Table 3. Selenium content (ppm) and *percent* of total cellular selenium content recovered in the sequential extraction of five nonconsecutive Sel-Plex® production batches

Extraction method	Batch 100	Batch 105	Batch 114	Batch 131	Batch 141
Water extract	514±21 (25%)	500±3 (24%)	479±5 (22%)	486±11 (24%)	508±19 (23%)
Driselase extract	732±20 (36%)	816±40 (39%)	679±42 (32%)	798±43 (40%)	843±30 (39%)
SDS extract	700±70 (34%)	593±31 (28%)	796±94 (37%)	651±15 (32%)	711±151 (33%)
Proteolytic extract	27±2 (1.3%)	35±5 (1.6%)	37±9 (1.7%)	32±7 (1.6%)	46±6 (2.1%)
TMAH extract	70±7 (3.4%)	150±9 (7%)	150±17 (7%)	37±2 (1.8%)	55±2 (2.5%)
Total from mineralization	2236±27	2161±81	2220±22	2223±71	2271±32
Total from sequential extraction	2042±120	2107±88	2140±167	2004±78	2164±208

SDS = sodium dodecyl sulfate; TMAH = Tetramethylammonium hydroxide; ppm = parts *per* million

This data indicates that the five batches of selenized yeast are similar in terms of selenium fractions, and considered by Alltech® to represent similarity between the five batches. Therefore, the Sel-Plex® specifications provided in Table 3 should be extended to incorporate the specific speciation provided in Table 4.

Table 4. Subcellular selenium distribution fingerprint for Sel-Plex®

Fraction	*Percent* total selenium (range)
Water soluble selenium species	22 – 25%
Water insoluble polysaccharide-bound selenium species	32 – 40%
Water insoluble protein-bound selenium species	28 – 37%
Residual protein-bound selenium species	1 – 2%
Residual TMAH-hydrolysable selenium species	2 – 7%

TMAH = Tetramethylammonium hydroxide

3.2. Manufacturing process

The manufacturing process of Sel-Plex® is conducted according to a typical batch-fed operation commonly used in the production of baker's yeast that is further used to produce a yeast biomass. This process involves incremental feeding of sugar-containing medium and represents the best practical method of producing yeast biomass without simultaneous production of sizable quantities of ethanol (Demirci *et al.*, 1999). During this process, the inorganic mineral source of selenium is transformed into organic forms. A graphical depiction of the manufacturing process is offered in Figure 4. The production of Sel-Plex® involves five processing steps: (1)

Isolation, characterization, and conservation of the yeast strain; (2) Propagation of the yeast culture; (3) Centrifugation and washing; (4) Filtration and drying; and (5) Packaging and storage.

The yeast used to produce Sel-Plex® is *S. cerevisiae* CNCM 1-3060, which has been defined by morphological, physiological, biochemical, and genetic characteristics, and has been deposited in the Pasteur Institute (Alltech, 2003). The yeast is grown on a medium containing malt and yeast extracts and the appropriate mineral composition, and stored as a master culture. Culture purity is routinely checked on subcultures of the master slants at monthly intervals. Expansion of the yeast initially occurs in the laboratory. The yeast is aseptically transferred to a fermentor (at the manufacturing site) that contains diluted cane molasses and appropriate minerals. The fermentation is aerated for approximately two days, then transferred to a series of commercial fermentors, which contain molasses as a carbon source, and the appropriate minerals. To the commercial fermentor liquid sodium selenite (10% solution) is added and the culture is fermented for approximately 17 hours.

After fermentation, the yeast product is separated with a nozzle centrifuge, vacuum filtered, and passed through a rotary vacuum wheel to produce a cake-like substance, which is then dried in drums to less than 5% moisture content. The final product (inactive dried yeast) is analyzed for selenium content using atomic absorption spectrometry, and stored in polyethylene low density bags with internal and external walls. The product is then analyzed for microbial contamination, and any contaminated batches are subjected to dry heat sterilization (93.3°C) to reduce microbial contamination to within specifications.

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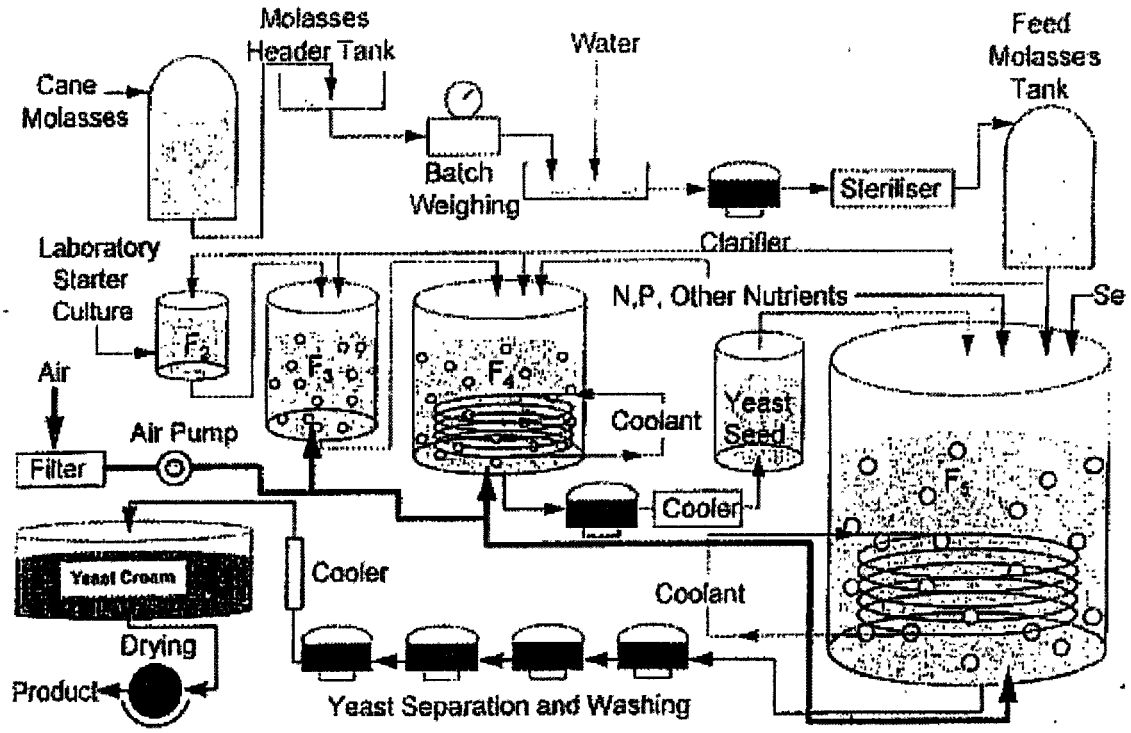

Figure 4. Sel-Plex® production scheme

3.3. Stability

Sel-Plex® is stable for ten months at room temperature (22-25°C) and nine months at 37°C, with minimal to no degradation of the critical component of Sel-Plex® (*e.g.*, selenomethionine) during these periods (Table 5 and Table 6) (Alltech, 1997).

Table 5. Levels of selenomethionine contained in Sel-Plex® tested for stability in storage at room temperature (Alltech, 1997)

Batch	Initial selenomethionine concentration (µg/100g)	Selenomethionine concentration and % recovery at 8 months	Selenomethionine concentration and % recovery at 10 months
BC101	173.8	152.2 (87.6%)	166.2 (95.6%)
BC201	175.9	160.1 (91%)	161.9 (92%)
BC202	174.7	161.3 (92.3%)	147.7 (84.5%)*
ES236	156.8	152.7 (97.4%)	157.4 (100.4%)

*Results of a repeat analysis due to accidental spillage of the original

Table 6. Levels of selenomethionine in Sel-Plex® tested for stability at 37°C(Alltech, 1997)

Batch	Initial Selenomethionine concentration (µg/100g)	Selenomethionine concentration and % recovery at 7 months	Selenomethionine concentration and % recovery at 9 months
BC101	173.8	165.7 (95.3%)	169.9 (97.7%)
BC201	175.9	177.4 (100.8%)	179.6 (102.1%)
BC202	174.7	175.6 (100.5%)	183.5 (105%)
ES236	156.8	165.5 (105.5%)	167.7 (106.9%)

The chemical stability of selenomethionine under these storage conditions demonstrates that the critical component of Sel-Plex® (*e.g.*, selenomethionine) is a stable food ingredient at room temperature and elevated temperature storage conditions. In order to calculate stability beyond ten months, a regression of either total selenium or selenomethionine was performed. The expected shelf life of the product is determined by the time at which the 95% one-sided confidence limit for the regression curve intersects the acceptable lower specification limit.[16] The regression of selenium content was not significant over the 13-month period of storage. Utilizing the regression analysis, it was concluded that for 24 months after the manufacturing date, at least 90% of the selenium remained in Sel-Plex®. The selenomethionine content was also found to remain stable for 24 months after the manufacturing date at room temperature.

Table 7. Stability of total selenium or selenomethionine contained in Sel-Plex® stored at room temperature

Parameter recorded	Results of stability studies	Percent of recovery (at 24 months)
Total selenium	Stable at least 11 months (10 batches), 13 months (1 batch), 20.4 months (1 batch), stable to a calculated 24 month period (at minimum)	90%
Selenomethionine	Stable at least 4 months (8 batches), 10 months (4 batches), 13 months (1 batch), 20.4 months (1 batch), stable to a calculated 24-month period (at minimum)	92.95%

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[16] The analyses were conducted with R software, version 1.8.1; R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-00-3 (Alltech, personal communication).

4. ESTIMATED DAILY INTAKE

The general food groups designated by Alltech® to which Sel-Plex® will be added are presented in Table 8, with the specific foods in APPENDIX I. All categories designated by Alltech® have been utilized in the calculations as appropriate; however, certain categories designated by Alltech® may contain foods or beverages for which a standard of identity exists, prohibiting the addition of ingredients not identified under regulations for the standard of identity for that food. Therefore, addition of Sel-Plex® to a food for which a standard of identity exists would demand that the food product be named other than that as indicated under the standard of identity.

Table 8. Food groups selected for Sel-Plex® supplementation*

Food category	Intended use level (ppm)
Yogurts	10
Breads	10
Instant cereals	10
Breakfast and granola-type bars	10
Soups	10
Beverages	10

*The general food categories correspond to those presented in APPENDIX I ; ppm=parts *per* million

The maximum concentration of Sel-Plex® suggested for addition to the food category was utilized in the consumption analysis, to ensure that the estimate includes individuals that consume larger amounts of the foods (90th percentile). Although the ingredient may be added to only one part of a complex food mixture (*i.e.*, "beef with barbeque sauce"), the consumption of the total food was utilized in the consumption analysis calculations. The means and 90th percentile estimated daily intake values (EDIs) were calculated for: (1) selenium intake from natural sources (current); (2) selenium intake following addition of Sel-Plex® to the selected food groups (added) and; (3) total EDI from natural sources combined with levels from addition to the foods (total).

Selenium consumption by Americans was reviewed by the Institute of Medicine (2006) and noted that the dietary selenium intake in the US ranged from 79 – 108 μg/day. Ervin *et al.* (2004) analyzed the dietary intake of selenium for the United States population and reported a mean consumption of selenium at 103.1 μg/day. Using this value as the mean for current consumption, the current 90th percentile EDI of selenium may be estimated by assuming two times greater consumption than the reported mean current EDI. Thus, the estimated current 90th percentile EDI of selenium is 206.2 μg *per* day.[17]

The intake profile (amount and frequency) by individuals in USDA's What We Eat In America (WWEIA) 2001-2002[18] was used to calculate the consumption of Sel-Plex® for individuals that will consume Sel-Plex®- containing foods. This nationwide dietary intake survey collected food-intake data from 9701 individuals over a two-day period. Comprehensive and detailed questions were posed to the participants, and the results were used to code individual foods and portion sizes consumed. The results were weighted to place more strength on foods that were consumed by more individuals, and extrapolated to the US population. If Sel-Plex® is added to the selected foods at the levels specified in Table 8, the added mean and 90th percentile Sel-Plex® consumption *per* person will be 7.2 and 15.6 mg Sel-Plex®/day, respectively (equivalent to a mean and 90th percentile Sel-Plex® consumption of 0.12 and 0.26 mg Sel-Plex®/kg/day, respectively). Selenium content in Sel-Plex® is 0.2%, resulting in mean and 90th percentile selenium consumption from Sel-Plex of 14.3 and 31.2 μg selenium/day, respectively.

Combining the endogenous (*i.e.*, current) and proposed added intake levels gives the total selenium consumption level. If Sel-Plex® was added to the selected foods at the levels specified in Table 8, the estimated total mean and 90th percentile consumption of selenium, would be 113.8 and 227.84 μg/day, respectively.

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[17]http://www.cfsan.fda.gov/~dms/opa-cg8e.html; estimating exposure to direct food additives and chemical contaminants in the diet; site visited March 23, 2007.
[18]What We Eat in America; http://www.ars.usda.gov/Services/docs.htm?docid=7674&pf=1&cg_id=0; site visited October 4, 2006.

Another possible source of selenium in the diet is from consumption of dietary supplements. Since selenium consumption from dietary supplements is difficult to quantitate because in part of the lack of statistical data available on consumption of dietary supplements containing selenium. The 1987 National Health Interview Survey identified 51.1% of the adults aged 19-99 years in the US as having consumed a vitamin/mineral supplement in the past year, but that only 23.1% did so daily (Subar and Block, 1990). Multivitamins were the most commonly consumed supplement at that time. Selenium from selenized yeast is currently available from several companies as a dietary supplement. For example, GNC Selenium 200 dietary supplement[19] provides up to 200 μg selenium/capsule, with the suggested daily intake at one capsule *per* day. As noted, because there are no statistical data available on consumption of dietary supplements containing selenium, we have used the levels suggested in product labels as a basis for estimating consumption.[20] Thus, the potential theoretical selenium consumption from dietary supplements would be a maximum of 200 μg/day. This estimate is added to those in Table 9 to arrive at the total potential theoretical background consumption of selenium from both conventional food and dietary supplements.

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[19]GNC Selenium 200, General Nutrition Centers, Inc. http://www.gnc.com/sm-gnc-selenium-200--pi-2133331.html; site visited February 22, 2007.

[20]New Chapter Selenium Food Complex; http://www.vitacost.com/New-Chapter-Selenium-Food-Complex; site visited April 9, 2007; Schiff Natural Selenium; http://www.vitacost.com/SchiffNaturalSelenium; site visited April 9, 2007; Country Life Selenium; http://www.vitacost.com/CountryLifeSelenium; site visited April 9, 2007; Solaray Selenomax®; http://smallplanethealth.com/solaray-selenomax; site visited April 9, 2007; NSI Selenium; http://www.vitacost.com/NSI-Selenium; site visited April 9, 2007

Table 9. Selenium: current intake, predicted intake following supplementation of selected foods at the indicated levels (Table 8) and total intake (predicted + current) for individuals consuming selected supplemented foods

Selenium intake from	*Per* user (µg selenium/day)	
	Mean	90th Percentile
Current food sources	103	206
Possible maximum consumption with Sel-Plex® as an added food ingredient	14.3	31.2
Total from conventional food (current + added)	117.3	237.2
Possible consumption from dietary supplements)*	200	200
Total from food + dietary supplements	317.3	437.2

*Recommended daily dose *per* label suggestion from the typical maximum intake *via* dietary supplement use

5. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION (ADME)

The primary forms of organic selenium in food are selenomethionine from plants and selenocysteine from animal-derived foods (*i.e.*, meat products). Ingestion of inorganic selenium is typically *via* dietary supplements. The bioactive constituents of Sel-Plex® are selenoproteins, mainly selenomethionine and selenocysteine.

5.1. Absorption and bioavailability

Absorption of dietary organic selenium from food sources is approximately 80%, and occurs mainly in the small intestine (Reilly, 1998; Institute of Medicine, 2006). Both inorganic and organic forms of selenium are absorbed, but organic selenium is absorbed more efficiently. Ingestion of radiolabeled (^{77}Se) selenized yeast (327 µg/person) by twelve male subjects resulted in selenium absorption and retention rates calculated at 90 and 75%, respectively (Sloth *et al.*, 2003). While inorganic selenium is transported across the intestinal brush border in competition with inorganic sulfur *via* a passive process, absorption of selenomethionine is an active process, utilizing the same enzyme transport mechanism as is employed for methionine absorption. Selenocysteine is hypothesized to be absorbed *via* the cysteine transport system (Reilly, 1998).

The bioavailability of selenium may vary when ingested as part of different forms of a biological molecule, or as an inorganic molecule (sodium selenate). Fox *et al.* (2004) evaluated the human bioavailability and elimination of selenium when ingested as either biosynthetically labeled selenium in cooked trout, biosynthetically labeled brewer's yeast, or isotopically labeled

sodium selenate in water (reference dose). The trout were fed pellets containing ^{74}Se, the brewer's yeast was grown in medium containing ^{77}Se, and the water was labeled with ^{82}Se. Male subjects (n = 35, aged 18 – 50) who enrolled in this parallel, randomized, placebo-controlled study, were divided into six groups and consumed the labeled food in four meals over two consecutive days. Groups 1 and 2 consumed biosynthetically ^{74}Se-labelled cooked fish, groups 3 and 4 consumed biosynthetically ^{74}Se-lebelled, raw enzyme treated, and salted fish, and groups 5 and 6 consumed biosynthetically ^{77}Se-labelled brewer's yeast. All groups consumed a reference dose of stable ^{82}Se-labeled sodium selenate in water. Selenium retention was calculated *via* absorption measured over ten post-ingestion days and urinary clearance of the various isotopic labels was measured over seven post-ingestion days.

The apparent absorption and retention of selenium from ^{77}Se-labeled brewer's yeast (53.5±6.9 and 59.3±12.5%, respectively) was significantly lower than selenium absorbed and retained from ^{74}Se-labeled cooked trout (87.8±5.4 and 85.3±7.3%, respectively) and ^{82}Se-labeled selenate absorbed and retained from water (93.4±3.4 and 65.4±13.2%, respectively) (P<0.001). This study indicates that selenium from selenized yeast is less bioavailable and not as well retained as selenate (Fox *et al.*, 2004). This is contrary to earlier research, in which the effects of selenium supplementation from different selenium sources were evaluated by Clausen and Nielsen (1988). Male and female subjects (n = 139) received daily oral doses of 200 μg selenium in the form of selenite, selenate,[21] L-selenomethionine, or selenized yeast for three months. Whole blood selenium levels and erythrocyte glutathione peroxidase (GSH-PX)[22] activity were determined during the three month supplementation period, followed by a withdrawal period of four months. Selenium supplementation (as selenite) increased GSH-PX activity to steady-state levels after one month of supplementation. Whole blood selenium levels in the groups receiving either L-selenomethionine or selenized yeast showed a steady rise (as determined by atomic absorption spectrophotometry) during the entire three-month supplementation period, while the selenium levels in subjects supplemented with either selenite or selenate leveled off after a

[21] Selenite and selenate are inorganic forms of selenium.
[22] Glutathione peroxidase levels are used primarily as nutritional biomarkers for selenium, as it's concentration is depressed in selenium deficiency and increases with increasing selenium supplementation until reaching a plateau level, determined by genetic and environmental factors (Burk *et al.*, 2006).

period of one to three months during supplementation. Blood selenium levels declined upon cessation of selenium supplementation, with inorganic blood selenium levels returning to baseline four months after completing the supplementation phase. Whole blood selenium levels of subjects who were administered organic selenium (*i.e.*, groups administered L-selenomethionine or selenized yeast) began to decline after completing the supplementation phase, but had not returned to baseline levels at the end of the four-month observation period. When the whole blood selenium level and the GSH-PX activity were considered, the authors judged selenium from selenized yeast or L-selenomethionine to be more bioavailable than selenate or selenite (Clausen and Nielsen, 1988). The length of selenium administration between the Fox *et al* (2004) and Clausen and Nielsen (1988) studies (two days *versus* three months, respectively) may have had a large influence on determining the bioavailability of selenium from selenized yeast. Alfthan *et al.* (2000) also found that when selenized yeast was supplemented at 200 μg/day to healthy schoolchildren 14-16 years of age (15 males and 15 females), plasma selenium values plateaued at 1.3±0.2 μmol/L, which is higher than the plasma selenium values when the same level of selenium supplementation was in the form of selenite (1.0±0.2 μmol/L). Conversely, Alfthan *et al.* (2000) concluded that the relative bioavailability of selenized yeast was similar to selenite, as measured by GSH-PX activity in plasma, red blood cells, and platelets. One possible reason for the contradictory results is that the study by Alfthan *et al.* (2000) was conducted in the Finnish population fifteen years after the selenium intake was raised to 100 μg/day by a nationwide addition of selenium to artificial fertilizers, resulting in a higher basal selenium intake. This intake would likely be sufficient to achieve maximal platelet GSH-PX activity. Clausen and Nielsen (1988) conducted their study on a Danish population that was not previously supplemented with selenium. Organic selenium may be preferentially incorporated into GSH-PX when the enzyme is deficient in selenium, but that preference is lost when selenium consumption is sufficient to obtain maximal GSHPX activity.

These studies indicate that selenium from organic sources is absorbed, retained, and available for incorporation into endogenous proteins in humans, dependent on the selenium status of the individual; depressed selenium status results in a higher bioavailability of selenium from organic sources than from inorganic selenium supplementation.

5.2. Distribution

Selenium is transported in the blood, typically bound to protein. A small fraction is bound to albumin, while the remainder is bound to the very low-density β-lipoprotein fraction (Reilly, 1998). Selenium is deposited in organs and tissues, dependent on the total amount and chemical composition of selenium ingested. Selenium accumulation is highest in the liver and kidney during high selenium intake. During periods of low selenium intake, liver concentrations are low while selenium concentrations in the kidney remain high. A recent randomized, controlled, short-term trial in men with organ-confined prostate cancer (n = 66) indicated that oral selenium (200 μg/day selenomethionine, administered 14-31 days prior to prostatectomy) accumulates preferentially in the human prostate gland, compared to the seminal vesicle. No selenium-related toxicity was observed, with mean serum selenium levels significantly greater after selenium supplementation, compared to controls (Sabichi *et al.*, 2006). Muscle tissue accounts for the highest proportion of total body selenium content, and is a major storage compartment for selenium. Total selenium body content ranges from approximately 15 mg in the USA to a reported 3 mg in New Zealand (Reilly, 1998). The total selenium body content for New Zealanders may be higher, as selenium intake is in New Zealand (55-80 μg/person/day) is only slightly lower than levels reported in the USA (106 μg/person/day) (Rayman, 2004).

5.3. Metabolism

Selenomethionine and other organic selenium-containing proteins from the human diet may be incorporated non-specifically into proteins such as albumin and hemoglobin in place of methionine (Figure 5). In addition, selenomethionine may be *trans*-selenated to selenocysteine, which is then converted to hydrogen selenide by a β-lyase. Hydrogen selenide may be converted to selenophosphate by selenophosphate synthetase; selenophosphate reacts with a tRNA-bound serinyl residue from which selenocysteine is inserted co-translationally, to produce selenoproteins (Rayman, 2004).

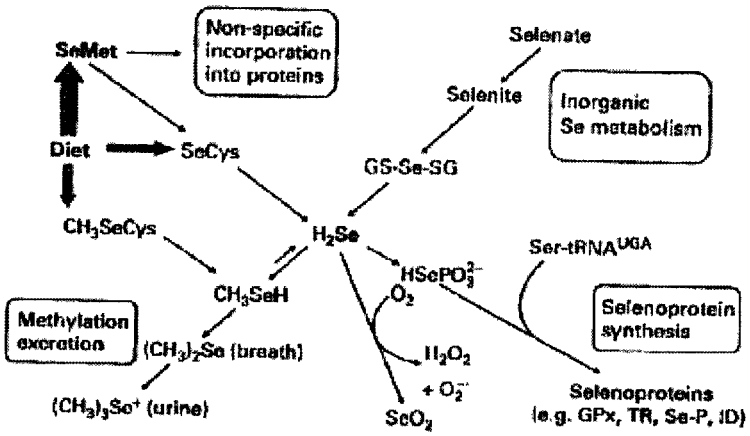

Figure 5. The metabolic fate of selenomethionine and other organic selenium compounds from the human diet. SeCys, selenocysteine; GS-Se-SG, selenodiglutathione; CH3-SeCys, Se-methyl-selenocysteine; GPX, glutathione peroxidase; TR, thioredoxin reductase; Se-P, seleno-protein P; ID, iodothyronine-5'-deiodinase (Rayman, 2004).

Excess selenium is detoxified by successive methylation of H_2Se, which results in the formation of methyl selenol (CH_3SeH), dimethyl selenide [$(CH_3)_2Se$], and trimethyl selenonium ion [$(CH_3)_3Se^+$]. Dimethyl selenide and trimethyl selenonium ion are excreted in the breath and urine, respectively. Selenized yeast contains a small concentration of Se-methyl-Se-cysteine (CH_3SeCys), which is metabolized by a β-lyase to give CH_3SeH directly (CH_3SeH has been proposed to be a potent anti-carcinogenic and anti-angiogenic substance (Ip, 1998; Combs Jr. and Lu, 2001; Whanger, 2004). Oxidized inorganic forms of selenium (*i.e.*, selenite, selenate) undergo reductive metabolism, yielding H_2Se, the starting point for the synthesis of selenoproteins. Excess H_2Se may be oxidized, leading to the production of superoxide and other reactive oxygen species (Combs Jr. and Lu, 2001).

5.4. Elimination

Selenium is excreted from the body either: (1) through the urine, largely in the form of the trimethyl-selenonium ion; (2) in the feces from unabsorbed dietary selenium or biliary, pancreatic, and intestinal secretions; (3) in exhaled air as volatile dimethyl-selenide; or (4) as a

small amount lost in hair, nails, and dead skin cells (Reilly, 1998). Burk *et al.* (2006) conducted a randomized, placebo-controlled trial to determine the effects of inorganic and organic selenium supplementation on the plasma selenium biomarkers selenoprotein P, glutathione peroxidase-3, and plasma selenium, and urinary selenium excretion in selenium-replete subjects. Healthy subjects (n = 81) were randomized to ingest placebo, sodium selenite, selenomethionine, or selenium-enriched yeast (analyzed to contain approximately 1200 μg Se/g, with 75% of its organic selenium in the form of selenomethionine). Each selenium treatment group was subdivided to receive a dose containing 200, 400, or 600 μg selenium. Baseline measurements (mean plasma selenium levels at 121±14 μg/l for women and 123±10 μg/l for men) were taken prior to selenium supplementation, then after Weeks 4, 8, 12, and 16 of the 16-week study. At each outpatient visit, subjects were evaluated for hair loss or changes in nail condition, menstrual cycle, appetite, or gastrointestinal function.

Plasma selenium concentrations increased ($P<0.05$) with selenomethionine and selenized yeast supplementation, but less with selenite supplementation (Burk *et al.*, 2006). Glutathione peroxidase and selenoprotein P concentrations did not increase during the study in any of the treatment groups. Urinary excretion of selenium by the placebo group was 55±22 μg/24 hour (n = 13). Because an unspecified amount of selenium was also lost from the body *via* the stool and sloughed skin cells, daily selenium loss must therefore have been greater than the recommended dietary allowance of 55 μg/day (Institute of Medicine, 2006). The *percentage* of the selenium dose excreted after 16 weeks of supplementation, when corrected for placebo excretion level and expressed as the *percentage* of administered selenium, did not vary significantly between the doses of a given form of selenium. The *percent* urinary excretion of selenium administered as selenized yeast was 52±23% (n = 18). The authors noted that some of the subjects in the study ingested in excess of 800 μg Se/day for 16 weeks, with no observed signs of selenium toxicity (as evaluated by the lack of hair loss and nail changes in the subjects) (Burk *et al.*, 2006).

The elimination kinetics of both inorganically and organically bound forms of selenium has been analyzed in humans. Plasma, urine, and fecal samples obtained from six subjects over a four-week period after a single oral 200 μg dose of enriched stable isotope tracer ^{74}Se (as

selenite, SeO_3) were evaluated to describe the kinetics of sodium selenite metabolism in humans (Patterson *et al.*, 1989). Three males and three females fasted for twelve hours before and three hours after receiving a single oral dose of 200 μg of enriched selenite ($^{74}SeO_3$). Blood was drawn immediately before the dose and at 0.5, 1 hour, and hourly for the next seven hours, daily for Days 1 – 5 and 11, then weekly for two-to-three weeks. Two-hour urine collections were made for the first eight hours, then a single four-hour collection, followed by a single twelve-hour collection. Twenty-four-hour collections were made for the next eleven days. Fecal samples were collected daily for twelve days, beginning on the first day of dosing. Compartmental analysis techniques were utilized to develop a kinetic model for human selenite metabolism, which described absorption, distribution along the gastrointestinal tract, and enterohepatic recirculation. The model included four kinetically distinct plasma components, a subsystem consisting of the liver and pancreas, and a slowly turning-over tissue pool. The ranges of mean residence time of the six subjects for the four plasma components are 0.2 – 1.1 hours, 3 – 8 hours, 9 – 42 hours, and 200 – 285 hours, respectively. The hepatopancreatic subsystem had a mean residence time of 4 – 41 days, with the tissue pool having a mean residence time of 115 – 285 days (Patterson *et al.*, 1989). Approximately 84% of the administered dose was absorbed, while approximately 65% remained in the body after twelve days. Patterson *et al.* (1989) concluded that approximately 35% of the administered selenium would be retained after 90 days, primarily in the tissues. The reported average whole-body half-life of selenite was 102 days.

Swanson *et al.* (1991) evaluated the pharmacokinetics of ^{74}Se as L-selenomethionine in humans, and described a model to account for the appearance and disappearance of the radiolabeled selenium in plasma, urine, and feces. The model included absorption *via* the gastrointestinal tract, uptake by the liver-pancreas subsystem, enterohepatic recirculation, transport through four plasma pool components, and distribution to two tissue pools. Selenium turnover time of the plasma components varied from 0.01 – 1.1 days, with turnover time in the liver-pancreas subsystem calculated at 1.6 – 3.1 days. The slowest turnover ranged from 61 – 86 days in the peripheral tissues, with the whole-body residence time at approximately five-fold greater than the tissue pool, resulting in a calculated selenium half-life of selenomethionine at

approximately 252 days. The authors concluded that the long whole-body residence time reflects substantial reutilization of labeled selenium (Levander *et al.*, 1983a; Swanson *et al.*, 1991).

Robinson *et al.* (1997) evaluated the excretion of selenium (200 μg/day) administered daily as either selenized yeast, brewer's yeast mixed with selenate, or yeast with no added selenium (placebo) in women between 18 and 23 years of age (n = 36). Mean daily selenium excretion increased for both selenium supplements: at Week 2 the selenate group excreted more selenium than the selenized yeast group (123 *vs.* 66 μg/day, respectively), but selenium output increased for the selenized yeast group until reaching a plateau at approximately 100 μg/day at Week 16. Plasma selenium also plateaued at 190 ng/ml at Week 16 in the selenized yeast group. Plasma selenium levels plateaued at 110 ng selenium/ml for the selenate group at Week 7. Renal plasma clearance in the selenized yeast group reached a plateau of 0.4 ml/min at Week 2, as plasma selenium increased almost 2-fold. Selenium clearance in the selenate group varied between 0.8-1.1 ml/min, and the plasma selenium concentrations remained almost constant at 110 ng/ml (Robinson *et al.*, 1997). Elevated selenium intake also results in significant (P<0.001) elevated urinary and fecal selenium excretion, indicating the body's ability to remove excess selenium (Hawkes *et al.*, 2003).

6. SAFETY EVALUATION

6.1. Acute studies

Acute studies comparing the acute toxicity of Sel-Plex® and sodium selenite are summarized in Table 10, and indicate that selenized yeast (Sel-Plex®) has an LD_{50} of greater than 2000 mg/kg (4 mg/kg Se), while the inorganic sodium selenite has an LD_{50} of between 5 and 25 mg/kg (2.2 and 10.8 mg/kg Se, respectively) (Griffiths *et al.*, 2006a). Vinson *et al.* (1984) found that selenized yeast had an LD_{50} of 37.33 mg/kg in male Sprague-Dawley rats (Griffiths *et al.*, 2006a).

Table 10. Effect on body weight in rats and mice acutely treated (*via* gavage) with either Sel-Plex® or sodium selenite (Levander *et al.*, 1983b; Griffiths *et al.*, 2006a)

Species	Substance	Dose (mg/kg)	Animals dosed	Sex	Body weight (mean ± S.E.M.)			Deaths
					Day 1	Day 7	Day 14	
Mouse	Sodium selenite	5, step 2	3	F	31.1±0.3	32.5±0.4	33.8±0.7	0
Mouse	Sodium selenite	5, step 3	3	F	32.7±0.8	35.0±2.0	35.6±1.2	0
Mouse	Sodium selenite	50, step 1	3	F	--	--	--	3
Mouse	Sel-Plex®	2000, step 1‡	3	F	30.8±0.9	30.8±0.6	30.2±0.9	0
Mouse	Sel-Plex®	2000, step 2	3	F	30.2±1.0	32.1±1.5	33.7±1.6	0
Rat	Sodium selenite	50, step 1	3	F	--	--	--	3
Rat	Sodium selenite	5, step 2	3	F	234.7±1.7	268.4±2.6	271.7±3.2	0
Rat	Sodium selenite	5, step 3	3	F	241.1±2.1	265.3±1.9	269.1±1.3	0
Rat	Sel-Plex®	25	3	M	206†	287.3	331.3	0
	Sel-Plex®	25	3	F	200.7†	221.3	232	0
Rat	Sel-Plex®	200	3	M	224.7†	295.7	338.7	0
	Sel-Plex®	200	3	F	210†	247	266.3	0
Rat	Sel-Plex®	2000	3	M	236.7†	298	345.7	0
	Sel-Plex®	2000	3	F	221.7†	245.7	268	0
Rat	Sel-Plex®	2000	3	F	241.2±4.0	257.7±8.0	258.8±8.6	0
Rat	Sel-Plex®	2000	3	F	233.1±1.1	253.7±2.3	256.7±3.9	0

†Rats weighed on Day 0; ‡The experimental design uses a stepwise procedure, with each step using three animals of a single sex. Absence or presence of test substance-related mortality of animals dosed at one step determines if: (1) no further testing is needed, (2) dosing of three additional animals with the same dose, or (3) dosing of three additional animals at the next higher or the next lower dose level; **average value of the remaining two animals; -- = analysis not conducted; F = female; M = male; S.E.M. = standard error of the mean.

Male Sprague-Dawley rats were administered (*via* gavage) an aqueous solution of selenium in either of two forms: sodium selenite or a selenized yeast (1000 μg selenium/g). The animals were observed for two weeks after dosing, and the number of mortalities were noted. The toxicity of the two forms of selenium is indicated in Table 11. The LD_{50} for the selenium from sodium selenite was calculated to be 12.7 mg/kg, while the LD_{50} for the selenium from selenized yeast was 37.33 mg/kg, indicating that organic selenium in the form of selenized yeast is less acutely toxic than inorganic selenium in the form of sodium selenite. The authors hypothesized that, compared with sodium selenite, the lower toxicity of the selenium yeast may be due to its slower absorption (Vinson *et al.*, 1984).

Table 11. Comparison of the acute toxicities of two forms of selenium given orally to rats (Vinson *et al.*, 1984)

Form of selenium	Selenium dose (mg/kg)	Deaths (%)
Sodium selenite	1.60	20
Sodium selenite	6.40	30
Sodium selenite	12.80	50
Selenized yeast	10.67	0
Selenized yeast	47.10	40
Selenized yeast	94.12	100
LD_{50} (mg/kg) of selenium		
Sodium selenite	12.66	
Selenized yeast	37.33	

LD_{50} = Calculated lethal concentration to 50% of the sample population

6.2. Subchronic studies

In a subchronic toxicity study, Sel-Plex® was administered as a dietary admixtrure to Sprague-Dawley rats (ten/sex/group) at dose levels of 0, 114, 179, and 303 mg/kg/day (resulting in additional (*i.e.* above background) intakes of 0, 0.23, 0.36, and 0.61 mg selenium/kg/day, respectively), for 13 weeks (Griffiths *et al.*, 2006a). Clinical and behavioral observations, body weight, food and water consumption, histopathology, necropsy, ophthalmology, urinalysis, hematology, blood chemistry, organ weights and histopathology parameters were evaluated. Sel-Plex® administration did not cause mortality, but animals of both sexes treated with 179 or 303 mg/kg/day showed clinical and behavioral changes (hunched posture and tiptoe gait), as well as reduced body weight (male 303 mg/kg/day dose group). No treatment-related behavioral responses were detected in the 114 mg/kg/day dose group. Reduced food consumption was also noted but this occurred in all treatment groups and was considered due to unpalatability of the diet. Changes in hematological values were noted in the 179 and 303 mg/kg/day female dose groups. No effects were noted in the male treatment groups, or in the 114 mg/kg/day female treatment group. Relative organ weights were increased (considered a consequence of reduced body weight). Various changes in blood chemistry values were noted in females in the 179 and 303 mg/kg/day dose groups, while the only blood chemistry change noted in the 114 mg/kg/day female dose group was a slight, although significant, increase in bilirubin values, compared to controls. No effects were noted in the treated male groups. Females at 303 mg/kg/day presented accentuated lobular pattern and/or a malformed liver at necropsy. One female treated with 179

mg/kg/day showed accentuated lobular pattern of the liver. Changes in histopathological indices relative to controls, were noted in the liver and adrenal glands in the 179 and 303 mg/kg/day female dose groups, and histopathological changes in the liver were noted in the 303 mg/kg/day male dose group. Hepatotoxicity was detected in animals treated with 179 or 303 mg/kg/day and was considered the primary effect of treatment. Other changes at these dose levels were considered a consequence of reduced palatability of the diet, which resulted in reduced bodyweight development and secondary stress responses. Minor changes at 114 mg/kg/day were considered not to represent an adverse health effect. The No Observed Adverse Effect Level (NOAEL) in this study was reported by the authors as 114 mg/kg/day Sel-Plex® for both sexes.

The potential toxicity of Sel-Plex® was also evaluated following daily gavage administration to beagle dogs for 13 weeks (Griffiths *et al.*, 2006a). Three groups of four male and four female dogs were administered 30, 100, or 300 mg/kg/day Sel-Plex® (0.06, 0.2, and 0.6 mg selenium /kg/day, respectively) for 13 weeks. An additional control group of four males and four females were dosed with vehicle only (0.5% aqueous methylcellulose in purified water). Hematological and blood biochemical investigations and urinalysis were performed prior to the treatment period, at Week 6 and at the end of the treatment period. The animals were euthanized upon completion of the study, and a full macroscopic examination was performed. A microscopic examination was also performed on selected tissues from randomly designated animals.

Clinical signs during the study included excessive salivation, vomiting, and regurgitation, which were commonly noted during gavage administration, and not considered adverse effects as vomiting and increased salivation in dogs may be related to irritation caused by the selenized yeast as it is broken down in the acidic environment in the stomach. An emaciated appearance was noted in two/four males administered 300 mg/kg/day Sel-Plex®, although body weight gain was similar or higher than controls in all Sel-Plex®-treated animals. Sel-Plex® at 30 mg/kg/day was clinically well tolerated, with no treatment related changes noted in hematology, blood biochemistry, or pathology endpoints. Hematological and biochemical parameters in dogs administered 100 mg/kg/day Sel-Plex® for 13 weeks indicated a decrease in the mean

hemoglobin concentration in the female dogs ($P<0.05$). No treatment related changes were noted upon microscopic examination of selected tissues at 30 or 100 mg/kg/day, including the liver, the apparent target organ in the rat study (see above). A significant increase in the mean cell hemoglobin levels and increased cholesterol levels were noted at 100 mg/kg/day dose in female dogs ($P<0.05$). At the 300 mg/kg/day Sel-Plex® dose level, changes in hematological (*i.e.*, decreased red blood cells and hemoglobin levels in male dogs; $P<0.05$) and biochemical parameters (*i.e.*, increased cholesterol and triglyceride levels in females; $P<0.05$) were noted. Liver toxicity was noted at doses greater than the 114 mg/kg/day Sel-Plex® dose in the rat study discussed above (Griffiths *et al.*, 2006a), and may correlate with the decreased red blood cell and hemoglobin levels noted in dogs at the 300 mg/kg/day Sel-Plex® dose level. Thymic lymphoid depletion was noted during pathologic examination of the selected tissues at the 300 mg/kg/day dose level in dogs, consistent with the decreased thymic weights noted in the 90-day rat study at the 303 mg/kg/day Sel-Plex® dose level. Therefore, based on the changes in clinical pathology parameters at 100 mg/kg/day, the authors stated a conservative No Observed Adverse Effect Level (NOAEL) of 30 mg/kg/day Sel-Plex® in dogs.

Because much of natural animal forage does not supply adequate selenium levels, selenized yeast has been added to a variety of different animal feeds. Pehrson *et al.* (1999) found that, compared to cows supplemented with sodium selenite (30 mg Se/kg/day), 90-days' supplementation with selenized yeast at 30 mg Se/kg/day) to cows with suckling calves significantly increased selenium concentrations in milk ($P<0.001$) and plasma ($P<0.005$) of cows fed the selenized yeast, while also increasing whole blood and plasma selenium levels in the suckling calves ($P<0.005$). Decreased selenium levels have been associated with decreased weight gain in cattle (Pehrson *et al.*, 1999).

In an eight-week study, Spallholz and Raftery (1984) compared the effects of dietary sodium selenite and selenized yeast when fed to weanling male Fisher 344 rats. Selenized yeast or sodium selenite was added to the diet to provide 0, 1, 4, 10, and 16 ppm selenium (approximately equal to 0, 0.1, 0.4, 1.0, and 1.6 mg/kg bw/day, respectively). The major organs (*i.e.*, heart, kidneys, liver, lungs, spleen, and thymus) were weighed and fixed in 10% buffered

formalin. A portion of muscle or liver was frozen for either selenium or GSH-PX activity assays, with fecal samples collected from trays in the last week of the experiment for selenium analysis. Body weights increased on average from 55g at the beginning of the study to 240 g at the end, except in the 1.0 and 1.6 mg/kg bw/day selenium (as sodium selenite) dose groups, where the average mean weights at the end of the study were 218 and 155 g, respectively. Rats fed the selenized yeast at 16 ppm (1.6 mg/kg bw Se/day) also showed growth reduction, but did not reach statistical significance ($P>0.05$). Food intake was not affected in the high dose selenized yeast (*i.e.*, 1.6 mg/kg selenium) diet, but food intake was noticeably reduced in animals receiving the 1.6 mg/kg selenite diet (Spallholz *et al.*, 1984).

The rats consuming the high dose selenite diet had extensive hepatic cirrhosis and splenomegaly at the end of the study, which was not apparent in the animals fed the 1.6 mg/kg selenium as selenized yeast diet. Pathological examination of the tissues revealed histological liver changes (*i.e.*, inflammatory infiltration of the triads by lymphocytes, histocytes, eosinophils, and fibrocytes; bile duct proliferation; marked central vein congestion; and frank cirrhosis in one half of the animals), splenic congestion, and a degree of heart failure due to a toxic myocarditis. Upon microscopic examination, the hearts of the animals fed the 1.6 mg/kg selenium as selenite diet had increased myocardial thickness in the ventricular wall, variation in staining of the sarcoplasm, retention of cross striations, increased number of perimyseal fibrocytes, and lymphatic cuffing of the small myocardial blood vessels; all consistent with mild cardiomyopathy. In animals with liver cirrhosis (1.6 mg/kg selenium as selenite diet), there was nearly a 50% reduction in GSH-PX activity (13.7±0.4 μmol NADPH oxidized /min/g liver), compared to controls (25.2±2.8). One group of 1.6 mg/kg selenized yeast-fed rats showed a nonsignificant reduction in GSH-PX activity (19.7±2.4), while the other 1.6 mg/kg selenium from selenized yeast group (*i.e.*, a different lot) had no reduction in GSH-PX activity (24.3±1.6). Administration of selenium from selenite at 1.6 mg/kg for eight weeks produced severe hepatotoxicity, cardiotoxicity, and produced splenomegaly, while selenium (as selenized yeast) at 1.6 mg selenium/kg/day had no toxic effect (Spallholz *et al.*, 1984). From this study, the authors indicate a lack of toxicosis (*i.e.*, NOAEL) for selenium from selenized yeast is 1.6 mg/kg

bw/day (1454 mg selenized yeast/kg) in male Fischer 344 rats, the highest selenized yeast dose tested. The NOAEL for selenium from sodium selenite is 1.0 mg/kg bw/day.

A canine study was conducted to evaluate the ability of selenium to significantly regulate the extent of genotoxic damage within the aging prostate (Waters *et al.*, 2005). Aged Beagle dogs (n=49; physiologically equivalent to 62-69 year-old men), were randomly assigned to control group, 3 μg/kg/day selenomethionine, 6 μg/kg/day selenomethionine, 3 μg/kg/day selenized yeast, or 6 μg/kg/day selenized yeast, for seven months. After the treatment period, the dogs were ensanguined, and brain and prostate tissues were evaluated for DNA damage. Selenium concentrations were analyzed in the prostate, brain, and toenails. This study did not evaluate typical toxicological endpoints for a food ingredient. The results indicated a U-shaped dose-response relationship between selenium status (determined through toenail selenium concentration) and the extent of DNA damage within the prostate. Toenail selenium concentrations correlated well with brain and prostate concentrations. The lowest and highest toenail selenium concentrations (a median of 0.6 ppm in the lowest quartile, and a median of 1.14 ppm in the highest quartile) correlated with an increased *percentage* of prostate cells with extensive DNA damage, while the middle quartiles of selenium toenail concentrations was correlated with a decrease in the percentage of prostate cells with extensive DNA damage. This study indicates that selenium supplementation of dogs with low selenium levels prevents DNA damage in the prostate and brain, while excessive selenium supplementation may increase DNA damage in these organs.

6.3. Genotoxicity

Selenium has been reported to have both anti-mutagenic and mutagenic properties, depending on the concentration and chemical form (Lu *et al.*, 1995). Shamberger (1985) indicated that at physiological levels found in the blood, selenium was anti-mutagenic and also anti-carcinogenic toward carcinogen-induced skin, liver, breast and colon cancer, but also that selenium concentrations that lead to mutagenic effects were very close to cytotoxic concentrations. Sodium selenite has a greater potential to produce mutations in various test

systems than sodium selenate. Anti-carcinogenic properties have been reported with selenized yeast against carcinogen-induced skin, liver, breast and colon cancers (Shamberger, 1985).

Karunasinghe *et al.* (2004) reported on a randomized, double-blinded, placebo-controlled, Phase III clinical trial that investigated the effects of selenium supplementation on prostate cancer development in high-risk patients (*i.e.*, those men with elevated prostate specific antigen (PSA), but having a negative biopsy for prostate cancer). This endpoint was evaluated by determining the effects of selenized yeast (as 0, 200, or 400 μg selenium/day (0, 0.003, or 0.007 mg/kg/day) for six months) on the stability of the DNA in blood leukocytes. The baseline average serum selenium level before randomization was 97±16.6 ng/ml. After a six-month selenized yeast supplementation treatment period, single cell gel electrophoresis analysis (*i.e.*, a comet assay) of the peripheral blood leukocytes harvested from volunteers that initially had an average serum selenium level below the mean (*i.e.*, 97±16.6 ng/ml) indicated that selenized yeast supplementation (and the resulting increase in serum selenium levels) showed a statistically significant inverse relationship (P=0.02) with overall accumulated blood leukocyte DNA damage. The population above the mean serum selenium level of approximately 100 ng/ml (prior to supplementation) had no correlation between subsequent increased serum selenium concentrations and DNA damage (after selenized yeast supplementation). The authors concluded that serum selenium levels of greater than 100 ng/ml are necessary for the prevention of human leukocyte DNA damage (Karunasinghe *et al.*, 2004).

The mutagenicity of Sel-Plex® was evaluated in an *in vitro* Ames assay in *Salmonella typhimurium* bacterial tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of metabolic activation (Griffiths *et al.*, 2006b). At Sel-Plex® concentrations below 1000 μg/plate, neither cytotoxicity (*i.e.*, significant lawn death) nor an increased number of revertants were noted for any test condition (Table 12). Thus, Sel-Plex® was not genotoxic under the conditions of this test.

Table 12. *Salmonella typhimurium* reversion mutation assay. Sel-Plex® was tested using the direct plate incorporation assay. Mean values are derived from 3 plates *per* strain *per* condition

Sel-Plex®	Number of revertants *per* plate									
	TA98		TA100		TA102		TA1535		TA1537	
S9 (µg/plate)	−	+	−	+	−	+	−	+	−	+
0	23	34	115	154	354	520	16	16	5	13
62.5	25	35	119	156	387	392	13	16	6	6
125	27	27	120	169	365	540	16	19	6	14
250	27	34	137	176	384	492	17	18	7	9
500	31	37	113	163	373	507	17	15	13	18
1000	33	48	128	172	441	537	17	20	5	14
Control	307[a]	1967[b]	341[3]	643[b]	1488[d]	2196[b]	521[c]	146[b]	921[e]	123[b]
Result*	-	-	-	-	-	-	-	-	-	-

Agents used for positive controls: [a] 2-Nitrofluorene; [b] 2-Anthramine; [c] Sodium azide; [d] Mitomycin C; [e] 9-Aminoacridine; *Conclusion of potential for Sel-Plex® to be mutagenic in the noted bacterial strain under these conditions

Sel-Plex® was also evaluated for potential to induce structural or numerical damage in mouse bone marrow cells (Griffiths *et al.*, 2006b). Three groups of five male and five female ICS Swiss ICo:OFI (IOPS Caw) mice were gavaged with Sel-Plex® at 500, 1000, or 2000 mg/kg/day over two days. Groups of mice were also concurrently administered vehicle or positive control. The animals were killed 24 hours after the last dose and bone marrow smears prepared. Sel-Plex® did not induce damage to the chromosomes or the mitotic apparatus of bone marrow cells after two oral administrations, with a 24 hour interval, at 500, 1000, or 2000 mg/kg/day in mice (Table 13). The results of this study suggest that Sel-Plex® does not exhibit mutagenic activity.

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Table 13. Micronucleus frequency in bone marrow cells from Swiss Ico:OFI mice orally administered 500, 1000, or 2000 mg/kg/day Sel-Plex® over a two-day period (Griffiths *et al.*, 2006b)

Dose	Sex	No. of animals	PE/NE ratio (mean *per* 1000 cells ± S.D.)	Micronucleated PE (mean *per* 1000 cells ± S.D.)
Vehicle control	F	5	0.5 ± 0.1	0.4 ± 0.4
	M	5	0.2 ± 0.1	0.1 ± 0.2
Sel-Plex® (mg/kg)				
500	F	5	0.4 ± 0.1	0.1 ± 0.3
	M	5	0.3 ± 0.1	0.3 ± 0.4
1000	F	5	0.5 ± 0.1	0.1 ± 0.3
	M	5	0.5 ± 0.2	0.5 ± 0.4
2000	F	5	0.5 ± 0.2	0.1 ± 0.2
	M	5	0.4 ± 0.1	0.3 ± 0.3
Sodium selenite (mg/kg)				
3.75	F	5	0.6 ± 0.1	1.2 ± 1.6
7.5	M	5	0.2 ± 0.0	0.4 ± 0.5
7.5	F	5	0.4 ± 0.1	0.1 ± 0.2
15	M	5	0.3 ± 0.1	0.2 ± 0.3
15	F	5	0.6 ± 0.2	0.1 ± 0.2
30	M	5	0.4 ± 0.3	1.2 ± 1.1**
CPA	F	5	0.6 ± 0.1	13.4 ± 7.8***
	M	5	0.4 ± 0.1	10.5 ± 3.7***

CPA = cyclophosphamide; F = Female; M = Male; PE = poly-chromatic erythrocytes; NE = normochromatic erythrocytes; **$p<0.01$; ***$p<0.001$

Sel-Plex® was evaluated for cytotoxicity *via* determination of the mitotic index, at Sel-Plex® concentrations ranging between 9.77 – 5000 μg/ml, with and without metabolic activation (S9) in an *in vitro* mammalian chromosome aberration test in cultured human lymphocytes. The effects of Sel-Plex® were compared with effects seen by treatment with sodium selenite. Sel-Plex® induced cytotoxicity at concentrations greater than 78.13 μg/ml, approximately 100-fold higher than sodium selenite-induced cytotoxicity (1.48 μg/ml). The potential of Sel-Plex® to induce chromosomal aberrations in cultured human lymphocytes was also evaluated at dose levels up to 625 μg/ml with and without S9 (3 hours treatment, 20 hours harvest), and compared to chromosomal aberrations induced by sodium selenite (at least 100 cells evaluated *per* concentration). No significant increases in the frequency of cells with structural chromosomal aberration were noted with Sel-Plex® treatment, while comparable concentrations of sodium selenite induced chromosomal aberrations. These studies indicate that Sel-Plex® does not induce genetic toxicity at non-cytotoxic concentrations.

6.4. Other preclinical studies

6.4.1. Dermal studies

The dermal irritation potential of Sel-Plex® following a single, four-hour, semi-occluded application to intact rabbit skin was assessed under the OECD Guideline No. 404 "Acute Dermal Irritation/Corrosion"[23] (Sanders, 1996). Sel-Plex® (0.5 g) was ground to a fine powder and applied to the shaved dorsal flank of three New Zealand White rabbits, then covered with a cotton gauze patch and wrapped in an elastic corset. Four hours after application the corset and patches were removed and any residual test material was removed with distilled water. Approximately 1, 24, 48, and 72 hours after patch removal, the test sites were examined for evidence of primary irritation[24] and scored according to the scale derived by Draize (1959). The scores for erythema and edema at the 24 and 72 hour readings were totaled for the three test rabbits (twelve values; 2 times of observation x 2 zones x 3 rabbits) and divided by six to give the primary irritation index, which was then classified according to the scheme devised by Draize (1959) for dermal toxicity. The results indicated that very slight erythema was noted at one treated skin site one hour after patch removal, with no other evidence of skin irritation noted during the study. The study director concluded that Sel-Plex® produced a primary irritation index of 0, and was classified as a non-irritant to rabbit skin, according to the Draize classification scheme (Draize, 1959; Sanders, 1996).

Three subsequent studies were conducted in New Zealand Albino rabbits to determine skin irritation potential of three different Sel-Plex® batches: ES-387 (Richard, 2002f), ES-1149 (Richard, 2002b), and ES-1211 (Richard, 2002d). The general protocol was conducted in accordance with the requirements of OECD Guideline No. 404, as described above, with three animals *per* study utilized and the test substance (0.5 g) applied to the skin (the right flank scarified and shaved and, the left flank non-scarified and shaved) of each rabbit. Each test area was covered with gauze that was held in place with an elastic tape. At the end of the 24 hour

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[23] Referenced as Method B4 of Commission Directive 92/69/EEC "Acute Dermal Irritation/Corrosion" (adopted 17 July 1992), which constitutes Annex V of Council Directive 67/548/EEC http://www.oecd.org/document/55/0,2340,en_2649_34377_2349687_1_1_1_1,00.html; site visited May 31, 2006.
[24] A primary irritant may be defined as a substance producing an injury on first contact (Draize, 1959).

exposure period, the dressing and residual test substance was removed by washing. Approximately one hour after dressing removal (24 hours after application), and again at 72 hours after application, any skin lesions were evaluated and graded. Edema and erythema scores for all three rabbits *per* study were summed, and the total of these numbers was divided by 12, which gave the cutaneous primary irritation index.

The application of Sel-Plex® batch ES-387 did not induce coloration of the application site, and only a very slight erythema was observed on the scarified flank of one rabbit at the 24 hour time point. No signs of irritation were noted at the 72 hour time point. Sel-Plex® batch ES-1149 did not produce any signs of irritation at any time point, while Sel-Plex® batch ES-1211 produced a very slight erythema on the scarified flanks of two rabbits at the 24 hour time point, with no irritation noted at the 72 hour time point. Under the experimental conditions noted in the study, the study director classified Sel-Plex® as a non-irritant for the skin of the rabbit in these three studies.

6.4.2. Eye studies

Sel-Plex® batches ES-387 (Richard, 2002e), ES-1149 (Richard, 2002a), and ES-batch ES-1211 (Richard, 2002c) have been analyzed separately for acute eye irritation/corrosion potential in the rabbit following a single ocular instillation, in accordance with OECD Guideline No. 405 and current Good Laboratory Practice (GLP).[25] Female New Zealand Albino rabbits (*n* = three *per* study) were administered 0.1 g of Sel-Plex®, introduced into the conjunctival sac of the left eye of each of the rabbits (Day 1). The eyelids were held closed for approximately ten seconds in order to avoid any loss of test substance. The non-treated eye was used as the control. Following treatment, the animals were kept in restraint cages for approximately one hour, to prevent rubbing of the eye. Approximately one hour after instillation of Sel-Plex®, and then again on Days 2, 3, 4, 5, and 8, any possible conjunctival, iris, or corneal lesions were evaluated, and graded using the scoring system in accordance with OECD Guideline No. 405. In the study that utilized Sel-Plex® batch ES-387, redness was observed in two rabbits one hour after test

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[25] Good Laboratory Practice released March 14, 2000, and Directive 99/11/EEC concerning GLP http://www.oecd.org/document/55/0,2340,en_2649_34377_2349687_1_1_1_1,00.html; site visited May 31, 2006.

substance instillation, with redness observed on Day 2 in one of the rabbits that had redness one hour following test substance instillation. No irritation reaction was seen in the iris or the cornea. In subsequent studies conducted with batch ES-1149 and batch ES-1211, redness was observed in the three animals *per* study one hour after Sel-Plex® administration, but no iris or corneal irritation were noted in either of the two studies. Therefore, under the study conditions, Sel-Plex® (based on batches ES-387, ES-1149, and ES-1211) was classified as slightly irritating to the eye of the rabbit.

6.5. Inhalation studies

A study was performed to assess the acute inhalation toxicity of Sel-Plex® and was compared against the acute inhalation toxicity of two forms of sodium selenite (Blagden, 1996). Sprague Dawley rats (*n* = ten *per* group, five males and five females) were exposed to a concentration of a dust atmosphere generated from Sel-Plex® or sodium selenite (Table 14). Sodium selenite was administered either alone or mixed with yeast prill.[26] The animals were exposed for up to four hours daily using a nose only exposure system. The method followed GLP and the OECD guideline No. 403 "Acute Inhalation Toxicity."[27]

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[26] Prill = to convert (as a molten solid) into spherical pellets usually by forming into drops in a spray and allowing the drops to solidify; http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=prill; site visited February 16, 2007.

[27] Referenced as Method B2 in Commission Directive 92/69/EEC "Acute Toxicity – Inhalation", which constitutes Annex V of Council Directive 67/548/EEC. http://www.oecd.org/document/55/0,2340,en_2649_34377_2349687_1_1_1_1,00.html ; site visited May 31, 2006.

Table 14. Mean achieved atmosphere concentrations; characteristics and mortality in an acute inhalation toxicity study (Blagden, 1996)

Parameter	Sel-Plex®	Sodium selenite/yeast prill	Sodium selenite
Mean selenium atmospheric concentration (mg/l)*	2.76±0.18	2.71±0.20	2.87±0.51
Atmospheric characteristics			
Mean mass median aerodynamic diameter (μm)	3.0	2.5	2.9
Inhalable fraction (% < 4 μm)	65.7	71.1	65.8
Geometric standard deviation	0.50	0.43	0.46
Mortality			
Males	0/5	0/5	5/5
Females	0/5	0/5	5/5
Total	0/10	0/10	10/10

*Mean ± standard deviation

Common signs of toxicity noted in exposed animals in all groups included wet fur, hunched posture, and piloerection, with isolated incidents of decreased respiratory rate and ptosis. Animals exposed to sodium selenite alone also experienced lethargy, ataxia, and labored respiration. Isolated incidents of decreased respiratory rate, gasping and noisy respiration, loss of righting reflex, tiptoe gait, pallor of the extremities, and red/brown staining around the snout were also noted in the sodium selenite group. All the animals exposed to sodium selenite alone were dead by Day 2.

Animals exposed to sodium selenite/yeast prill also showed evidence of increased respiratory rate, lethargy, pallor of the extremities, red/brown staining around the snout, and ptosis. Animals in the Sel-Plex® and sodium selenite/yeast prill dose groups recovered quickly and appeared normal one to three days after exposure. No animals died in these two dose groups, and with the exception of one female that showed body weight loss and two females that showed body weight gain during Week 1 following exposure to Sel-Plex®, normal body weight gain was noted in the surviving animals.

Necropsy results from all animals exposed to sodium selenite alone showed lung abnormalities that included swelling, darkened appearance and incidents of abnormal redness and hemorrhage, and all animals had liver changes that included darkening, patchy pallor, and

accentuated lobular patterning. Congestion, hemorrhage, and reddening of the intestinal tract were also observed. Two animals had excessive clear fluid in the thoracic cavity.

Two animals exposed to Sel-Plex® and three animals exposed to sodium selenite/yeast prill showed dark foci on the lungs, and one male exposed to sodium selenite/yeast prill had dark patches on the lungs. No other abnormalities were detected in the surviving animals at necropsy (Blagden, 1996).

In summary, although inhalation, dermal and ocular studies are of limited value in a GRAS determination in which primary human exposure is oral, they are presented as part of the comprehensive review of the toxicity information. Sprague-Dawley rats exposed by nose only inhalation to an atmosphere of sodium selenite at 2.87 mg/l died within two days of exposure. Two similar groups of rats exposed to either Sel-Plex® or sodium selenite/yeast prill at similar concentrations (2.76 or 2.71 mg/l, respectively) displayed only slight clinically observable signs of toxicity and no deaths. Ocular studies indicate Sel-Plex® as only slightly irritating, and dermal studies result in the determination of Sel-Plex® as a non-irritant.

6.6. Observations in humans

Selenium toxicity (*i.e.*, selenosis), caused by excessive selenium intake, has occurred on a large scale in seleniferous regions in China during the increased consumption of selenium-containing foods (approximate daily intake of 3-6.5 mg Se/day) (Yang *et al.*, 1983). Selenosis has also been reported in individuals who consumed excessive amounts of selenium supplements. The most common symptoms of selenosis are loss of hair, deformity, and loss of nails. Increased blood selenium levels, diarrhea, fatigue, a garlic-like odor of the breath and bodily secretions, irritability, peripheral neuropathy, and skin lesions have been reported (Reilly, 1998). Selenium intake levels that cause selenosis have not yet been well defined. Studies in China suggest that approximately 3 –5 mg/day (0.05 – 0.08 mg/kg/day) will cause selenosis. Residents of seleniferous regions in South Dakota who consumed approximately 700 μg

selenium/day (0.01 mg/kg/day) showed no symptoms of selenosis. The EPA proposed an oral reference dose (RfD) of 0.005 mg/kg bw/day, or 350 μg/day.[28]

Clinical descriptions of endemic selenium intoxication of humans in China indicate that hair, finger and toe nails, skin, the nervous system, and possibly skin are most affected. Yang *et al.* (1983) reported that dietary intake of selenium in an outbreak of selenosis averaged 4.99 mg (range 3.20 – 6.69 mg; 0.05 – 0.11 mg/kg) *per* day, and hair and blood selenium levels averaged 32.2 μg/g and 3.2 μg/ml (3200 μg/l), respectively. The average hair selenium content of residents in the high selenium area with chronic selenosis was about eight times that noted in a high selenium area without selenosis, and 100 times that in an area with typical selenium soil selenium levels. Blood selenium levels in the chronic selenosis subjects were approximately 30 times that from subjects in an area with adequate selenium levels (Yang *et al.*, 1983). To determine whether high dietary selenium intake was associated with adverse effects, Longnecker *et al.* (1991) evaluated the effects of selenium concentrations in the diet, blood and toenails on the health of adults residing in areas of South Dakota and Wyoming known to have high soil selenium soil (Longnecker *et al.*, 1991). Over a two-year period, subjects (n = 142) were evaluated for selenium consumption and selenium levels in blood, urine, and toenails. Approximately half of the subjects had selenium intakes greater than 200 μg/day (0.0033 mg/kg/day), with a range of 68 – 724 μg selenium/day, and 16% had average selenium intakes greater than 400 μg/day (0.0067 mg/kg/day). No evidence of selenium-induced toxicity (nail loss, alopecia, liver enlargement, or muscle fasciculation) was noted in any of the subjects whose intake was as high as 724 μg/day (0.012 mg/kg/day). Yellowed sclera were noted in two subjects, abnormal proprioception in two subjects, and abnormal muscle strength to extend the fingers in three subjects; however, the whole-blood selenium concentrations in these subjects was less than 3.18 μmol/l (251.1 μg/l) and the authors concluded that the effects were too infrequent to support a meaningful statistical association with selenium indices (Longnecker *et al.*, 1991).

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[28] Selenium and compounds (CASRN 7782-49-2); http://www.epa.gov/iris/subst/0472.htm; site visited June 19, 2006.

In contrast, a significant reduction in plasma selenium levels also has detrimental effects. Li *et al.* (2004) reported on a prospective study of the relationship between plasma selenium levels and prostate cancer risk utilizing plasma samples obtained from healthy men.[29] In this nested case-control study, plasma selenium was monitored in 586 prostate cancer patients and 577 control subjects over 13 years, with an inverse relationship identified between plasma selenium and the risk of advanced prostate cancer ($P<0.05$). The inverse association was observed only for subjects with elevated baseline PSA levels, and was particularly strong for those with baseline PSA levels of 10 ng/ml or greater ($P<0.001$) (Li *et al.*, 2004).

Many clinical trials have been conducted to assess the safety and efficacy of various forms of selenium for ingestion. Selenized yeast (200 µg selenium *per* day; 0.0033 mg/kg/day) or a placebo were administered for four years to 226 residents (113 *per* treatment) of Qidong county, Jiang-su province, China, who exhibited hepatitis B virus surface antigen carriers (HBVsAg+), a major risk factor for primary liver cancer (PLC) (Yu *et al.*, 1991). The blood selenium levels of treated patients at the end of the study were 152±22 µg/l, compared with 107±19 µg/l in placebo-treated controls.[30] During the four-year study, there was no incidence of PLC in selenized yeast-treated subjects while five of 113 subjects administered the placebo were identified with primary liver cancer ($P<0.05$). A subsequent four-year follow up study in which none of the subjects received selenized yeast, the incidence of PLC increased to control values (Yu *et al.*, 1997). In addition, Yu *et al.* (1991) described a two-year randomized clinical trial that evaluated the effects of daily supplementation of 200 µg selenium (as selenized yeast) *versus* placebo in 2474 members of families with a high risk of PLC. During the study, 13 of 1030 controls (1.26%) developed PLC, compared to 10 of 1444 of the selenized yeast-treated subjects (0.69%, $P<0.05$). The authors indicated that the dosages of selenium used in the trials were "health-safe" and effective for reducing PLC incidence rates (Yu *et al.*, 1991).

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[29] The men were enrolled in the Physicians' Health Study (a randomized, double-blind, placebo-controlled trial of aspirin and *beta*-carotene treatment among 22,071 healthy US male physicians, aged 40-84 years conducted in 1982).
[30] *P* value not stated.

Fairris *et al.* (1989) evaluated the effect of selenized yeast supplementation (600 μg selenium/day; 0.01 mg/kg/day) on 69 patients with moderate or severe chronic stable plaque psoriasis in a 12-week double-blind, placebo controlled trial. Mean selenium concentrations in whole blood and plasma in the patients with psoriasis were significantly reduced compared with those of the matched healthy controls ($P<0.001$), but GSH-PX activity in red cells was normal. Plasma ($P<0.01$), platelet ($P<0.01$), and whole blood ($P<0.001$) selenium levels, as well as platelet GSH-PX activity ($P<0.01$) increased over the first four weeks, then plateaued for the remainder of the twelve week supplementation period. Twelve weeks after supplementation had ceased, all selenium levels returned to pre-supplementation levels. None of the patients developed symptoms or signs that could be related to selenium toxicity, and levels of hemoglobin, white cell counts, platelet counts, and plasma urea, creatinine, alkaline phosphatase, and aspartate transaminase remained unchanged. The authors concluded that the increase in platelet GSH-PX activity indicated selenium bioavailability, but was not toxic and did not improve conditions related to psoriasis (Levander *et al.*, 1983a).

Supplementation with selenized yeast (100 μg Se/day; 0.0017 mg/kg/day) to lactating mothers during the first six months of breast-feeding significantly increased the mother's serum selenium levels from 50 to 140 μg/l during the first four months ($P<0.0003$), which then plateaued for the remaining two months of supplementation (Kumpulainen *et al.*, 1985). The infants' serum selenium also significantly increased from 40 to 85 μg/l over the six month period ($P<0.0003$), compared to mean serum selenium in control-mother's infants; their serum selenium increased steadily from 41 to 53 μg/l ($P<0.0001$). This study indicates that selenized yeast intake by lactating mothers at up to 100 μg/day promotes selenium levels in nursing infants. In a similar fashion, Peretz *et al.* (1991) noted that supplementation of 22 elderly subjects with selenized yeast (100 μg Se/day) for six months significantly increased plasma selenium levels from 0.84±0.26 μmol/l (66.33±20.53 μg/l) to a plateau of 1.55±0.33 μmol/l (122.39±26.06 μg/l) after two months of supplementation ($P<0.001$); that plateau level remained constant throughout the rest of the study.

Selenized yeast (200 μg Se/day; 0.003 mg/kg/day) was also evaluated in a double blind, randomized, placebo-controlled trial for the ability to alter oxidative damage and hormone status in 36 healthy adult male volunteers (El-Bayoumy *et al.*, 2002). Supplementation with either 200 μg Se/day as selenized yeast (n = 17) or placebo (n = 19) occurred for nine months, after which all subjects were placed on placebo for an additional three months. Plasma selenium concentrations significantly increased in the first three months compared to controls (P<0.001), then remained at a plateau for the remainder of the nine-month supplementation period. After the three month washout period, plasma selenium levels in the treatment group were reduced from the three- and nine-month values, but did not completely return to baseline levels. Blood glutathione levels (a cellular antioxidant) were 19% (P<0.005) greater in the selenized yeast-treated group than in controls at nine months of treatment, but this increase disappeared after the three-month washout period. Protein-bound glutathione levels (utilized as a marker of oxidative stress) were significantly lower at nine months, compared to controls (P<0.005). After the three-month washout period, the protein bound glutathione levels returned to near baseline levels. Selenized yeast also significantly decreased plasma PSA levels after three and nine months of treatment (P<0.0001), with no significant difference at the twelve-month evaluation. Selenized yeast supplementation did not affect plasma androgen levels. Each participant was contacted at four-week intervals to assess adverse effects. No adverse effects were noted in this study (El-Bayoumy *et al.*, 2002).

Administration of selenium (as either selenium-enriched yeast or selenium amylase) at 200-300 μg/day (0.003 – 0.005 mg/kg) orally for eight – twelve weeks was found to suppress symptoms of chronic hepatitis (He *et al.*, 2004). Membrane fluidity, stimulated[31] interleukin-2 (IL-2) production, and interleukin-2 receptor (IL-2R) expression in peripheral blood mononuclear cells (PBMC), as well as plasma malondialdehyde (MDA) and lipid peroxide (LPO) concentrations were determined in chronic hepatitis patients (n = 45) and healthy donors (n = ten) before and after selenium treatment. Patients with chronic hepatitis had significantly lower levels of membrane fluidity, IL-2 production and IL-2R expression (P<0.01) and

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[31] Stimulated with concanavalin A, a lectin derived from the jack bean.

significantly higher levels of plasma MDA ($P<0.01$), when compared to healthy blood donors. Selenium supplementation significantly improved PBMC membrane fluidity ($P<0.05$), and both IL-2 and IL-2R production ($P<0.01$) during antigen stimulation, while decreasing lipid peroxide ($P<0.01$) in chronic hepatitis patients (He *et al.*, 2004).

Critical to the determination of the safety of Sel-Plex® is the evaluation of the pharmacokinetics of selenized yeast consumption. Reported whole-body half-lives of selenomethionine and selenite in human subjects are 252 and 102 days, respectively, which implies that selenomethionine is retained in the body 2.5 times longer than selenite. Due to long half-lives, there have been published concerns over the consumption of organic selenium-containing substances. The EC Scientific Committee on Food[32] expressed concerns in 2002 that organic selenium (*e.g.*, from selenomethionine or selenized yeast) could accumulate in body tissues. Concurrent with this theory, a clinical study by Lombeck *et al.* (1996) found that supplementation with low doses (25 $\mu g/m^2$ body surface area/day of selenium)[33] of selenomethionine increased the plasma and whole blood selenium values over a nine-month period in children diagnosed with phenylketonuria. The mean plasma selenium value before supplementation was 17±5 μg/l, increasing by nine months to 88±18 μg/l. These subjects initially had low selenium levels, which steadily increased upon selenomethionine supplementation without reaching a plateau, leading the authors to conclude that supplementation with selenomethionine could lead to toxic levels of selenium in the body.

However, a study by Clark *et al.* (1996) indicated that plasma selenium increased over an initial twelve-month period, and then plateaued at approximately 190 μg/l for the remainder of the 144 month observation period employed in this study. This study employed a randomized, double-blind, placebo-controlled design in a cancer prevention trial using a nutritional dose (200 μg selenium supplied as a 500 mg high-selenium brewer's yeast tablet; 0.003 mg/kg/day)) to patients with histories of squamous cell carcinomas (SCC) and basal cell carcinoma (BCC) skin cancers. Patients were randomized to a selenium group (n=653) and placebo group (n=659), and

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[32] http://ec.europa.eu/food/fs/sc/scf/out80g_en.pdf; site visited February 16, 2007.
[33] This dose is approximately equivalent to 0.67 μg Se/kg/day, or 40 μg/day for a 60 kg adult.

scheduled for clinical examinations every six months for new dermatologic problems and potential signs of selenium toxicity, with a sample of whole blood collected for plasma selenium concentration determinations. Treatment with selenized yeast or placebo occurred for a mean of 4.5±2.8 years, with a total follow-up period of 6.4±2.0 years. The primary endpoints were skin BCC and SCC. Safety endpoints included known signs of frank selenosis (pathologic nail changes, brittle hair, and garlicky breath). Secondary endpoints included total mortality and cancer mortality, as well as the incidence of lung, colorectal, and prostate cancers. The mean plasma selenium concentration at the time of randomization was 114±23 μg/l,[34] which is in the lower range of normal plasma levels reported in the United States (Clark *et al.*, 1996). Plasma selenium concentrations in the placebo group remained constant (114 ng/ml), while the selenium group had increased plasma selenium concentrations to approximately 190 μg/l within six to nine months of supplementation; thereafter, plasma selenium stabilized.

No dermatologic signs of selenium toxicity were observed. A total of 35 patients withdrew from the study (selenium group = 21, placebo group = 14), complaining of adverse effects, most of which involved gastrointestinal upset. Within each group, patients reporting adverse effects did not have significantly different plasma selenium concentrations from patients not reporting adverse effects. This study indicates that long-term consumption of selenized yeast at up to 500 mg/day (200 μg/day; 0.003 mg/kg/day) does not induce selenium-related toxicity (Clark *et al.*, 1996) and indicates that the study by Lombeck *et al.* (1996) summarized above may not have been of sufficient duration for a plateau in plasma selenium levels to be reached by the low levels of selenized yeast supplementation.

In a continuation of the Clark *et al.* (1996) clinical trial, all of its participants were informed of their treatment status, given the opportunity to take selenium supplements (200 μg of selenium *per* day in a 0.5 g selenized yeast tablet), and re-consented to participate in an "Open-Label" phase of the trial (Duffield-Lillico *et al.*, 2002). As a result, Duffield-Lillico *et al.* (2003) evaluated the entire blinded treatment period initiated with the work by Clark *et al.* (1996), which resulted in the evaluation of a total of 9904 person-years (n = 1250 patients). The

[34] Mean±Standard Deviation.

ingestion of 200 μg selenium/day (0.003 mg/kg/day) as a 0.5g high-selenium baker's yeast tablet did not result in any reported toxicological effects. The results through the entire blinded period showed that selenium supplementation was not significantly associated with the risk of basal cell carcinoma, although there was an elevated risk of squamous cell carcinoma and of total nonmelanoma skin cancer. Earlier work by Alfthan *et al.* (1991) reported that 16 weeks of selenium supplementation with 200 μg Se/day (0.003 mg Se/kg/day) as selenized yeast in ten subjects increased plasma selenium concentrations from 1.40±0.12 μmol/l (110.5±9.47 μg/l) to a plateau at 2.12 ±0.26 μmol/l (167.40±20.53 μg/l) after eleven weeks ($P<0.05$), and remained at that level for the rest of the study. Four weeks after the end of supplementation, the plasma selenium concentration decreased to 1.78±0.18 μmol/l (140.55±14.21 μg/l), which was still higher than placebo levels ($P<0.05$). Selenized yeast supplementation also increased red blood cell selenium concentrations ($P<0.05$), but did not affect platelet GSH-PX activity. Urinary selenium excretion increased during the first eleven weeks of selenized yeast supplementation ($P<0.01$), then returned to baseline values after it stopped, which indicated greater selenium excretion during increased selenium consumption (Alfthan *et al.*, 1991)

Early research analyzed plasma selenium levels in subjects supplemented with organic selenium (selenized yeast), which included two individuals who had ingested 350 and 600 μg selenium/day (0.006 and 0.01 mg/kg/day, respectively) for 18 months, and found their blood selenium levels at 0.35 and 0.62 μg selenium/ml (350 and 620 μg/l), respectively (Schrauzer and White, 1978). Both subjects had normal levels of glutathione peroxidase *per* mg of hemoglobin, and were in good health. The high-dose subject complained of a tendency to develop symptoms resembling hay fever and other mild allergic symptoms of uncertain origin, with analysis revealing a borderline high reticulocyte count and borderline high serum glutamic pyruvic transaminase (SGPT) levels, although these was not considered suggestive of a pathological condition, because other blood analysis (LDH, SGOT, and total bilirubin)[35] did not reveal liver pathology. Schrauzer and White (1978) also reported on a six-week study of four subjects that were supplemented with 150 μg selenium/day (0.0025 mg/kg/day). From baseline levels of 0.16

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[35] LDH = lactate dehydrogenase; SGOT = serum glutamic oxaloacetic transaminase.

μg/ml (160 μg/l), blood selenium steadily increased to 0.21 μg/ml (210 μg/l) for the first thirty days of the study, reaching a plateau for the last twelve days of the study, with a slow decline in blood selenium levels after termination of the supplementation, and all subjects reached 0.17 μg/ml (170 μg/l) after 98 days of observation (Schrauzer and White, 1978).

Selenized yeast (200 μg selenium/day; 0.003 mg/kg/day) supplemented to healthy female subjects (n = 5) for eight weeks significantly increased plasma selenium levels from 0.95 to 1.80 μmol/L (75.01 to 142.13 μg/l, respectively) over the eight-week period (P<0.001) (Borglund and Akesson, 1988). The patients then discontinued the selenized yeast supplementation, and were monitored over the next 16 weeks. The majority of the increase in plasma selenium had disappeared by eight weeks following cessation of supplementation; plasma selenium levels were slightly increased over pre-supplementation values even after 16 weeks without supplementation. Plasma glutathione peroxidase activity increased during supplementation, a trend that continued after supplementation ceased. Plasma glutathione peroxidase activity reached statistical significance compared to pre-supplementation (control) values at eight weeks after the end of selenized yeast supplementation (P<0.05) and then declined back to near baseline levels by the end of the 24-week observation period (16 weeks after the end of selenized yeast supplementation).

In the same manner, Persson-Moschos *et al.* (1998) assessed possible changes in plasma selenoprotein P[36] in healthy subjects who consumed supplements consisting of 200 μg (0.003 mg/kg) selenium as selenium-enriched yeast, sodium selenate, or selenium-enriched wheat (Trial I), or selenium-enriched yeast, sodium selenate, or sodium selenite (Trial II). Trials I and II lasted 11 and 16 weeks, respectively. Selenoprotein P is a selenium-rich plasma protein, and its concentration has been used as an indicator of overall selenium status (Hill *et al.*, 1996; Burk *et al.*, 2003; Burk *et al.*, 2006). For Trials I and II, the subjects were divided into one placebo group (n = 15 and 20, respectively), and three treatment groups (n = ten for each treatment).

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[36] Selenoprotein P is a selenium-rich protein which may serve as a defense against extracellular oxidants and a selenium transport protein, and accounts for approximately 40% of the total selenium in plasma (Burk *et al.*, 2003).

The mean baseline intake of selenium for Trial I was 40 μg/day (0.0007 mg/kg/day). Plasma samples from Trial I were available at time point 0 (before supplementation), 2, 4, 7, and 11 (during the supplementation period), and 21 weeks (five weeks after the supplementation period). The mean plasma selenoprotein P values in all the supplemented groups increased significantly, which plateaued at two weeks and reached a maximum at four weeks (a mean increase of 34%, $P<0.05$). In Trial II, the mean baseline intake of selenium was 100 μg/day (0.0017 mg/kg/day), an increase due to a nationwide supplementation of fertilizers started in Finland (the study site) in 1985, resulting in consumption of crops containing greater concentrations of selenium. Trial II plasma samples were obtained at time points 0, 4, 7, and 16 weeks. In Trial II the mean selenoprotein P levels of the supplemented groups were not significantly different from each other or from the placebo group at the start or at any time point of the supplementation period. The same study group participated in the two similar selenium supplementation trials, with Trial II mean baseline intake of selenium higher compared to that during Trial I (100 μg/day *versus* 40 μg/day, respectively). No supplement-specific differences in selenoprotein P levels were observed for selenium obtained from selenium-enriched yeast, sodium selenate, or selenium-enriched wheat supplements. The authors concluded that at a low selenium status, the selenoprotein P levels increased in a similar fashion with the different forms of selenium, but in high selenium-status subjects, supplementation with the same level of selenium did not alter mean selenoprotein P levels (Persson-Moschos *et al.*, 1998). In general, these studies indicate that increased selenized yeast consumption does increase blood selenium levels to a plateau state, and these levels return to near baseline levels after termination of the selenium consumption.

Daily treatment of 18 preterm infants (average gestational age of 27 weeks) with 4.8 mg selenized yeast (containing 5 μg selenium) *via* a nasogastric drip during the first 14 postnatal days resulted in a significant increase in mean serum selenium concentration (36.1±12.8 μg/l to 43.5±7.9 μg/l), compared to serum selenium in 18 control infants ($P<0.01$) (Bogye *et al.*, 1998). The mean serum selenium concentration in control infants significantly decreased (34.4±20.4 to

26.1±16.6 μg/l) during this period ($P<0.005$).[37] No complications or side effects of enteral 4.8 mg/day selenized yeast supplementation were observed in these infants.

Selenium's antioxidant properties have formed the backdrop for several clinical studies that evaluated the effects of selenium supplementation on patients with various conditions. Peretz *et al.* (2001) analyzed the effects of selenium supplementation in 55 rheumatoid arthritis (RA) patients in a randomized, double blind, placebo-controlled trial. The patients consumed capsules containing either placebo or selenium-enriched yeast (200 μg selenium/day; 0.003 mg/kg) daily for 90 days. Clinical and biological parameters that were evaluated on Days 0, 20, 60, and 90 consisted of the visual analog scale, the Ritchie index,[38] the number of painful and swollen joints, C-reactive protein levels, erythrocyte sedimentation rate, and the rheumatoid factor. Selenium supplementation was well tolerated in most patients, with only mild to moderate adverse events reported equally by the subjects in each treatment group. Seven patients (12.7%) did not complete the trial (number of patients not completing the trial *per* group was not stated). Two patients had gastro-intestinal symptoms (dyspepsia), one patient presented an exacerbation of the disease, one patient suffered from another new disease (unrelated to selenium consumption), and three patients decided to stop their participation. Six patients reported digestive manifestations, including two subjects from the selenium-treated groups. The visual analog scale, the Ritchie index, the number of swollen and painful joints, and morning stiffness significantly decreased with time in both groups ($P<0.001$), but there was no difference between groups. Significant improvement in arm movements and health feeling were reported ($P<0.01$). The authors concluded that selenium treatment did not show clinical benefit on RA, but a placebo effect was present. Although the positive effects in this study may have been a placebo effect, the tolerance of selenium-enriched yeast was satisfactory and no serious adverse events were reported (Peretz *et al.*, 2001).

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[37] This study was conducted in an area containing low levels of selenium, which may have contributed to the decrease in selenium levels in the placebo control infants.

[38] A grading system for a quantitative assessment of long-term effect of rheumatoid arthritis on joint swelling, tenderness, pain on motion, limited motion, and deformity (Sokka and Pincus, 2005).

Combs *et al.* (1997) evaluated the effect of supplemental selenium (200 μg Se/day; 0.003 mg/kg/day as selenized yeast) in 1312 patients with histories of basal/squamous cell carcinomas (BCC/SCC) of the skin, for a total of 8269 person-years of observation. Patients were randomized to either placebo (n=659) or selenized yeast (n=653) dose groups. Plasma selenium concentrations were determined at six-to-twelve month intervals. Plasma selenium concentrations in the placebo group remained constant throughout the trial (114±23 μg/l), while mean plasma selenium for the selenized yeast group increased to 190 μg/l within six – nine months, and stayed at that level for the remainder of the trial (time on treatment was 4.9 years for selenized yeast treatment and 4.7 years for placebo). No dermatologic signs of selenium-induced toxicity were observed. Patient side effect complaints were low (mostly gastrointestinal upset), with patient withdrawal from treatment not significantly different between treatment groups. Patients reporting side effects in each treatment group did not have significantly different plasma selenium concentrations from those not reporting side effects. Statistically significant differences between treatment groups in the rates of new BCC/SCC did not occur, although total cancer mortality was 52% less in the selenized yeast treatment group *versus* the placebo group (P<0.001). Lung cancer deaths, which comprised approximately half of all cancer deaths, were significantly lower in the treatment group (P<0.05). Total cancer incidence was significantly lower in the selenized yeast treatment group, which also had 45% fewer total carcinomas (P<0.0005), less prostate cancer (P=0.0004), and less colorectal cancer (P=0.025) than the placebo group. Rates of mortality from cardiovascular disease and other causes were similar in both groups (Combs Jr. *et al.*, 1997). These findings suggest that selenized yeast consumption at 200 μg Se/day (0.003 mg/kg/day) is well tolerated, and resulted in an increase in plasma selenium concentration, which plateaued within six – nine months of the start of selenized yeast consumption.

Karunasinghe *et al.* (1985) analyzed the relation between serum selenium concentrations and the activities of two key selenoenzymes, hemolysate thioredoxin reductase (TR) and glutathione peroxidase (GPx) in men (n=43) with elevated prostate-specific antigen, but negative for prostate cancer. In this randomized, double-blind, placebo-controlled trial, the men received either a placebo, 200 or 400 μg selenium *per* day, as selenized yeast. After the six-month

supplementation period, approximately 66% of the group being supplemented with selenized yeast, the TR activity increased by 80%, relative to baseline, but did not affect GPx activity.

Selenized yeast has been administered as part of a 24-month controlled clinical trial analyzing selenium as a chemopreventative agent for prostate cancer progression (Reid *et al.*, 2004). Biopsy-proven prostate cancer patients (24 men, age 45-85) were initiated into a one-month run-in period,[39] and then randomized to receive either 1600 μg (0.026 mg/kg) (n = eight) or 3200 μg (0.053 mg/kg) (n=16) *per* day of selenized yeast. Follow-up visits were scheduled for every three months throughout the 24-month study period. The subjects were evaluated for toxicity, which included queries concerning selenium-specific symptoms: garlic breath, and nail or hair brittleness or cracking. Positive symptoms were followed up with selenium serum chemistry and hematology tests. Blood samples were collected on a semi-annual basis for measuring levels of plasma selenium, PSA, serum glutamic oxaloacetic transaminase (SGOT), SGPT, albumin, alkaline phosphatase, total bilirubin, hematocrit, hemoglobin and creatinine levels.

Within the first month, plasma selenium levels increased in both selenized yeast treatment groups. The 1600 μg/day group reached a plasma selenium plateau within three to six months and, in the 3200 μg/day selenized yeast group, plasma selenium levels plateaued at nine to twelve months (mean ± SD,[40] Figure 6). Selenium-related side effects were also noted in the 3200 μg/day group (Table 15) and, while total bilirubin, alkaline phosphatase, hematocrit, hemoglobin were elevated in this group at all measurements, the levels were still within normal ranges. Brittle nails, hair, garlic breath, and stomach upset are generally considered the first signs of selenium-related toxicity; however, these symptoms did not correlate with peaks in plasma selenium levels, and the subjects with the highest plasma levels did not exhibit symptoms of selenium toxicity. Following a review by a collaborating physician, it was concluded that no severe adverse events were found to be related to selenized yeast supplementation (Reid *et al.*,

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[39]A period prior to randomization during which potential participants who have met all entry criteria for a randomized clinical trial are assigned the same regimen, either the control or the experimental treatment, to eliminate participants who are placebo responders or noncompliers (Spilker, 2005).
[40] Standard deviation.

2004). These results suggest that doses of organic selenium as high as 3200 μg/day (0.053 mg/kg/day) can be administered in controlled situations for extended periods of time with no severe adverse events reported.

Table 15. Frequency of reported symptoms of potential selenium-induced adverse effects, by treatment group[a] (Reid *et al.*, 2004)

Reported symptom	1600 μg group (n = 8)	3200 μg group (n = 16)
Garlic breath	0	6
Brittle nails	1	3
Brittle hair	0	1
Stomach upset	1	2
Dizziness	1	3

[a]All toxicity reports were assigned National Cancer Institute (NCI) attributes from 'unlikely related' to 'possibly related' to selenium supplementation and were graded according to the NCI criteria as mild.

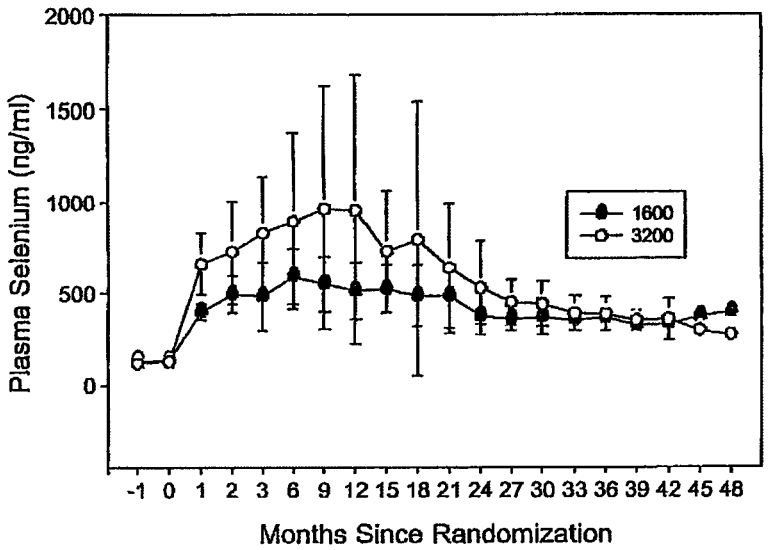

Figure 6. Plasma selenium response curves by dose with error bars (Mean±SD) (Reid *et al.*, 2004)

Recently, additional research has been published on the potential association between multivitamin use and the risk of prostate cancer (Lawson *et al.*, 2007). Men enrolled in the National Institues of Health-AARP Diet and Health Study (n=295,344) were followed for five years and evaluated for incident prostate cancer (either localized, advanced, or fatal cancers).

Multivitamin use was assessed at baseline as part of a self-administered, mailed food-frequency questionnaire. No association was observed between multivitamin use and the risk of localized prostate cancer. An increased risk of advanced and fatal prostate cancers was found among men reporting excessive use (more than seven times *per* week) of multivitamins, when compared with those who never took multivitamins. In addition, the positive associations with excessive multivitamin use were strongest in men with a family history of prostate cancer or who took individual micronutrient supplements, including selenium, β-carotene, or zinc. Among men who reported using a selenium supplement (defined as taking a single supplement at least once *per* month in each of the past 12 months), heavy multivitamin use (*versus* never use) was associated with a significant 37% increased risk of localized prostate cancer. In addition, a similar effect modification was noted for supplemental vitamin E and folate use. An increased risk of advanced prostate cancer was also observed for heavy multivitamin users with tomato product intakes above the population mean ($P<0.05$). The authors indicate that the positive association with heavy multivitamin use along with certain supplements may be due to detection bias, as prostate cancer PSA screening was most frequent among heavy users of multivitamins. Although this study indicates an increased risk of prostate cancer with heavy multivitamin users and selenium supplementation, the study did not find an association between selenium supplement use alone and prostate cancer.

In contrast to the Lawson *et al* (2007) study, Peters *et al.* (2007) performed a nested case-control studying which serum selenium samples were compared between 724 incident prostate cancer case subjects and 879 control subjects. Serum selenium levels were not associated with reduced prostate cancer risk ($P=0.7$). However, higher serum selenium levels (median of 170.4 ng/mL) were associated with lower prostate cancer risks in men reporting a high vitamin E intake ($P<0.01$) and in multivitamin users ($P=0.05$). Among smokers, high serum selenium concentrations were also related to reduced prostate cancer risk ($P<0.01$). Therefore, these studies indicate that additional research is necessary to determine the interaction between selenium and multivitamin supplementation and the risk of prostate cancer.

Using the third National Health and Nutrition Examination Survey (NHANES III)[41] as a data source, Rubin *et al.* (2003) conducted a retrospective epidemiological analysis of 7505 children and adolescents (4-16 years old), evaluating a possible asthma-induction relationship among selenium and serum antioxidants (*i.e.*, β-carotene and vitamins C and E). Separate models indicated that a 10-20% reduction in asthma prevalence was associated with increase plasma β-carotene, vitamin C, and selenium, with the selenium-asthma inverse association stronger in youth who were exposed to tobacco smoke ($P = 0.075$). Furthermore, a plasma selenium increase of one standard deviation was associated with a 50% reduction in asthma prevalence in youth with passive smoke exposure compared to a 10% reduction in youth with no smoke exposure (Rubin *et al.*, 2003).

Because selenium is known to be important for brain function, Rayman *et al.* (2006) conducted a double blind, placebo-controlled study that evaluated the effects of placebo, 100, 200, or 300 μg selenium/day (0.002, 0.003 or 0.005 mg/kg/day) on mood, when administered for six months to 501 participants aged 60-74 years. From a mean baseline plasma selenium value (±SD) of 90±19 ng/g (*i.e.*, 92±20 μg/l), selenium supplementation significantly increased plasma selenium to 144±27, 191±41, and 227±53 ng/g (148±28, 196±42, and 233±54 μg/l, respectively) in the 100, 200, and 300 μg selenium groups, respectively ($P<0.001$). Even the placebo group had a significant increase in plasma selenium to 91±26 ng/g (93.5±26.7 μg/l) at $P<0.001$. Thirty-four participants (7%) withdrew from the study within the first six months, with no significant differences between groups (7, 10, 5, and 12 in the placebo, 100, 200, and 300 μg groups, respectively). Of the 34, 13 withdrew because of adverse events, seven of which were abdominal/stomach problems. No evidence was identified in these elderly volunteers that indicated a benefit to mood or quality of life associated with selenium supplementation.

A 16-week randomized, placebo-controlled trial evaluated the effects of up to 600 μg (0.01 mg/kg) daily selenium supplementation in various forms on plasma selenium biomarkers in

[41] A cross-sectional, multistage, complex sample survey conducted from 1988-1994 and sponsored by the United States Department of Health and Human Services, Center for Disease Control. http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm, date visited March 22, 2007.

83 subjects (Burk *et al.*, 2006). Moderate (approximately 200 μg/day; 0.003 mg/kg) to large (approximately 600 μg/day) supplementation with sodium selenite (202±30, 380±56, and 601±49 μg selenium *per* dose group *per* day), high-selenium yeast (226±16, 439±27, and 703±48 μg selenium *per* dose group *per* day), or L-selenomethionine (158±17, 338±34, and 507±25 μg selenium *per* dose group *per* day) were ingested in 83 selenium-replete subjects with urinary selenium excretion and plasma selenium biomarkers[42] evaluated. Four subjects withdrew due to the odor of the capsules or minor gastrointestinal complaints. Some of the subjects had total daily selenium intakes (background selenium consumption in addition to supplementation) in excess of 800 μg selenium for 16 weeks, with no signs of selenium toxicity. Plasma selenium concentrations markedly increased with yeast and selenomethionine supplementation with the largest increase occurring in the first four weeks of supplementation. Plasma selenium also increased with selenite supplementation but to a much lesser extent. The plasma selenium levels in the selenomethionine and selenized yeast groups were approaching a plateau at the end of the 16-week study. Selenium supplementation as selenomethionine at 158, 338, and 507 μg/day (0.003, 0.006, and 0.008 mg Se/kg, respectively) resulted in significant plasma selenium concentration increases of 71%, 108%, and 178%, respectively ($P<0.05$ for all) (Burk *et al.*, 2006). Supplementation as selenized yeast at 226, 439, and 703 μg/day (0.004, 0.007, and 0.012 mg Se/kg, respectively) also resulted in significantly increased plasma selenium concentrations (46%, 108%, and 182% increases, respectively; $P<0.05$ for all). However, only the highest dose of selenite (601 μg) raised plasma selenium concentrations after 16 weeks (26% increase; $P<0.05$) and plasma glutathione peroxidase activity and selenoprotein P levels did not increase with selenite supplementation in any treatment group during the 16-week period. When corrected for urinary excretion of selenium by the control group (55 ± 22 μg Se/24 hours; $n = 13$) and then expressed as a *percentage* of administered selenium, the *percentage* of the dose excreted did not vary significantly between the doses of a given form of selenium; however, selenomethionine excretion (60 ±26%, $n = 26$) was significantly greater than selenite excretion (41 ±15%; $n = 20$). Urinary excretion of selenium administered as selenized yeast was 52 ±23% ($n = 18$), not significantly different from the other two selenium forms administered. The authors concluded

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[42] Selenium concentration, selenoprotein P concentration, and glutathione peroxidase activity.

that plasma selenium concentrations were responsive to supplements in proportion to their selenomethionine content, and that plasma selenium concentrations may be used to ensure safety of selenomethionine supplementation (Burk *et al.*, 2006).

7. EVALUATION

Sel-Plex® is a selenized yeast substance. It is composed of the intact, dried (non-viable) yeast strain, *Saccharomyces cerevisiae* CNCM I-3060, which is enriched with selenium and yeast-derived selenoproteins. Sel-Plex® is stable for ten months at room temperature, and for nine months at 37°C.

Selenium from Sel-Plex® is well-absorbed and bioavailable. It reaches a concentration plateau in the plasma, has a mean residence time of 4 – 41 days in the hepatopancreatic subsystem, and is retained in the tissues with a mean residence time of 115-285 days, resulting in a whole-body half-life of approximately 100-250 days.

Acute oral toxicity studies with Sel-Plex® indicate LD_{50}'s of greater than 2000 mg/kg (4 mg Se/kg) for both rats and mice. An acute rat inhalation study reported that a four-hour exposure to Sel-Plex® at a concentration of 2.76±0.18 mg/l produced clinical signs of toxicity (*i.e.*, hunched posture, piloerection, decreased respiratory rate and ptosis), but no mortality. Exposure to a similar concentration of a sodium selenate/yeast prill substance resulted in comparable effects but exposure to sodium selenate alone at analogous concentrations resulted in 100% mortality.

Subchronic studies in several animal species found that selenized yeast supplementation increased plasma selenium levels. In a subchronic study in rats, Sel-Plex® was administered *via* the diet at dose levels of 0, 114, 179, and 303 mg/kg/day (resulting in 0, 0.230, 0.360, and 0.610 mg Se/kg/day, respectively) for 13 weeks. Hepatotoxicity occurred in animals treated with 179 or 303 mg/kg/day; additional changes were considered a result of the reduced palatability of the diet. The NOAEL in this study was determined as 114 mg/kg/day Sel-Plex® for both sexes. In a 13-week dog gavage study of the effects of 0, 30, 100 or 300 mg/kg/day Sel-Plex® (equivalent daily Se intake at 0, 0.06, 0.20 or 0.60 mg/kg/day), 30 mg/kg/day was well tolerated, with no

relevant changes noted in hematology, blood biochemistry, or pathology endpoints. Slight hematological and biochemical parameters were noted at the 100 mg/kg/day Sel-Plex® dose group. The NOAEL for Sel-Plex® in dogs was 30 mg/kg/day.

Sel-Plex® was evaluated for mutagenicity in the Ames assay utilizing five different tester strains of *Salmonella typhimurium*, in which no cytotoxicity or genotoxicity was noted (with or without S9 mix) at up to 1000 μg/plate. Sel-Plex® did not induce structural or numerical damage in the bone marrow of mice treated by gavage for two days with up to 2000 mg/kg/day (4 mg Se/kg/day), and did not induce chromosomal aberrations in cultured human lymphocytes at concentrations up to 1250 μg/ml.

Selenized yeast was consumed by healthy men and women in a double blind, randomized, placebo-controlled trials at a dose of 600 μg selenium/day (0.01 mg/kg/day) for twelve weeks. In a 16-week study, total daily intake of selenium at up to 800 μg did not result in selenium-related toxicity, while significantly increasing plasma selenium concentrations. Selenized yeast has been administered to biopsy-proven prostate cancer patients at up to 3200 μg/day (0.053 mg/kg/day) for approximately twelve months with no identified selenium-associated adverse effects. Overall, human supplementation with selenized yeast at up to 800 μg Se/day (0.013 mg/kg/day) resulted in increased plasma selenium concentrations, with no toxicity noted.

There is sufficient qualitative and quantitative scientific evidence to determine the safety-in-use (*i.e.*, the ADI) for Sel-Plex®. An ADI is determined following a critical and comprehensive evaluation of the available toxicity/safety data and, is most often based on the lowest NOAEL from the most appropriate study (animal or human). The conservative NOAEL for Sel-Plex® in dogs is 30 mg [30,000 μg]/kg/day. The highest tolerable intake of selenium in humans was reported to be in excess of 800 μg/day. Thus, addition of Sel-Plex® to food categories stated in Table 8 at 10 ppm resulting in a mean consumption of 0.12 mg Sel-Plex®/kg/day or 7.2 mg/day Sel-Plex® for a 60 kg individual and a 90th percentile consumption at 0.26 mg Sel-Plex®/kg/day or 15.6 mg/day is safe (these consumption levels are equal to daily consumption of selenium at 14.3 and 31.2 μg/day, respectively).

Therefore the use of Sel-Plex® at no more than 10 ppm in the foods specified in APPENDIX I is safe according to the standard of a reasonable certainty of no harm.

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8. CERTIFICATION

The undersigned authors of this document - a dossier in support of GRAS status determination for use of Sel-Plex® - hereby certify that, to the best of their knowledge and belief, this document is a complete and balanced representation of all available information, favorable as well as unfavorable, known by the authors to be relevant to evaluation of the substance described herein.

(b) (6)

24 JULY 07

Ray A. Matulka, Ph.D.
Toxicologist
Burdock Group

Date

(b) (6)

24 July 2007

George A. Burdock, Ph.D., D.A.B.T., F.A.C.N.
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Date

9. CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the information summarized above (Dossier prepared by the Burdock Group) and conclude that Sel-Plex®, produced in accordance with current Good Manufacturing Practice (cGMP) and meeting the specifications described herein, is safe for use in foods at the levels specified in Appendix I of the Dossier. We further conclude that these uses of Sel-Plex® are Generally Recognized As Safe by scientific procedures. It is our opinion that other experts qualified by scientific training and experience to evaluate the safety of food and food ingredients would concur with these conclusions.

10. SIGNATURES

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APPENDIX I

Proposed Foods to which Sel-Plex® will be added

USDA food code	Food description	Sel-Plex (ppm)
11410000	YOGURT, NS AS TO TYPE OF MILK/FLAVOR	10
11411010	YOGURT, PLAIN, NS AS TO TYPE OF MILK	10
11411100	YOGURT, PLAIN, WHOLE MILK	10
11411200	YOGURT, PLAIN, LOWFAT MILK	10
11411300	YOGURT, PLAIN, NONFAT MILK	10
11420000	YOGURT, VANILLA, LEMON, COFFEE, NS AS TO MILK TYPE	10
11421000	YOGURT, VANILLA, LEMON, COFFEE, WHOLE MILK	10
11422000	YOGURT, VANILLA, LEMON, COFFEE, LOWFAT MILK	10
11423000	YOGURT, VANILLA, LEMON, COFFEE, NONFAT MILK	10
11424000	YOGURT, VANILLA, LEMON, COFFEE, NONFAT MILK, LOW CAL SWEET	10
11425000	YOGURT, CHOCOLATE, NS AS TO TYPE OF MILK	10
11426000	YOGURT, CHOCOLATE, WHOLE MILK	10
11427000	YOGURT, CHOCOLATE, NONFAT MILK	10
11430000	YOGURT, FRUIT VARIETY, NS AS TO MILK TYPE	10
11431000	YOGURT, FRUIT VARIETY, WHOLE MILK	10
11432000	YOGURT, FRUIT VARIETY, LOWFAT MILK	10
11433000	YOGURT, FRUIT VARIETY, NONFAT MILK	10
11433500	YOGURT, FRUITED, NONFAT MILK, LOW CAL SWEETENER	10
11444000	YOGURT, FRUIT & NUTS, NS AS TO TYPE OF MILK	10
11445000	YOGURT, FRUIT & NUTS, LOWFAT MILK	10
14710100	CHEDDAR CHEESE SOUP	10
14710110	CHEDDAR CHEESE SOUP, CANNED, UNDILUTED	10
14710200	BEER SOUP, MADE W/ MILK	10
25140110	SWEETBREADS, COOKED	10
27311610	BEEF, POT, & VEG (INCL CAR/DK GRN), (MUSHROOM) SOUP	10
27311620	BEEF, POT, & VEG (NO CAR/DK GREEN), (MUSHROOM) SOUP	10
27313310	BEEF, NOODLES, VEG(INCL CARROTS/DK GREEN), SOUP	10
27313320	BEEF, NOODLES, VEG (NO CARROTS/DK GREEN), SOUP	10
27315310	BEEF, RICE & VEGETABLES (W/ CARROTS/DK GREEN), SOUP	10
27315320	BEEF, RICE & VEGETABLES (NO CARROTS/DK GREEN), SOUP	10
27350410	TUNA NOODLE CASSEROLE W/ VEG & (MUSHROOM) SOUP	10
27414100	BEEF W/ VEG (INCL CAR/DK GRN, NO POT), SOUP	10
27414200	BEEF W/ VEG (NO CAR/DK GRN, NO POT), SOUP	10
28310150	OXTAIL SOUP	10
28310210	CHILI BEEF SOUP	10
28310220	CHILI BEEF SOUP, CHUNKY	10
28310230	MEATBALL SOUP, MEXICAN STYLE (SOPA DE ALBONDIGAS)	10
28310320	BEEF NOODLE SOUP, P.R. (SOPA DE CARNE Y FIDEOS)	10
28310330	BEEF & NOODLE SOUP, ORIENTAL (VIETNAMESE PHO BO)	10
28310420	BEEF & RICE SOUP, P.R.	10
28311010	PEPPERPOT (TRIPE) SOUP (INCL MENUDO/MONDONGO SOUP)	10
28315100	BEEF VEG SOUP W/POTATO, STEW TYPE (INCL CHUNKY STY)	10
28315110	BEEF NOODLE SOUP, CHUNKY STYLE	10
28315120	BEEF VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYLE	10
28315130	BEEF VEG SOUP W/ RICE, STEW TYPE, CHUNKY STYLE	10
28315140	BEEF VEGETABLE SOUP,MEXICAN STYLE (SOPA / CALDO DE RES)	10

USDA food code	Food description	Sel-Plex (ppm)
28315150	MEAT & CORN HOMINY SOUP, MEXICAN STYLE (POZOLE)	10
28316020	BEEF & MUSHROOM SOUP, CANNED, LOW SODIUM (INCL BEEF	10
28317010	BEEF STROGANOFF SOUP, CHUNKY STYLE	10
28320110	PORK & RICE SOUP, STEW TYPE, CHUNKY STYLE	10
28320120	PORK VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYLE	10
28320130	HAM, RICE, & POTATO SOUP, P.R.	10
28320140	HAM, NOODLE & VEGETABLE SOUP, P.R.	10
28320150	PORK, VEGETABLE SOUP W/ POTATOES, STEW TYPE	10
28320300	PORK W/VEG (NO CAR,BROC,&/OR DK GREEN)SOUP,ORIENTAL	10
28321130	BACON SOUP, CREAM OF, PREPARED W/ WATER	10
28331110	LAMB, PASTA & VEGETABLE SOUP, P.R.	10
28340150	MEXICAN STYLE CHICKEN BROTH SOUP STOCK	10
28340210	CHICKEN RICE SOUP, P.R. (SOPA DE POLLO CON ARROZ)	10
28340220	CHICKEN SOUP W/ NOODLES & POTATOES, P.R.	10
28340310	CHICKEN GUMBO SOUP	10
28340510	CHICKEN NOODLE SOUP, CHUNKY	10
28340520	CHICKEN SOUP, CANNED, UNDILUTED	10
28340530	CHICKEN SOUP	10
28340550	SWEET & SOUR SOUP	10
28340580	CHICKEN SOUP,W/VEGS(BROC,CRT,CELERY,POTS)ORIENTAL	10
28340590	CHICKEN CORN SOUP WITH NOODLES, HOME RECIPE	10
28340610	CHICKEN VEGETABLE SOUP, STEW TYPE (INCL CHUNKY)	10
28340620	TURKEY NOODLE SOUP, CHUNKY	10
28340630	CHICKEN VEG SOUP W/ RICE, STEW TYPE, CHUNKY STYLE	10
28340640	CHICKEN VEG SOUP W/ NOODLES, STEW TYPE, CHUNKY STYL	10
28340650	CHICKEN VEG SOUP W/ RICE, STEW TYPE, PREP W/ MILK	10
28340660	CHICKEN OR TURKEY VEGETABLE SOUP, HOME RECIPE	10
28340670	CHICKEN VEGETABLE SOUP,W/RICE,MEXICAN(SOPA / CALDO DE POLLO)	10
28340690	CHICKEN VEG SOUP W/ POTATO & CHEESE, CHUNKY	10
28340700	BIRD'S NEST SOUP (CHICKEN, HAM, NOODLES)	10
28340750	HOT & SOUR SOUP (INCLUDE HOT & SPICY CHINESE SOUP)	10
28340800	CHICKEN SOUP W/ VEGETABLES & FRUIT, ORIENTAL STYLE	10
28345010	CHICKEN/TURKEY SOUP, CM OF, CAN, RED SOD, NS W/ MILK/WATER	10
28345020	CHICKEN/TURKEY SOUP, CM OF, CAN, RED SOD, W/ MILK	10
28345030	CHICKEN/TURKEY SOUP, CM OF, CAN, RED SOD, W/ WATER	10
28345040	CHICKEN/TURKEY SOUP, CM OF, CAN, RED SOD, UNDILUTED	10
28345110	CHICKEN SOUP, CREAM OF, NS AS TO MILK OR WATER	10
28345120	CHICKEN/TURKEY SOUP,CREAM OF, W/ MILK	10
28345130	CHICKEN SOUP, CREAM OF, PREPARED W/ WATER	10
28345140	CHICKEN SOUP, CREAM OF, CANNED, UNDILUTED	10
28345160	CHICKEN & MUSHROOM SOUP, CREAM OF, W/ MILK	10
28345170	DUCK SOUP	10
28350050	FISH CHOWDER (INCL FISHERMAN'S SOUP, SEAFOOD CHOWD)	10
28350110	CRAB SOUP, NS AS TO TOMATO-BASE OR CREAM	10
28350120	CRAB SOUP, TOMATO BASE	10
28350310	TURTLE & VEGETABLE SOUP (INCLUDE SNAPPER SOUP)	10
28351110	FISH & VEGETABLE SOUP,NO POTATOES (SOPA DE PESCADO)	10
28351120	FISH SOUP, W/ POTATOES (SOPA DE PESCADO)	10
28351160	CODFISH, RICE & VEGETABLE SOUP, P.R.	10

USDA food code	Food description	Sel-Plex (ppm)
28351170	CODFISH SOUP W/ NOODLES, P.R.	10
28355210	CRAB SOUP, CREAM OF, W/ MILK	10
28355350	SALMON SOUP, CREAM STYLE	10
28355410	SHRIMP SOUP, CREAM OF, NS AS TO MILK/WATER ADDED	10
28355420	SHRIMP SOUP, CREAM OF, W/ MILK	10
28355430	SHRIMP SOUP, CREAM OF, W/ WATER	10
28355450	SEAFOOD SOUP W/ POTATOES & VEGETABLES (INCL DK GREEN LEAF)	10
28355460	SEAFOOD SOUP W/ POTATOES & VEGETABLES (EXCL DK GREEN LEAF)	10
28355470	SEAFOOD SOUP W/ VEGETABLES (INCL DK GREEN LEAFY)	10
28355480	SEAFOOD SOUP W/ VEGETABLES (EXCL DK GREEN LEAFY)	10
28360210	SPANISH VEGETABLE SOUP, P.R. (CALDO GALLEGO)	10
32300100	EGG DROP SOUP	10
32301100	GARLIC EGG SOUP, P.R. (SOPA DE AJO)	10
41435110	HIGH PROTEIN BAR, CANDY-LIKE, SOY & MILK BASE	10
41601010	BEAN SOUP, NFS	10
41601020	BEAN W/ BACON OR PORK SOUP	10
41601030	BLACK BEAN SOUP	10
41601040	LIMA BEAN SOUP	10
41601050	SOYBEAN SOUP, MADE W/ MILK	10
41601060	BEANSOUPW/MACARONI&MEAT(INCL PASTA E FAGIOLE W/MEAT	10
41601070	SOYBEAN SOUP, MISO BROTH	10
41601080	PINTO BEAN SOUP	10
41601090	BEAN SOUP W/ MACARONI (INCL PASTA E FAGIOLI)	10
41601100	PORTUGUESE BEAN SOUP	10
41601110	BEAN & HAM SOUP, CHUNKY STYLE (INCL CAMPBELL'S OLD	10
41601120	BEAN SOUP W/ VEG, RICE, & PORK (INCL CAMPBELL'S CHU	10
41601130	BEAN SOUP, MIXED BEANS (INCL 15-BEAN SOUP)	10
41601140	BEAN SOUP, HOME RECIPE	10
41601160	BEAN & HAM SOUP, CAN, REDUCED SODIUM, W/ WATER/RTS	10
41601170	BEAN & RICE SOUP	10
41601180	BEAN & HAM SOUP, HOME RECIPE	10
41602010	CHUNKY PEA & HAM SOUP	10
41602020	GARBANZO OR CHICKPEA SOUP	10
41602030	SPLIT PEA & HAM SOUP	10
41602040	PEA SOUP, INSTANT TYPE	10
41602050	SPLIT PEA SOUP	10
41602070	SPLIT PEA SOUP, CAN, REDUCED SODIUM, W/ WATER/RTS	10
41602090	SPLIT PEA & HAM SOUP, CAN, REDUCED SODIUM, W/ WATER/RTS	10
41603010	LENTIL SOUP	10
41610100	WHITE BEAN SOUP, P.R.	10
51000100	BREAD, NS AS TO MAJOR FLOUR	10
51000110	BREAD, NS AS TO MAJOR FLOUR, TOASTED	10
51000180	BREAD, HOMEMADE/PURCH AT A BAKERY, NS AS TO FLOUR	10
51000190	BREAD, HOMEMADE/PURCH AT A BAKERY, TOASTD,NS FLOUR	10
51101000	BREAD, WHITE	10
51101010	BREAD, WHITE, TOASTED	10
51101050	BREAD, WHITE, HOMEMADE OR PURCHASED AT A BAKERY	10
51101060	BREAD, WHITE, HOMEMADE OR PURCH AT A BAKERY TOASTED	10

USDA food code	Food description	Sel-Plex (ppm)
51107010	BREAD, FRENCH OR VIENNA	10
51107040	BREAD, FRENCH OR VIENNA, TOASTED	10
51108010	FOCACCIA, ITALIAN FLATBREAD, PLAIN	10
51109010	BREAD, ITALIAN, GRECIAN, ARMENIAN	10
51109040	BREAD, ITALIAN, GRECIAN, ARMENIAN, TOASTED	10
51109100	BREAD, PITA	10
51109110	BREAD, PITA, TOASTED	10
51111010	BREAD, CHEESE (INCLUDE ONION CHEESE)	10
51111040	BREAD, CHEESE, TOASTED (INCLUDE ONION CHEESE)	10
51113010	BREAD, CINNAMON	10
51113100	BREAD, CINNAMON, TOASTED	10
51119100	BREAD, LOWFAT, 98% FAT FREE	10
51119110	BREAD, LOWFAT, 98% FAT FREE, TOASTED	10
51121010	BREAD, GARLIC	10
51121040	BREAD, GARLIC, TOASTED (INCLUDE TEXAS TOAST)	10
51121110	BREAD, ONION	10
51122000	BREAD, REDUCED CALORIE/HIGH FIBER	10
51122010	BREAD, REDUCED CALORIE/HIGH FIBER, TOASTED	10
51122050	BREAD, REDUCED CALORIE/HIGH FIBER, ITALIAN	10
51122060	BREAD, REDUCED CALORIE/HIGH FIBER, ITALIAN,TOASTED	10
51122100	BREAD, REDUCED CALORIE/ HIGH FIBER, W/ FRUIT/NUTS	10
51122110	BREAD, REDUCED CALORIE/HI FIBER, W/FRUIT/NUTS,TOAST	10
51122300	BREAD, WHITE, SPECIAL FORMULA, ADDED FIBER	10
51122310	BREAD,WHITE,SPECIAL FORMULA,ADDED FIBER,TOASTED	10
51123010	BREAD, HIGH PROTEIN	10
51123020	BREAD, HIGH PROTEIN, TOASTED	10
51129010	BREAD, RAISIN	10
51129020	BREAD, RAISIN, TOASTED	10
51130510	BREAD, WHITE, LOW SODIUM OR NO SALT	10
51130520	BREAD, WHITE, LOW SODIUM/NO SALT, TOASTED	10
51133010	BREAD, SOUR DOUGH	10
51133020	BREAD, SOUR DOUGH, TOASTED	10
51184000	BREAD STICK, HARD	10
51184010	BREAD STICK, SOFT	10
51184020	BREAD STICK, NS AS TO HARD OR SOFT	10
51184030	BREAD STICK, SOFT, PREP W/ GARLIC & PARMESAN CHEESE	10
51184100	BREAD STICK, HARD, LOW SODIUM	10
51201010	BREAD, 100% WHOLE WHEAT	10
51201020	BREAD, 100% WHOLE WHEAT, TOASTED	10
51201060	BREAD, 100% WHOLE WHEAT, HOME-MADE	10
51201070	BREAD, 100% WHOLE WHEAT, HOME-MADE, TOASTED	10
51201110	BREAD, 100% WHOLE WHEAT, W/ RAISINS	10
51201120	BREAD, 100% WHOLE WHEAT, W/ RAISINS, TOASTED	10
51201150	BREAD, PITA, 100% WHOLE WHEAT	10
51201160	BREAD, PITA, 100% WHOLE WHEAT, TOASTED	10
51204010	BREAD, WHEAT GERM	10
51204020	BREAD, WHEAT GERM, TOASTED	10
51207010	BREAD, SPROUTED WHEAT	10
51207020	BREAD, SPROUTED WHEAT, TOASTED	10
51300110	BREAD, WHOLE WHEAT, OTHER THAN 100%/NS AS TO 100%	10
51300120	BREAD, WHOLE WHEAT, OTHER THAN 100%/NS 100%, TOAST	10

USDA food code	Food description	Sel-Plex (ppm)
51300140	BREAD, "WHOLE" WHEAT, HOME RECIPE/BAKERY	10
51300150	BREAD, "WHOLE" WHEAT, HOME RECIPE/BAKERY, TOASTED	10
51300210	BREAD, WHOLE WHEAT, NS AS TO 100%, W/ RAISINS	10
51300220	BREAD, WHOLE WHEAT,NS AS TO 100%,W/ RAISINS,TOASTED	10
51301010	BREAD, WHEAT OR CRACKED WHEAT	10
51301020	BREAD, WHEAT OR CRACKED WHEAT, TOASTED	10
51301040	BREAD, CRACKED WHEAT, HOME RECIPE/BAKERY	10
51301050	BREAD, CRACKED WHEAT, HOME RECIPE/BAKERY, TOASTED	10
51301120	BREAD, WHEAT OR CRACKED WHEAT, W/ RAISINS	10
51301130	BREAD, WHEAT OR CRACKED WHEAT, W/ RAISINS, TOASTED	10
51301510	BREAD, CRACKED WHEAT, REDUCED CALORIE/ HIGH FIBER	10
51301520	BREAD, CRACKED WHEAT, RED CALORIE/ HI FIBER, TOAST	10
51301540	BREAD, FRENCH, "WHOLE" WHEAT, HOMEMADE	10
51301550	BREAD, FRENCH, "WHOLE" WHEAT, HOMEMADE, TOASTED	10
51301600	BREAD, PITA, "WHOLE" WHEAT	10
51301610	BREAD, PITA, "WHOLE" WHEAT, TOASTED	10
51301620	BREAD, PITA, CRACKED WHEAT	10
51301630	BREAD, PITA, CRACKED WHEAT, TOASTED	10
51302010	BREAD, WHEAT BRAN	10
51302020	BREAD, WHEAT BRAN, TOASTED	10
51302050	BREAD, WHEAT BRAN, W/ RAISINS	10
51302060	BREAD, WHEAT BRAN, W/ RAISINS, TOASTED	10
51306000	BREAD STICK, HARD, WHOLE WHEAT, NS AS TO 100 %	10
51401010	BREAD, RYE	10
51401020	BREAD, RYE, TOASTED	10
51401030	BREAD, MARBLE RYE & PUMPERNICKEL	10
51401040	BREAD, MARBLE RYE & PUMPERNICKEL, TOASTED	10
51401060	BREAD, RYE, REDUCED CALORIE/ HIGH FIBER (INCL LESS)	10
51401070	BREAD, RYE, REDUCED CALORIE/ HIGH FIBER, TOASTED	10
51404010	BREAD, PUMPERNICKEL	10
51404020	BREAD, PUMPERNICKEL, TOASTED	10
51407010	BREAD, BLACK	10
51407020	BREAD, BLACK, TOASTED	10
51501010	BREAD, OATMEAL	10
51501020	BREAD, OATMEAL, TOASTED	10
51501040	BREAD, OAT BRAN	10
51501050	BREAD, OAT BRAN, TOASTED	10
51501060	BREAD, OAT BRAN, REDUCED CALORIE/ HIGH FIBER	10
51501070	BREAD, OAT BRAN REDUCED CALORIE/HI FIBER, TOASTED	10
51601010	BREAD, MULTIGRAIN, TOASTED	10
51601020	BREAD, MULTIGRAIN	10
51601210	BREAD, MULTIGRAIN, W/ RAISINS	10
51601220	BREAD, MULTIGRAIN, W/ RAISINS, TOASTED	10
51602010	BREAD, MULTIGRAIN, REDUCED CALORIE/ HIGH FIBER	10
51602020	BREAD, MULTIGRAIN, REDUCED CALORIE/ HI FIBER, TOAST	10
51801010	BREAD, BARLEY	10
51802010	BREAD, TRITICALE	10
51802020	BREAD, TRITICALE, TOASTED	10
51803010	BREAD, BUCKWHEAT	10
51803020	BREAD, BUCKWHEAT, TOASTED	10
51804010	BREAD, SOY	10

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51804020	BREAD, SOY, TOASTED	10
51805010	BREAD, SUNFLOWER MEAL	10
51805020	BREAD, SUNFLOWER MEAL, TOASTED	10
51806010	BREAD, RICE	10
51806020	BREAD, RICE, TOASTED	10
51808000	BREAD, LOW GLUTEN	10
51808010	BREAD, LOW GLUTEN, TOASTED	10
52201000	CORNBREAD, PREPARED FROM MIX	10
52202060	CORNBREAD, HOMEMADE	10
52202500	CORNBREAD, MADE WITH EGG SUBSTITUTE, HOMEMADE	10
52206010	CORNBREAD MUFFIN, STICK, ROUND	10
52206020	CORNBREAD MUFFIN, STICK, ROUND, TOASTED	10
52206060	CORNBREAD MUFFIN, STICK, ROUND, HOMEMADE	10
52401000	BREAD, BOSTON BROWN	10
52403000	BREAD, NUT	10
52404060	BREAD, PUMPKIN (INCLUDE W/ RAISINS)	10
52405010	BREAD, FRUIT, W/O NUTS	10
52405100	BREAD, FRUIT & NUT	10
52406010	BREAD, WHOLE WHEAT, W/ NUTS	10
52407000	BREAD, ZUCCHINI (INCL SQUASH BREAD; W/ NUTS)	10
52408000	BREAD, IRISH SODA	10
53540000	BREAKFAST BAR, NFS	10
53540200	BREAKFAST BAR, CEREAL CRUST W/ FRUIT FILLING, LOWFAT	10
53540250	BREAKFAST BAR, CEREAL CRUST W/ FRUIT FILLING, FAT FREE	10
53540500	BREAKFAST BAR, DATE, W/ YOGURT COATING	10
53541200	MEAL REPLACEMENT BAR (INCL SLIM FAST BAR)	10
53542100	GRANOLA BAR W/ OATS, SUGAR, RAISINS, COCONUT	10
53542200	GRANOLA BAR, OATS, FRUIT, NUTS, LOWFAT	10
53542210	GRANOLA BAR, NONFAT	10
53543100	GRANOLA BAR W/ PEANUTS, OATS, SUGAR, WHEAT GERM	10
53544200	GRANOLA BAR, CHOCOLATE-COATED	10
53544210	GRANOLA BAR, W/ COCONUT, CHOCOLATE-COATED	10
53544220	GRANOLA BAR W/ NUTS, CHOCOLATE-COATED	10
53544250	GRANOLA BAR, COATED W/ NONCHOCOLATE COATING	10
53544300	GRANOLA BAR, HIGH FIBER, YOGURT COATING, NOT CHOC	10
53544400	GRANOLA BARS, W/ RICE CEREAL	10
53544450	POWERBAR (FORTIFIED HIGH ENERGY BAR)	10
54207010	CRISPBREAD, WHEAT, LOW SODIUM	10
54222000	CRISPBREAD, RYE, LOW SODIUM	10
54305000	CRISPBREAD, WHEAT, NO ADDED FAT	10
54305500	CRISPBREAD,WHEAT / RYE, EXTRA CRISPY	10
54322000	CRISPBREAD, RYE, NO ADDED FAT	10
54420010	MULTIGRAIN MIXTURE, PRETZELS, CEREAL &/ CRACKERS,NUTS	10
54420200	MULTIGRAIN MIX, BREAD STICKS, SESAME NUGGETS, PRETZ	10
56200300	CEREAL, COOKED, NFS	10
56200350	CEREAL, COOKED, INSTANT, NS AS TO GRAIN	10
56207190	WHOLE WHEAT CEREAL, COOKED, NS AS TO ADDED FAT	10
56207200	WHOLE WHEAT CEREAL, COOKED, NO FAT ADDED	10
56207210	WHOLE WHEAT CEREAL, COOKED, FAT ADDED	10
56207300	WHOLE WHEAT CEREAL, W/ BARLEY, COOKED, NO FAT ADDED	10
56207330	WHOLE WHEAT CEREAL, WHEAT & BARLEY, FAT ADDED	10

USDA food code	Food description	Sel-Plex (ppm)
56207340	WHOLE WHEAT CEREAL, WHEAT & BARLEY, ADDED FAT NS	10
56207350	WHEAT CEREAL, CHOC FLAVORED, COOKED W/ MILK	10
56207360	WHEAT CEREAL, CHOC FLAVORED, COOKED, NO FAT ADDED	10
56207370	WHEAT CEREAL, CHOC FLAV,COOKED,NS AS TO ADDED FAT	10
56208500	OAT BRAN CEREAL, COOKED, NO FAT ADDED	10
56208510	OAT BRAN CEREAL, COOKED, FAT ADDED	10
56208520	OAT BRAN CEREAL, COOKED, NS AS TO ADDED FAT	10
56208530	OAT BRAN CEREAL, MADE W/ MILK, NO FAT ADDED	10
56208540	OAT BRAN CEREAL, MADE W/ MILK, FAT ADDED	10
56208550	OAT BRAN CEREAL, MADE W/ MILK, NS AS TO ADDED FAT	10
56210000	NESTUM, CEREAL	10
57000000	CEREAL, NFS	10
57000050	KASHI CEREAL, NS AS TO READY-TO-EAT OR COOKED	10
57000100	OAT CEREAL, NFS	10
57100100	CEREAL, READY-TO-EAT, NFS	10
57101000	ALL-BRAN CEREAL	10
57101020	ALL BRAN CEREAL W/ EXTRA FIBER	10
57102000	ALPEN CEREAL	10
57103000	ALPHA-BITS CEREAL	10
57103020	ALPHA-BITS W/ MARSHMALLOWS CEREAL	10
57103050	AMARANTH FLAKES CEREAL	10
57103500	APPLE CINNAMON SQUARES MINI-WHEATS CEREAL, KELLOGG'S	10
57104000	APPLE JACKS CEREAL	10
57106050	BANANA NUT CRUNCH CEREAL (POST)	10
57106100	BASIC 4 (RTE CEREAL)	10
57107000	BOOBERRY CEREAL	10
57110000	ALL-BRAN BRAN BUDS CEREAL, KELLOGG'S (FORMERLY BRAN BUDS)	10
57111000	BRAN CHEX CEREAL	10
57117000	CAP'N CRUNCH CEREAL	10
57117500	CAP'N CRUNCH'S CHRISTMAS CRUNCH CEREAL	10
57119000	CAP'N CRUNCH'S CRUNCH BERRIES CEREAL	10
57120000	CAP'N CRUNCH'S PEANUT BUTTER CRUNCH CEREAL	10
57124000	CHEX CEREAL, NFS	10
57124200	CHOCOLATE FLAVORED FROSTED PUFFED CORN CEREAL	10
57124500	CINNAMON GRAHAMS CEREAL, GENERALMILLS	10
57125000	CINNAMON TOAST CRUNCH CEREAL	10
57125900	HONEY NUT CLUSTERS CEREAL	10
57126000	COCOA KRISPIES CEREAL	10
57126500	COCOA BLASTS CEREAL, QUAKER	10
57127000	COCOA PEBBLES CEREAL	10
57128000	COCOA PUFFS CEREAL	10
57128880	COMMON SENSE OAT BRAN CEREAL, PLAIN	10
57130000	COOKIE-CRISP CEREAL (INCLUDE ALL FLAVORS)	10
57131000	CRUNCHY CORN BRAN CEREAL, QUAKER	10
57132000	CORN CHEX CEREAL	10
57137000	CORN PUFFS CEREAL	10
57139000	COUNT CHOCULA CEREAL	10
57143000	CRACKLIN' OAT BRAN CEREAL	10
57144000	CRISP CRUNCH CEREAL	10
57148000	CRISPIX CEREAL	10

USDA food code	Food description	Sel-Plex (ppm)
57148500	CRISPY BROWN RICE CEREAL	10
57148600	HARMONY CEREAL, GEN MILLS	10
57151000	CRISPY RICE CEREAL	10
57152000	CRISPY WHEATS'N RAISINS CEREAL	10
57201800	DISNEY CEREALS, KELLOGG'S	10
57206000	FAMILIA CEREAL	10
57206700	FIBER ONE CEREAL	10
57206800	FIBER 7 FLAKES CEREAL, HEALTH VALLEY	10
57207000	BRAN FLAKES CEREAL, NFS (FORMERLY 40% BRAN FLAKES, NFS)	10
57209000	NATURAL BRAN FLAKES CEREAL, POST	10
57211000	FRANKENBERRY CEREAL	10
57212100	FRENCH TOAST CRUNCH CEREAL, GENERAL MILLS	10
57213000	FROOT LOOPS CEREAL	10
57213850	FROSTED CHEERIOS CEREAL	10
57214000	FROSTED MINI-WHEATS CEREAL (INCL ALL FLAVORS)	10
57215000	FROSTY O'S CEREAL	10
57216000	FROSTED RICE CEREAL, NFS	10
57218000	FROSTED RICE KRISPIES CEREAL	10
57219000	FRUIT & FIBRE CEREAL, NFS	10
57221000	FRUIT & FIBRE CEREAL, W/ DATES, RAISINS, & WALNUTS	10
57221800	FRUIT WHIRLS CEREAL	10
57223000	FRUITY PEBBLES CEREAL	10
57224000	GOLDEN GRAHAMS CEREAL	10
57230000	GRAPE-NUTS CEREAL	10
57231200	GREAT GRAINS, RAISIN, DATE, & PECAN,WHOLE GRAIN CEREAL, POST	10
57231250	GREAT GRAINS DOUBLE PECAN WHOLE GRAIN CEREAL, POST	10
57232100	HEALTHY CHOICE ALMOND CRUNCH CEREAL W/ RAISINS	10
57237100	HONEY BUNCHES OF OATS CEREAL	10
57238000	HONEYCOMB CEREAL, PLAIN	10
57239000	HONEYCOMB CEREAL, STRAWBERRY	10
57239100	HONEY CRUNCH CORN FLAKES CEREAL, KELLOGG'S	10
57240100	HONEY NUT CHEX CEREAL	10
57241200	HONEY NUT SHREDDED WHEAT CEREAL, POST	10
57244000	JUST RIGHT CEREAL	10
57245000	JUST RIGHT FRUIT & NUT CEREAL (W/ RAISINS, DATES, NUTS)	10
57301100	KABOOM CEREAL	10
57302100	KING VITAMAN CEREAL	10
57303100	KIX CEREAL	10
57304100	LIFE CEREAL (PLAIN & CINNAMON)	10
57305100	LUCKY CHARMS CEREAL	10
57305150	FROSTED OAT CEREAL W/ MARSHMALLOWS	10
57305170	MALT-O-MEAL COCO-ROOS CEREAL	10
57305180	MALT-O-MEAL CORN BURSTS CEREAL	10
57305200	MALT-O-MEAL CRISPY RICE CEREAL	10
57305500	MALT-O-MEAL HONEY & NUT TOASTY O'S CEREAL	10
57305600	MALT-O-MEAL MARSHMALLOW MATEYS CEREAL	10
57306100	MALT-O-MEAL PUFFED RICE CEREAL	10
57306120	MALTO-O-MEAL PUFFED WHEAT CEREAL	10
57306500	MALT-O-MEAL GOLDEN PUFFS CEREAL (FORMERLY SUGAR PUFFS)	10

USDA food code	Food description	Sel-Plex (ppm)
57306700	MALT-O-MEAL TOASTED OAT CEREAL	10
57306800	MALT-O-MEAL TOOTIE FRUITIES (RTE CEREAL)	10
57307150	MARSHMALLOW SAFARI CEREAL, QUAKER	10
57307500	MILLET, PUFFED (CEREAL)	10
57308150	MUESLIX CEREAL, NFS	10
57311700	NU SYSTEM CUISINE TOASTED GRAIN CIRCLES CEREAL	10
57316410	APPLE CINNAMON OATMEAL CRISP CEREAL (OATMEAL CRISP W/ APPLES	10
57316450	OATMEAL CRISP W/ ALMONDS CEREAL	10
57316500	OATMEAL RAISIN CRISP CEREAL	10
57316710	OH'S, HONEY GRAHAM CEREAL	10
57316750	OH'S, FRUITANGY CEREAL	10
57318000	100% BRAN CEREAL	10
57319000	100% NATURAL CEREAL, PLAIN, QUAKER	10
57320500	100 % NATURAL CEREAL, W/ OATS,HONEY & RAISINS,QUAKER	10
57321500	100% NATURAL WHOLEGRAIN CEREAL W/ RAISINS, LOWFAT, QUAKER	10
57322500	OREO O'S CEREAL, POST	10
57323000	SWEET CRUNCH CEREAL, QUAKER (FORMERLY POPEYE)	10
57323050	SWEET PUFFS CEREAL, QUAKER	10
57325000	PRODUCT 19 CEREAL	10
57327450	QUAKER OAT BRAN CEREAL	10
57327500	QUAKER OATMEAL SQUARES CEREAL (FORMERLY QUAKER OAT SQUARES)	10
57328000	QUISP CEREAL	10
57329000	RAISIN BRAN CEREAL, NFS	10
57330000	RAISIN BRAN CEREAL, KELLOGG	10
57331000	RAISIN BRAN CEREAL, POST	10
57332100	RAISIN NUT BRAN CEREAL	10
57335500	RAISIN SQUARES MINI-WHEATS CEREAL (FORMERLY RAISIN SQUARES)	10
57335550	REESE'S PEANUT BUTTER PUFFS CEREAL	10
57336000	RICE CHEX CEREAL	10
57339000	RICE KRISPIES CEREAL	10
57339500	RICE KRISPIES TREATS CEREAL (KELLOGG'S)	10
57340000	PUFFED RICE CEREAL	10
57341000	SHREDDED WHEAT 'N BRAN CEREAL	10
57344000	SPECIAL K CEREAL	10
57347000	CORN POPS CEREAL	10
57347500	STRAWBERRY SQUARES MINI-WHEATS CEREAL(STRAWBERRY SQUARES)	10
57355000	GOLDEN CRISP CEREAL	10
57401100	TOASTED OAT CEREAL	10
57404100	MALT-O-MEAL TOASTY O'S CEREAL	10
57406100	TOTAL CEREAL	10
57407100	TRIX CEREAL	10
57408100	UNCLE SAM'S HI FIBER CEREAL	10
57409100	WAFFLE CRISP CEREAL, POST	10
57410000	WEETABIX WHOLE WHEAT CEREAL	10
57411000	WHEAT CHEX CEREAL	10
57412000	WHEAT GERM CEREAL, PLAIN	10

USDA food code	Food description	Sel-Plex (ppm)
57413000	WHEAT GERM CEREAL, W/ SUGAR & HONEY	10
57416000	PUFFED WHEAT CEREAL, PLAIN	10
57418000	WHEATIES CEREAL	10
57603200	RICE BRAN CEREAL, UNCOOKED	10
58132113	PASTA, W/ TOMATO SAUCE & CHEESE, CANNED	10
58132313	PASTA W/ TOMATO SAUCE & MEAT/MEATBALLS, CANNED	10
58132713	PASTA W/ TOMATO SAUCE & FRANKFURTERS/HOT DOGS, CANNED	10
58146100	PASTA W/ TOMATO SAUCE, MEATLESS	10
58146110	PASTA W/ MEAT SAUCE (INCLUDE AMER CHOP SUEY)	10
58146120	PASTA W/ CHEESE & MEAT SAUCE	10
58146130	PASTA W/ CARBONARA SAUCE	10
58146150	PASTA W/ CHEESE & TOMATO SAUCE, MEATLESS	10
58146200	PASTA, MEAT-FILLED, W/ GRAVY, CANNED	10
58146300	PASTA, WHOLE WHEAT, WITH MEAT SAUCE	10
58146310	PASTA, WHOLE WHEAT, W/ TOMATO SAUCE, MEATLESS	10
58147100	PASTA W/ PESTO SAUCE	10
58147510	FLAVORED PASTA (INCL LIPTON BEEF, CHICKEN FLAVORS)	10
58148110	MACARONI OR PASTA SALAD	10
58148120	MACARONI OR PASTA SALAD WITH EGG	10
58148130	MACARONI OR PASTA SALAD WITH TUNA	10
58148140	MACARONI OR PASTA SALAD WITH CRAB MEAT	10
58148150	MACARONI OR PASTA SALAD WITH SHRIMP	10
58148160	MACARONI OR PASTA SALAD WITH TUNA AND EGG	10
58148170	MACARONI OR PASTA SALAD WITH CHICKEN	10
58148180	MACARONI OR PASTA SALAD WITH CHEESE	10
58148500	PASTA OR MACARONI SALAD W/ OIL & VINEGAR-TYPE DRESSING	10
58148550	PASTA OR MACARONI SALAD W/ MEAT & OIL & VINEGAR DRESSING	10
58148600	PASTA TETRAZZINI,DRY MIX,PREPARED W/ WATER	10
58305200	PASTA,SPINACH,W/VEGETABLES&CHEESE SCE(DIET FRZ MEAL	10
58305250	PASTA,W/ VEGETABLES & CHEESE SAUCE (DIET FROZ MEAL)	10
58400000	SOUP, NFS	10
58400100	NOODLE SOUP, NFS	10
58400200	RICE SOUP, NFS	10
58401010	BARLEY SOUP (INCLUDE BEEF/CHICKEN/MUSHROOM BARLEY)	10
58401200	BARLEY SOUP,SWEET,W/ OR W/O NUTS, ORIENTAL STYLE	10
58402000	BEEF NOODLE SOUP, CANNED, UNDILUTED	10
58402010	BEEF NOODLE SOUP	10
58402020	BEEF DUMPLING SOUP	10
58402030	BEEF RICE SOUP	10
58402100	BEEF NOODLE SOUP, HOME RECIPE	10
58403010	CHICKEN NOODLE SOUP (INCLUDE CHICKEN & STARS SOUP)	10
58403020	CHICKEN NOODLE SOUP, CANNED, UNDILUTED	10
58403030	CHICKEN NOODLE SOUP, CANNED, LOW SODIUM	10
58403040	CHICKEN NOODLE SOUP, HOME RECIPE	10
58403050	CHICKEN NOODLE SOUP, CREAM OF	10
58403060	CHICKEN NOODLE SOUP,CAN,RED SODIUM,READY-TO-SERVE	10
58403100	NOODLE & POTATO SOUP, P.R.	10
58404010	CHICKEN RICE SOUP (INCL TURKEY RICE SOUP)	10
58404020	CHICKEN & RICE SOUP, CANNED, UNDILUTED	10

USDA food code	Food description	Sel-Plex (ppm)
58404030	CHICKEN OR TURKEY RICE SOUP, HOME RECIPE	10
58404040	CHICKEN RICE SOUP, CAN, RED SODIUM, PREP W/ WATER/RTS	10
58404050	CHICKEN RICE SOUP, CAN, REDUCED SODIUM, W/ MILK	10
58404100	RICE AND POTATO SOUP, P.R.	10
58404500	MATZO BALL SOUP	10
58404510	CHICKEN SOUP W/ DUMPLINGS, POTATOES	10
58404520	CHICKEN SOUP W/ DUMPLINGS	10
58406010	TURKEY NOODLE SOUP	10
58406020	TURKEY NOODLE SOUP, HOME RECIPE	10
58407000	INSTANT SOUP, NFS	10
58407010	INSTANT SOUP, NOODLE (INCLUDE MEAT & VEG FLAVORS)	10
58407030	SOUP, MOSTLY NOODLES(INCL SPAGHETTI SOUP,TOP RAMEN)	10
58407040	INSTANT SOUP, RICE (INCLUDE MEAT/CHICKEN FLAVOR)	10
58407050	INSTANT SOUP, NOODLE W/ EGG, SHRIMP OR CHICKEN	10
58408010	WON TON (WONTON) SOUP	10
58408500	NOODLE SOUP W/ VEGETABLES,ORIENTAL STYLE	10
58409000	NOODLE SOUP,W/ FISH BALL,SHRIMP,&DK GREEN LEAFY VEG	10
58410100	RICE SOUP, MADE W/ TEA	10
58421000	SOPA SECA (DRY SOUP), Mexican style, NFS	10
58421020	SOPA DE FIDEO AGUADA, MEXICAN STYLE NOODLE SOUP	10
58421060	SOPA SECA DE ARROZ (DRY RICE SOUP), MEXICAN STYLE	10
58421080	SOPA DE TORTILLA, MEXICAN STYLE TORTILLA SOUP	10
58450300	NOODLE SOUP, MADE W/ MILK	10
63415000	SOUP, SOUR CHERRY	10
63415100	SOUP, FRUIT	10
71801000	POTATO SOUP, NS AS TO MADE W/MILK OR WATER	10
71801010	POTATO SOUP, CREAM OF, W/ MILK	10
71801020	POTATO SOUP, PREPARED W/ WATER	10
71801040	POTATO SOUP, INSTANT, MADE FROM DRY MIX	10
71801100	POTATO & CHEESE SOUP	10
71802010	MACARONI & POTATO SOUP	10
71851010	PLANTAIN SOUP, P.R. (SOPA DE PLATANO)	10
72302000	BROCCOLI SOUP (INCLUDE CREAM OF BROCCOLI SOUP)	10
72302100	BROCCOLI CHEESE SOUP, PREP W/ MILK	10
72305000	ESCAROLE SOUP	10
72307000	SPINACH SOUP	10
72308000	DARK-GREEN LEAFY VEGETABLE SOUP,W/MEAT,ORIENTAL	10
72308500	DARK-GREEN LEAFY VEGETABLE SOUP,MEATLESS,ORIENTAL	10
73501000	CARROT SOUP, CREAM OF, W/ MILK	10
73501010	CARROT W/ RICE SOUP, CREAM OF, W/ MILK	10
74601000	TOMATO SOUP, NFS	10
74601010	TOMATO SOUP, CREAM OF,PREP W/ MILK	10
74602010	TOMATO SOUP, PREPARED W/ WATER	10
74602030	TOMATO SOUP, CANNED, UNDILUTED	10
74602050	TOMATO SOUP, INSTANT TYPE, PREPARED W/ WATER	10
74602100	TOMATO SOUP, CANNED, LOW SODIUM, READY-TO-SERVE	10
74602200	TOMATO SOUP, CAN, RED. SODIUM, PREP. W/ WATER	10
74602300	TOMATO SOUP, CAN, RED. SODIUM, PREP W/ MILK	10
74603010	TOMATO BEEF SOUP, PREPARED W/ WATER	10
74604010	TOMATO BEEF NOODLE SOUP, PREPARED W/ WATER	10
74604100	TOMATO BEEF RICE SOUP, PREPARED W/ WATER	10

USDA food code	Food description	Sel-Plex (ppm)
74604500	TOMATO NOODLE SOUP, PREPARED W/ WATER	10
74604600	TOMATO NOODLE SOUP, CREAM OF	10
74605000	TOMATO RICE SOUP, CANNED, UNDILUTED	10
74605010	TOMATO RICE SOUP, PREPARED W/ WATER	10
74606010	TOMATO VEGETABLE SOUP, PREP W/ WATER	10
74606020	TOMATO VEGETABLE SOUP W/NOODLES, PREPARED W/ WATER	10
75600150	SOUP, CREAM OF, NFS	10
75601000	ASPARAGUS SOUP, CREAM OF, NS AS TO W/ MILK OR WATER	10
75601010	ASPARAGUS SOUP, CREAM OF,W/ MILK	10
75601020	ASPARAGUS SOUP, CREAM OF, PREPARED W/ WATER	10
75601100	BEET SOUP (BORSCHT)	10
75601200	CABBAGE SOUP	10
75601210	CABBAGE W/ MEAT SOUP	10
75602010	CAULIFLOWER SOUP, CREAM OF, W/ MILK	10
75603000	CELERY SOUP, CREAM OF, NS AS TO MILK OR WATER ADDED	10
75603010	CELERY SOUP, CREAM OF, W/ MILK	10
75603020	CELERY SOUP, CREAM OF, PREPARED W/ WATER	10
75603030	CELERY SOUP, CREAM OF, CANNED, UNDILUTED	10
75604010	CORN SOUP, CREAM OF, W/ MILK	10
75604020	CORN SOUP, CREAM OF, PREPARED W/ WATER	10
75604510	CUCUMBER SOUP, CREAM OF, W/ MILK	10
75605010	LEEK SOUP, CREAM OF, PREP W/ MILK	10
75605030	LEEK SOUP, MADE FROM DRY MIX	10
75607000	MUSHROOM SOUP, NFS	10
75607010	MUSHROOM SOUP, CREAM OF, PREP W/ MILK	10
75607020	MUSHROOM SOUP, CREAM OF, PREPARED W/ WATER	10
75607030	MUSHROOM SOUP, CANNED, UNDILUTED (INCL CREAM OF)	10
75607040	MUSHROOM SOUP, W/ MEAT BROTH, PREPARED W/ WATER	10
75607050	MUSHROOM SOUP, CM OF, LOW SOD, PREP W/ WATER	10
75607060	MUSHROOM SOUP, CREAM OF, NS AS TO W/ MILK OR WATER	10
75607080	MUSHROOM W/ CHICKEN SOUP, CREAM OF, PREP W/ MILK	10
75607090	MUSHROOM SOUP, CREAM OF, CAN, RED. SOD., NS W/ MILK/WATER	10
75607100	MUSHROOM SOUP, CREAM OF, CAN, RED. SODIUM, PREP W/ MILK	10
75607130	MUSHROOM SOUP, MADE FROM DRY MIX	10
75607140	MUSHROOM SOUP, CM OF, CAN, RED SOD, PREP W/ WATER	10
75607150	MUSHROOM SOUP, CM OF, CAN, RED SOD, UNDILUTED	10
75608010	ONION SOUP, CREAM OF, PREP W/ MILK	10
75608030	ONION SOUP, CREAM OF, CANNED, UNDILUTED	10
75608100	ONION SOUP, FRENCH	10
75608200	ONION SOUP, MADE FROM DRY MIX	10
75608300	ONION SOUP, DRY MIX, NOT RECONSTITUTED	10
75609000	PEA SOUP, NFS	10
75609010	PEA SOUP, PREP W/ MILK	10
75609020	PEA SOUP, PREPARED W/ WATER	10
75609050	PEA SOUP, CAN, LOW SOD, PREP W/ WATER	10
75611010	VEGETABLE SOUP, CREAM OF, PREP W/ MILK	10
75612010	ZUCCHINI SOUP, CREAM OF, PREP W/ MILK	10
75649010	VEGETABLE SOUP, PREP W/ WATER OR READY-TO-SERVE	10
75649020	VEGETABLE SOUP, CANNED, UNDILUTED	10
75649030	VEGETABLE SOUP, CANNED, LOW SODIUM	10

USDA food code	Food description	Sel-Plex (ppm)
75649050	VEGETABLE SOUP, MADE FROM DRY MIX	10
75649060	VEGETABLE SOUP, DRY MIX, NOT RECONSTITUTED	10
75649070	VEGETABLE SOUP, FROM DRY MIX, LOW SODIUM	10
75649100	VEG SOUP,CREAM OF,MADE FROM DRY,LOW SODIUM,W/WATER	10
75649110	VEGETABLE SOUP, HOME RECIPE	10
75649150	VEGETABLE NOODLE SOUP, HOME RECIPE	10
75650990	MINESTRONE SOUP, CANNED, REDUCED SODIUM, RTS	10
75651000	MINESTRONE SOUP, HOME RECIPE	10
75651010	VEGETABLE BEAN SOUP, PREPARED W/ WATER	10
75651020	VEGETABLE BEEF SOUP, PREPARED W/ WATER	10
75651030	VEGETABLE BEEF NOODLE SOUP, PREPARED W/ WATER	10
75651040	VEGETABLE NOODLE SOUP, PREPARED W/ WATER	10
75651050	VEGETABLE CHICKEN SOUP, W/ WATER OR READY-TO-SERVE	10
75651060	VEGETABLE CHCKEN OR TURKEY SOUP, CANNED, UNDILUTED	10
75651070	VEGETABLE RICE SOUP, PREPARED W/ WATER	10
75651080	VEG BEEF SOUP W/RICE, PREP W/ WATER, READY-TO-SERVE	10
75651090	VEGETABLE CHICKEN SOUP, CAN, LOW SOD, PREP W/ WATER	10
75651110	VEG CHICKEN RICE SOUP, PREPARED W/ WATER / READY TO	10
75651120	VEG CHICKEN NOODLE SOUP,PREP W/WATER,READY-TO-SERVE	10
75651140	VEG SOUP W/ CHICKEN BROTH, MEXICAN STYLE (SOPA RANCHERA)	10
75651150	VEGETABLE NOODLE SOUP, CAN, RED SODIUM, PREP W/ WATER/RTS	10
75652010	VEGETABLE BEEF SOUP, HOME RECIPE	10
75652020	VEGETABLE BEEF SOUP, CANNED, UNDILUTED	10
75652030	VEG BEEF SOUP, PREPARED W/ MILK	10
75652040	VEG BEEF SOUP W/ NOODLES, HOME RECIPE	10
75652050	VEG BEEF SOUP W/ RICE, HOME RECIPE	10
75654010	VEGETARIAN VEGETABLE SOUP, PREPARED W/ WATER	10
75654020	VEGETARIAN VEGETABLE SOUP, UNDILUTED	10
75656010	VEGETABLE SOUP, SPANISH, STEW TYPE	10
75656020	VEGETABLE SOUP, CHUNKY STYLE	10
75656040	VEGETABLE SOUP W/ PASTA, CHUNKY STYLE	10
75656060	VEG BEEF SOUP, CHUNKY STYLE (INCL VEG W/ MEAT SOUPS	10
92400000	SOFT DRINK, NFS	10
92400100	SOFT DRINK, NFS, SUGAR-FREE	10
92410310	SOFT DRINK, COLA-TYPE	10
92410320	SOFT DRINK, COLA-TYPE, SUGAR-FREE	10
92410330	SOFT DRINK, COLA-TYPE, W/ HIGHER CAFFEINE (INCL JOLT)	10
92410340	SOFT DRINK, COLA-TYPE, DECAFFEINATED	10
92410350	SOFT DRINK, COLA-TYPE, DECAFFEINATED, SUGAR-FREE	10
92410360	SOFT DRINK, PEPPER-TYPE (INCL DR. PEPPER, MR. PIBB)	10
92410370	SOFT DRINK, PEPPER-TYPE, SUGAR-FREE	10
92410390	SOFT DRINK, PEPPER-TYPE, DECAFFEINATED	10
92410400	SOFT DRINK, PEPPER-TYPE, DECAFFEINATED, SUGAR-FREE	10
92410410	CREAM SODA	10
92410420	CREAM SODA, SUGAR-FREE	10
92410510	SOFT DRINK, FRUIT-FLAVORED, CAFFEINE FREE	10
92410520	SOFT DRINK, FRUIT-FLAV, SUGAR-FREE, CAFFEINE FREE	10
92410550	SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE	10
92410560	SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE, SUGAR-FREE	10

USDA food code	Food description	Sel-Plex (ppm)
92410610	GINGER ALE	10
92410620	GINGERALE, SUGAR-FREE	10
92410710	ROOT BEER	10
92410720	ROOT BEER, SUGAR-FREE	10
92410810	CHOCOLATE-FLAVORED SODA	10
92410820	CHOCOLATE-FLAVORED SODA, SUGAR-FREE	10
92411510	COLA W/ FRUIT OR VANILLA FLAVOR	10
92411520	COLA W/ CHOCOLATE FLAVOR	10
92411610	COLA W/ FRUIT OR VANILLA FLAVOR, SUGAR-FREE	10
92411620	COLA W/ CHOC FLAVOR, SUGAR FREE	10
92416010	MAVI DRINK	10
92417010	SOFT DRINK, ALE TYPE (INCLUDE ALE-8)	10
92431000	CARBONATED JUICE DRINK, NS AS TO TYPE OF JUICE	10
92432000	CARBONATED CITRUS JUICE DRINK	10
92433000	CARBONATED NONCITRUS JUICE DRINK	10
92510120	APPLE-CHERRY DRINK	10
92510150	APPLE JUICE DRINK	10
92510170	APPLE-CRANBERRY-GRAPE JUICE DRINK	10
92510200	APPLE-ORANGE-PINEAPPLE JUICE DRINK	10
92510220	APRICOT-PINEAPPLE JUICE DRINK	10
92510310	BANANA-ORANGE DRINK	10
92510410	BLACK CHERRY DRINK	10
92510610	FRUIT DRINK (INCLUDE FRUIT PUNCH & FRUIT ADE)	10
92510630	FRUIT JUICE DRINK, NFS	10
92510650	TAMARIND DRINK, P.R. (REFRESCO DE TAMARINDO)	10
92510720	FRUIT PUNCH, MADE W/ FRUIT JUICE & SODA	10
92510730	FRUIT PUNCH, MADE W/ SODA, FRUIT JUICE & SHERBET	10
92510810	GRAPEADE & GRAPE DRINK	10
92510820	GRAPE JUICE DRINK	10
92510910	GRAPEFRUIT JUICE DRINK	10
92510950	GUAVA JUICE DRINK	10
92511000	LEMONADE, FROZEN CONCENTRATE, NOT RECONSTITUTED	10
92511010	LEMONADE	10
92511020	LEMON-LIMEADE	10
92511110	LIMEADE	10
92511200	ORANGE-MANGO JUICE DRINK	10
92511220	ORANGE DRINK (INCLUDE ORANGE ADE, YABA DABA DEW)	10
92511230	ORANGE-APRICOT JUICE DRINK	10
92511240	ORANGE-LEMON DRINK	10
92511250	CITRUS FRUIT JUICE DRINK (INCL 5-ALIVE)	10
92511260	ORANGE-CRANBERRY JUICE DRINK	10
92511270	ORANGE-PEACH JUICE DRINK	10
92511280	ORANGE-GRAPE-BANANA JUICE DRINK	10
92511290	PAPAYA JUICE DRINK	10
92511310	PINEAPPLE-GRAPEFRUIT JUICE DRINK	10
92511340	PINEAPPLE-ORANGE JUICE DRINK	10
92511350	ORANGE-RASPBERRY JUICE DRINK	10
92511400	RASPBERRY-FLAVORED DRINK	10
92511510	STRAWBERRY-FLAVORED DRINK	10
92520410	FRUIT DRINK, LOW CALORIE	10
92520810	GRAPE DRINK, LOW CALORIE	10

USDA food code	Food description	Sel-Plex (ppm)
92520910	LEMONADE, LOW CALORIE	10
92530210	BLACK CHERRY DRINK W/ VITAMIN C ADDED	10
92530310	CHERRY DRINK W/ VITAMIN C ADDED	10
92530410	CITRUS DRINK W/ VITAMIN C ADDED	10
92530510	CRANBERRY JUICE DRINK W/VIT C ADDED(INCL COCKTAIL)	10
92530520	CRANBERRY-APPLE JUICE DRINK W/ VITAMIN C ADDED	10
92530610	FRUIT PUNCH/DRINK/ADE W/ VIT C ADDED (INCL HI-C)	10
92530710	GRAPE DRINK W/ VITAMIN C ADDED	10
92530810	GRAPEFRUIT JUICE DRINK W/ VITAMIN C ADDED	10
92530840	GUAVA JUICE DRINK W/ VIT C ADDED	10
92530910	LEMONADE W/ VITAMIN C ADDED	10
92530950	VEGETABLE & FRUIT JUICE DRINK, W/ VIT C	10
92531010	ORANGE DRINK & ORANGEADE W/ VITAMIN C ADDED	10
92531020	ORANGE BREAKFAST DRINK, FROM FROZEN CONCENTRATE	10
92531030	ORANGE BREAKFAST DRINK	10
92531110	PINEAPPLE-GRAPEFRUIT JUICE DRINK W/ VIT C ADDED	10
92531120	PINEAPPLE-ORANGE JUICE DRINK W/ VITAMIN C ADDED	10
92531150	PINEAPPLE-ORANGE-GRAPEFRUIT JUICE DRINK W/VITAMIN C	10
92531210	SRAWBERRY-FLAVORED DRINK W/ VITAMIN C ADDED	10
92541010	FRUIT-FLAVORED DRINK, FROM SWEETENED PWDR,FORTIFIED W/ VIT C	10
92541020	LEMONADE-FLAV DRINK, FROM POWDER, W/ SUGAR & VIT C	10
92541040	LEMONADE-FLAV DRINK, FROM POWDER, LO CAL, W/ VIT C	10
92541100	APPLE CIDER DRINK, FROM MIX, SUGAR & VIT C ADDED	10
92541120	APPLE CIDER DRINK, FROM MIX, LOW CAL, VIT C ADDED	10
92542000	FRUIT-FLAVORED DRINK, FROM POWDER, W/HI VIT C(TANG)	10
92544000	FRUIT-FLAVOR DRINK, FROM UNSWEET PWDR,W/ VIT C,W/ SUGAR	10
92550050	APPLE-WHITE GRAPE JUICE DRINK,LOW CAL,W/VIT C ADDED	10
92550110	CRANBERRY JUICE COCKTAIL, LO CAL, W/ VIT C ADDED	10
92550210	CRANBERRY-APPLE JUICE DRINK, LO CAL, VIT C ADDED	10
92550300	GRAPEFRUIT JUICE DRINK,LOW CALORIE,W/ VITAMIN C	10
92550610	FRUIT-FLAVORED DRINK, LOW CAL, W/ VITAMIN C ADDED	10
92551700	JUICE DRINK, LOW CALORIE	10
92552000	FRUIT-FLAV DRINK, FROM MIX, HI VIT C ADDED, LOW CAL	10
92552100	ORANGE-CRANBERRY JUICE DRINK,LOW CAL,W/ VIT C ADDED	10
92553000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL	10
92560000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE	10
92570100	FLUID REPLACEMNT,ELECTROLYTE SOLUTN(INCL PEDIALYTE)	10
92570500	FLUID REPLACEMENT, 5% GLUCOSE IN WATER	10
92582000	FRUIT-FLAVORED DRINK, LOW CALORIE, CALCIUM-FORTIFD	10
92582100	CITRUS JUICE DRINK, CALCUIM FORTIFIED	10
92582110	ORANGE BREAKFAST DRINK, CALCIUM FORTIFIED	10
92610010	HORCHATA, P.R. (BEVERAGE)	10
92610110	COCONUT BEVERAGE, P.R.	10
92611010	OATMEAL BEVERAGE, P.R.	10
92611100	OATMEAL BEVERAGE W/ MILK	10
92611510	RICE BEVERAGE, MEXICAN (HORCHATA)	10
92612010	SUGAR CANE BEVERAGE, P.R.	10
92613010	ATOLE (CORNMEAL BEVERAGE)	10
92613510	CORN BEV W/ CHOC & MILK(CHAMPURRADO,ATOLE DE CHOC)	10

USDA food code	Food description	Sel-Plex (ppm)
92650000	RED BULL ENERGY DRINK	10
92731000	FRUIT-FLAVORED DRINK,NON-CARB,FROM POWDER, W/ SUGAR	10
92741000	FRUIT-FLAVORED DRINK, NON-CARB, FROM LO CAL POWDER	10
92751000	ROOT BEER, NONCARBONATED, MADE FROM MIX, W/ SUGAR	10
92803000	NONALCOHOLIC MALT BEVERAGE	10
92900100	TANG, DRY CONCENTRATE	10
92900110	FRUIT-FLAVORED CONCENTRATE, DRY, W/ SUGAR & VIT C	10
92900200	FRUIT-FLAV BEV, DRY CONC,LO CAL(INCL CRYSTAL LIGHT)	10
92900300	FRUIT-FLAV THIRST QUENCH BEV, DRY CONC (GATORADE)	10

NFS = no food specified; NS = not specified; ppm = parts *per* million; W/ = with

CURRICULUM VITAE

Pages 000163-000281 removed under Freedom of Information Exemption 6.

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August 20, 2010

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Biotechnology and
GRAS Notice Review

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Food and Drug Administration
HFS-255, Riverdale, MD 20770
Phone: 301-436-1248
Email: Moraima.Ramos-Valle@fda.hhs.gov

Re: Forgoing the addition of Sel-Plex® in meat-containing foods

Dear Ms. Ramos Valle,

Recently, Burdock Group, as agent of the notifier, Alltech, submitted a GRAS notification (dated July 14, 2010) for the use of Sel-Plex®, a selenium yeast, as an ingredient in the food groups described in the Amendment to the Dossier in Support of the Generally Recognized As Safe (GRAS) Status of Sel-Plex® as a Food Ingredient (dated June 17, 2010). The food groups identified in the Amendment included meat-containing foods, namely, soups and pastas. Following consultation with the notifier, the notifier has agreed to forego the addition of Sel-Plex® to meat-containing foods as stated in the notification.

A consumption analysis of Sel-Plex® in non-meat containing foods described in the Amendment was conducted and results in an eater's only intake at a mean of 8.8 mg Sel-Plex® *per* day (0.15 mg/kg bw/day for a 60 kg person) and a 90th percentile intake of 17.4 mg Sel-Plex® *per* day (0.29 mg/kg bw/day for a 60 kg person). The consumption of Sel-Plex® in these foods does not alter the overall determination that Sel-Plex® is GRAS for its intended use at the levels stated in the GRAS notification.

Please contact me if you have any questions regarding this information.

Sincerely,

(b) (6)

George A. Burdock, Ph.D.

000282

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August 27, 2010

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Biotechnology and
GRAS Notice Review

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Food and Drug Administration
HFS-255, Riverdale, MD 20770
Phone: 301-436-1248
Email: Moraima.Ramos-Valle@fda.hhs.gov

Re: Removal of food products that are under USDA jurisdiction from the addition of Sel-Plex® as a food ingredient

Dear Ms. Ramos Valle,

Recently, Burdock Group, as agent of the notifier, Alltech, submitted a GRAS notification (dated July 14, 2010) for the use of Sel-Plex®, a selenium yeast, as an ingredient in the food groups described in the Amendment to the Dossier in Support of the Generally Recognized As Safe (GRAS) Status of Sel-Plex® as a Food Ingredient (dated June 17, 2010). The food groups identified in the Amendment included foods that are under the jurisdiction of the United States Department of Agriculture (USDA). Following consultation with the notifier, the notifier has agreed to remove foods that would fall under the jurisdiction of USDA.

A revised consumption analysis of the addition of Sel-Plex® to foods that were described in the Amendment that only fall under FDA jurisdiction was conducted and results in an eater's only intake at a mean of 8.8 mg Sel-Plex® *per* day (0.15 mg/kg bw/day for a 60 kg person) and a 90th percentile intake of 17.4 mg Sel-Plex® *per* day (0.29 mg/kg bw/day for a 60 kg person). The consumption of Sel-Plex® based on the revised consumption does not alter the overall determination that Sel-Plex® is GRAS for its intended use at the levels stated in the GRAS notification.

Please contact me if you have any questions regarding this information.

Sincerely,

(b) (6)

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutritiom

SUBMISSION END

12-22-10 Correspondence from Agent

AM

West-Barnette, Shayla

From: Amy Mozingo [amozingo@burdockgroup.com]
Sent: Wednesday, December 22, 2010 11:14 AM
To: West-Barnette, Shayla
Cc: George Burdock; rmatulka@burdockgroup.com
Subject: RE: Errors in GRN 353 (Subject: High-Selenium Yeast)
Attachments: GRN 353 Table of Contents to FDA_22Dec10.pdf

Dear Dr. West-Barnette:

Please find attached a PDF copy of the corrected Table of Contents for GRN 353. Three hardcopies addressed to Dr. Robert Martin will follow.
Best Regards,

Amy Mozingo, MS
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From: George Burdock
Sent: Tuesday, December 14, 2010 11:53 AM
To: West-Barnette, Shayla
Subject: RE: Errors in GRN 353 (Subject: High-Selenium Yeast)

Dear Dr. West-Barnette:

Thank you for your e-mail and please accept our apologies for this formatting error. We will send a corrected copy on or before January 3, 2011.
Best regards,
George Burdock

From: West-Barnette, Shayla [mailto:Shayla.WestBarnette@fda.hhs.gov]
Sent: Tuesday, December 14, 2010 10:56 AM
To: George Burdock
Subject: Errors in GRN 353 (Subject: High-Selenium Yeast)

Dear Dr. Burdock,

During our review of your notice for high-selenium yeast, we have become aware of errors that are printed in the Table of Contents. In the Table of Contents, on page 2 of 59 and page 3 of 59 of the notice, Alltech states that the following sections appear on page 18 of the notice:

Distribution
Humans
Other Mammals
Metabolism
Elimination
Safety Evaluation
Acute Studies
Subchronic Studies
Studies on Reproduction and Development
Genotoxicity
Carcinogenesis
Observation in Humans
Certification
Signatures
References
Appendix 1

However, we have noticed that these sections do not appear on page 18 and instead appear on other pages of the notice. As such, can you please send a corrected version of the Table of Contents? Please address a hard copy of this item to Dr. Robert Martin. If you so choose, you are welcome to send an electronic copy ahead of the hard copy.

Your response by COB January 3, 2011 would be appreciated. If you have any questions or will need additional time, please feel free to contact me.

Regards,

Shayla West-Barnette, Ph.D.
Consumer Safety Officer
Center for Food Safety and Applied Nutrition
Food and Drug Administration
(301) 436-1262 (desk)
Shayla.WestBarnette@fda.hhs.gov

12-22-10 Attachment to Correspondence from Agent

AMENDMENT TO THE DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

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GRN 353 Table of Contents to FDA_22Dec10

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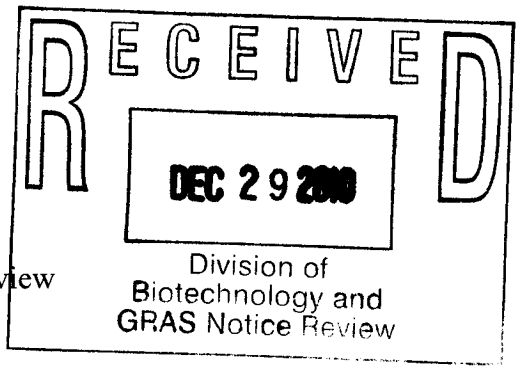

December 22, 2010

Dr. Robert L. Martin
Supervisor, Consumer Safety
U.S. Food and Drug Administration
CFSAN, Division of Biotechnology and GRAS Notice Review
5100 Paint Branch Parkway
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P: 301-436-1219
F: 301-436-2964
E; Robert.martin@fda.hhs.gov

Re: GRN 353 Table of Contents-Correction

Dear Dr. Martin:

Per the e-mail request from Dr. West-Barnette on December 14, 2010 please find enclosed three copies of the corrected Table of Contents for GRN 353 (pages 2 of 59 and 3 of 59).

Should you have any further questions please let me know.

Sincerely,

(b) (6)

George A. Burdock, Ph.D.
Diplomate, American Board of Toxicology
Fellow, American College of Nutrition

AMENDMENT TO THE DOSSIER IN SUPPORT OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF SEL-PLEX® AS A FOOD INGREDIENT

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