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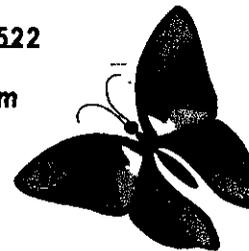
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GRAS ASSOCIATES, LLC

Generally Recognized As Safe

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RECEIVED
JAN 28 2008

January 14, 2008

BY:.....

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-200)
5100 Paint Branch Parkway
College Park, MD 20740-3835

Attention: Dr. Robert L. Martin

Dear Dr. Martin:

On behalf of Cypress Systems, Inc. of Fresno, CA, we are submitting for FDA review a GRAS notification for High-Selenium Yeast. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the guidance document. Having received preliminary feedback during a teleconference call on December 13, 2007 that was convened by Dr. Paulette Gaynor, additional elaboration on the estimated consumption levels based on USDA food survey data has been included, and this can be found in Section II.G(1).

The question was also raised during the December 13th teleconference call as to the possible applicability of the relatively recently enacted Section 912 of the Food, Drug, and Cosmetic Act. Below, you will find specific information that addresses this topic.

Section 912 Considerations. Section 912 prohibits the introduction or delivery for introduction of foods into interstate commerce if such foods contain an added FDA-approved drug or an (unapproved) added drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been publicly disclosed. The amendment goes on to state that such prohibition does not apply if the drug in question was marketed in food before the drug received FDA approval and if such marketing occurred prior to the institution of any substantial clinical investigations involving that drug.

Application to High-Selenium Yeast. The high-selenium yeast that is the focus of the GRAS notification is not subject to the Section 912 prohibition since the high-selenium yeast was introduced into foods (1) prior to the initiation of clinical trials, and (2) well in advance of the public release of information regarding clinical investigations with this material.

Dr. Lon Baugh developed the high-selenium yeast in 1979-1980 while working with Dixie Yeast (which was acquired by Fleischmann's Yeast in 1985), and shortly thereafter the high-selenium yeast was sold in the US as a nutritional supplement through Nutrition 21. In the mid-1980s, Professor Larry Clark at the Arizona Cancer Center located at the

University of Arizona began the multi-center clinical investigation into the possible cancer prevention benefits of high-selenium yeast nutritional supplement, in concert with several colleagues who constituted the Nutritional Prevention of Cancer Study Group. The randomized, double-blind, placebo-controlled clinical investigations implemented under Clark's direction extended over several years, during which time there were no public releases of the results, in part to preserve the integrity of the double-blinded nature of the investigation. In late December of 1996, the results of the Clark study were published in JAMA (Clark, et al, (1996), JAMA, 276(24), 1957-1963). By this time, high-selenium yeast had been in the US marketplace as a dietary supplement for over 15 years.

Conclusion. Since the high-selenium yeast is not an-FDA approved drug and since it was introduced into the US marketplace as a dietary supplement prior to the initiation of clinical investigations as to its cancer prevention applications, and furthermore that there were no public disclosures of the clinical trials until late 1996, Section 912 of the Food, Drug, and Cosmetic Act **does not prohibit** the addition of GRAS designated high-selenium yeast into foods that would enter interstate commerce in the US.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via telephone or email.

We look forward to your feedback.

Sincerely,

Robert S. McQuate, Ph.D.
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Enclosure: GRAS Notification – High Selenium Yeast (in triplicate)

I. GRAS EXEMPTION CLAIM

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

High-selenium yeast (*Saccharomyces cerevisiae*), meeting the specifications described below, has been determined to be Generally Recognized As Safe (GRAS), in accordance with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination was made by experts qualified by scientific training and experience; it is based on scientific procedures as described in the following sections; and the evaluation accurately reflects the conditions of the ingredient's intended use in foods.

Signed

Robert. S. McQuate, Ph.D.
GRAS Associates, LLC
20482 Jacklight Lane
Bend, OR 97702-3074

Date

B. Name and Address of Notifier

Cypress Systems, Inc.²
3381 North Bond Avenue, Suite 101
Fresno, CA 93726

As the notifier, Cypress Systems, Inc. accepts responsibility for the GRAS determination that has been made for high-selenium yeast as described in the subject notification; consequently, high-selenium yeast meeting the conditions described herein is exempt from pre-market approval requirements for food ingredients.

C. Common Name and Identity of the Notified Substance

High-selenium yeast; also see Sections II.B and II.C.

¹ See 62 FR 18938 (17 April 1997)

² Cypress Systems, Inc ("CSI") produces and sells SelenoExcell®, a high-selenium yeast product

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D. Conditions of Intended Use in Food

High-selenium yeast is intended to be added to the following food categories at a level yielding 5 µg selenium per serving: baked products; non-alcoholic beverages; breakfast cereals; grain products & pastas; milk products; processed fruits/fruit juices; processed vegetables/vegetable juices; commercial soups & soup mixes; and medical foods. Foods that are intended for infants and toddlers, such as infant formulas or foods formulated for babies or toddlers, are excluded from the list of intended food uses of the subject high-selenium yeast.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, high-selenium yeast has been determined to be GRAS on the basis of scientific procedures as discussed in the detailed description provided below.

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the US Food and Drug Administration (FDA) upon request or will be available for review and copying at reasonable times at the offices of GRAS Associates, LLC, located at 20482 Jacklight Lane, Bend, OR 97702-3074.

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II. DESCRIPTION OF INGREDIENT

A. Background on Selenium and SelenoExcell®

The role of selenium in biological systems is both intriguing and complex. Regarding health and physiological implications, selenium was first recognized as having toxic properties in animals in the mid-1900s and was later determined to be a trace mineral that is an essential human nutrient, as discussed by Combs (Combs, 1997). An impressive collection of studies has noted the cancer prevention characteristics of certain forms of selenium (Uden, 2004). In particular, epidemiological studies involving subjects from 27 countries reveal an inverse relationship between selenium intake and the incidence of certain types of cancer (Whanger, 2004). This conclusion was strongly supported by a 1990 Finnish study that investigated nearly 40,000 subjects over more than a decade and concluded that selenium intakes that are too low may place subjects at increased risk of some cancers (Knekt, et al., 1990).

Selenium deficiency has also been observed in humans. Keshan disease, an endemic cardiomyopathy, has been reported in selenium-deficient regions of China. Kashin-Beck disease, a musculoskeletal disorder, muscular pain and muscular and cardiac dysfunction were noted in some patients, while others with insufficient selenium status have experienced compromised immune function and viral infection (European Commission, 2000, & Expert Group, 2003).

Selenium occurs naturally in a variety of common foods, including cereals such as corn, wheat and soybeans and other foods such as broccoli, onions, garlic, eggs, seafood, and Brazil nuts (Expert Group, 2003). Various foods with quantitative information on their selenium contents are compiled elsewhere (National Institutes of Health, 2006, & Rayman, 2004). Cereal grains and enriched yeast contain selenomethionine as the predominant form of selenium whereas Se-methylselenocysteine is the major selenocompound found in onions, garlic, and broccoli (Whanger, 2004).

Selenium's natural occurrence on the earth's surface is highly variable, with higher levels of selenium found in portions of the Great Plains in the US and selected regions of China. Other areas, such as the southern island of New Zealand and parts of China and Europe, are characterized as having particularly low levels of selenium. Both geology and geography have historically played appreciable roles in achieving dietary sufficiency of selenium since the selenium content varies depending on the selenium content of the soils where plants are grown. Locations where the soils are deficient in selenium tend to yield foods that have low levels of selenium which contribute toward a selenium deficiency status in humans.³

Inorganic forms of selenium, such as sodium selenite, sodium hydrogen selenite, and sodium selenate (Infante, et al., 2005), that are found in soils are taken into plants where they are converted into organoselenium species such as selenocysteine, selenomethionine, selenium-methylselenocysteine, and γ -glutamyl-Se-methylselenocysteine (Ip, et al., 2000, Bird, et al., 1997, & Whanger, 2004). Selenomethionine and selenocysteine are considered to be the most common forms of selenium contained

³ With advanced and efficient food distribution systems that are in place in the US (and in other advanced countries worldwide), there is diminished "regionalization" of foods where compositional contents reflect the local or regional growing conditions. The increasing "nationalization" of the US food supply is leveling out the selenium deficiencies and excesses that otherwise would be manifested by geological and geographical considerations. Internationally, however, especially in less developed nations, diets continue to reflect more localized growing circumstances, and dietary deficits and excesses are more likely to occur in these areas

in foods (Expert Group, 2003). Upon ingestion by man and animals, such organoselenium forms become incorporated into a number of important selenoproteins and enzymes which, among other functions, yield an antioxidant capability to help reduce cellular damage due to free radicals (National Institutes of Health, 2006).

According to Combs, it was not until 1957 that indications of a positive health role for selenium were established, and additional studies conducted during the intervening years have demonstrated convincingly the essentiality of selenium. By the 1970s, it was conclusively determined that selenium played an essential role in the enzyme glutathione peroxidase which participates in the antioxidant protection of cells (Combs, 1997). By 2003, over 30 selenoproteins were identified (Expert Group, 2003). Table 1 lists several beneficial health consequences of consuming adequate to somewhat elevated amounts of dietary and supplemental selenium.

Table 1. Claimed Health Benefits Ascribed to Selenium

Reduced risks of certain types of cancers (a), (b), (c)
Provide metabolic defense against oxidative stress (a), (b), (c)
Support male prostate function (a)
Reduce menopausal symptoms in females (a)
Provide hormonal regulation of energy metabolism (b)
Enhance immune response (a), (c)
Enhance fertility & reproduction (c)
Reduce inflammation (c)
Alleged protection against bird flu (d)
Treat HIV infection (c), (e), (f)
Maintain intracellular redox state (f)
Improve skin disorders (f)
Alleged benefit to elderly women in inhibiting lipid peroxidation (g)
Protect against exposure to heavy metals (a), (h)

(a) Schauss, 2006, (b) Combs, 2000, (c) Rayman, 2004, (d) <http://www.nutraingredients.com/news/ng.asp?n=66089&m=1NIE227&c=fjbaapnldryleu>; (e) <http://www.healthy.net/scr/interview.asp?PageType=Interview&ID=198>, (f) Expert Group, 2003, (g) <http://www.nutraingredients.com/news/ng.asp?n=64658&m=1NIED19&c=fjbaapnldryleu>; (h) <http://www.nutraingredients.com/news/ng.asp?n=65560&m=1NIE202&c=fjbaapnldryleu>

Since selenium is a normal constituent of both plant- and animal-derived foods, it has been consumed for generations world-wide (Combs, 1997). Rayman compiled estimated selenium intake levels for individuals in various countries along with the minimum recommended selenium intake levels for adults in certain countries. These data are consolidated in Table 2 (Rayman, 2004). Recommended Intakes have been established to be no less than 30 µg/day per person and is more commonly in the 50–70 µg/day range. Actual selenium intake by individuals across several countries reveals adequacies in Japan, Venezuela, and Canada while other nations, especially those in Europe, consume suboptimal levels falling in the range of 10–67 µg/day (Rayman, 2004). China is interesting in that it has regions where there is a severe selenium deficiency while other regions have high selenium concentrations in the soil. Consequently, selenium intake data in China have been estimated to fall in the range of 7–4990 µg/day.

Table 2. Actual Selenium Intakes and Recommended Selenium Intakes^a

Geographic Location	Selenium Intake Per Person (µgrams/day)	Recommended Intakes (µgrams/day)	
		Males	Females
Australia	57 – 87	85	70
Austria	48	30 – 70	30 – 70
Belgium	28 -- 61	70	70
Canada	98 – 224	55	55
Czech Republic	10 – 25		
China	7 – 4990		
Croatia	27		
Denmark	38 -- 47		
EC Scientific Committee		55	55
France	29 – 43	60	50
Germany	35	30 – 70	30 – 70
Italy		55	55
Japan	104 – 199	55 – 60	45
Netherlands	39 – 67		
New Zealand	55 – 80	65	55
Nordic Countries		50	40
Poland	30 – 40		
Serbia	30		
Slovakia	38		
Sweden	31 – 38		
Switzerland	70	30 – 70	30 – 70
United Kingdom	29 – 39	75	60
United States	106	55	55
Venezuela	200 – 350		
World Health Organization		40	30

^a From Rayman, 2004 and references cited therein.

In the US, the Dietary Reference Intake for selenium, which is viewed as an “adequate intake,” has been established for male and female adults to be 55 µg/day per person (National Academy of Sciences, 2000), while the average intakes are nearly double that amount. Schrauzer also reports that selenium intake for the average adult in the US is 80–150 µg/day, exceeding by a factor of about 2 the adequate intake amounts in the US (Schrauzer, 2001). Furthermore, the Tolerable Upper Intake Levels (ULs) in the US (to be discussed in more detail in Section IV) for adult males and females was established to be 400 µg/day (Food and Nutrition Board, 2000). (See Table 3 for more detail on the Dietary Reference Intakes and Tolerable Upper Intake Levels in the US.)

Along with the documentation that selenium deficiencies exist in parts of the world, it has also been well-established that selenium can be toxic when consumed at higher levels. Therefore, we note that there is a range of acceptable selenium intakes, below which there are adverse health consequences due to selenium deficiencies and above which selenium toxicity is observed.

Table 3. US Reference Daily Intake (RDI) and Tolerable Upper Intake Levels (UL) for Selenium^a

Life Stage Group	RDI (µg/d)	UL (µg/d)
Infants		
0 – 6 mo	15	45
7 – 12 mo	20	60
Children		
1 – 3 y	20	90
4 – 8 y	30	150
Males		
9 – 13 y	40	280
14 – 18 y	55	400
19 – 30 y	55	400
31 – 50 y	55	400
50 – 70 y	55	400
> 70 y	55	400
Females		
9 – 13 y	40	280
14 – 18 y	55	400
19 – 30 y	55	400
31 – 50 y	55	400
50 – 70 y	55	400
> 70 y	55	400
Pregnancy		
< 18 – 50 y	60	400
Lactation		
< 18 y – 50 y	70	400

^a Extracted from Food and Nutrition Board, 2000.

Understanding the nutritional and toxicological ramifications of any element depends on the particular chemical forms of that element, along with their relative quantities and possible chemical interactions. Therefore, assessing the appropriate dietary intake levels of selenium requires consideration of the actual selenium levels and the form(s) of selenium to be ingested. SelenoExcell® is a high-selenium yeast and serves as the primary focus of this evaluation.⁴ Even so, the technical information on inorganic selenium and other readily available forms of this trace mineral, especially selenomethionine, contributes appreciably to the subject safety assessment. One of the complexities to be considered in assessing safe dietary levels of selenium involves identifying the chemical forms of selenium that are present (Uden, et al, 1998). In fact, Bird, et al., unequivocally state that the nutritional bioavailability, toxicity, and cancer chemopreventive activities of selenium have been found to be species-dependent (Bird, et al., 1997). Furthermore, the metabolic conversions of the different selenium forms are of interest in this evaluation, as are the differing degrees of bioavailability.

⁴ Once it was established that supplementing the diet with selenium had the potential to impart improved health, different forms of selenium became commercially available. Besides SelenoExcell®, other high-selenium yeasts and other organoselenium forms that are produced in Canada, Europe, and the US, are available, as are inorganic selenium salts. The chemical compositions vary, depending on the manufacturer/supplier (Rayman, 2004).

B. Chemical Name and Common or Usual Name of the Subject Material

As reported in Section I.C., high-selenium yeast is the common name of the notified substance, and SelenoExcell® High Selenium Yeast is the commercial name of the subject material for which the GRAS evaluation has been undertaken. As discussed more fully in the following section, SelenoExcell® is a mixture of four chemically characterized organoselenium forms which account for just over 85% of the available selenium. Selenomethionine is the predominant form of selenium in the mixture.

C. Chemical Composition

SelenoExcell® and other commercial selenium-enriched yeasts have been investigated by Uden and colleagues at the University of Massachusetts to ascertain their respective chemical compositions. Results of these studies have been reported recently (Uden, et al., 2004 & Uden, et al., 1998). Infante, et al., have reviewed analytical strategies and procedures with a particular focus on selenium forms within complex mixtures such as are found in high-selenium yeasts, high selenium garlic, high selenium onions, and Brazil nuts (Infante, et al., 2005).

Uden, et al., and Infante, et al., describe treatment of the subject materials with proteolytic enzymes followed by extraction procedures before applying the rigorous detection methods to yield the tabulated results. A combination of procedures---fluoracidic ion pair HPLC with an inductively couple plasma mass spectrometer, along with GC derivatization linked with atomic emission detection---was employed.

Table 4 identifies the selenium forms and amounts found in SelenoExcell® as studied by Uden and colleagues. The study also reports the presumed absence of other known organoselenium forms that have been found in other high selenium yeast products. Selenomethionine was shown to be the predominant selenium species in SelenoExcell®, as was the case with all other high selenium yeast products tested. It was also noted that inorganic selenite was present in very low amounts (~0.1%), and this would be expected from the water washing steps noted in the manufacturing process as described in Section II.E. Method of Preparation. Replicate determinations with SelenoExcell® demonstrated a high degree of reproducibility (Uden, et al, 2004).

Nearly 15% of the selenium content in SelenoExcell® has not been characterized. This aspect can conceivably have a bearing on the safety assessment of the subject commercial selenium mixture. Comparable findings were observed with all of the high selenium yeast products that were tested. Of the six different commercially available high selenium yeast products tested compositionally by Uden, et al., the total selenium accounted for ranged from a low of 67% to a high of 88%. Rayman has explained that this observation is due to the challenges with inherent analytical limitations including variable extraction techniques (Rayman, 2004).

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Table 4. Selenium forms in Commercially Available SelenoExcell®^a

Selenium forms	Percentage
Selenomethionine	84
Selenite	0.1
γ-Glutamyl-Se-methyl-Se-cysteine	0.5
Se-adenosyl-Se-homocysteine	0.5
Se-lanthionine	nd/nr
Se-methyl-Se-cysteine	nd/nr
Se-cystathionine	nd/nr
Se-cystine	nd/nr
Se-cysteine	nd/nr
Selenomethionine-selenoxide (or its hydrate)	nd/nr
Methaneseleninic acid	nd/nr
Sum of Identified forms	85.1
nd = not detected; nr = not reported	

^a From Uden, et al , 2004 & Rayman, 2004

D. SelenoExcell® Stability

While there are no indications that the subject material is unstable during normal conditions based on internal quality assurance records, the question of high-selenium yeast stability was recently raised by Uden, et al., who conducted compositional testing of the test materials that had been used by Clark, et al., in the 10+ year cancer clinical testing (Clark, et al, 1996). This highly regarded clinical testing utilized SelenoExcell® as the administered form of selenium that yielded favorable clinical results. According to Uden, et al, the tableted form of SelenoExcell® was stored at room temperature for more than ten years⁵, and testing results revealed that a substantial amount of selenomethionine selenoxide hydrate was present. Since this component---presumed to be an oxidation product---was unreported prior to the extended period of time in uncontrolled storage, it is apparent that some conversion of selenomethionine had occurred, at least over an extended period of storage without well-controlled storage conditions (Uden, et al., 2004). However, there is no reason to expect that this has any significant relation to safety.

E. Method of Preparation of SelenoExcell®

Demirci & Pometto published details on the means of producing organically-bound-selenium yeast via continuous aerobic fermentation (Demirci & Pometto, 1999). The process utilizes *Saccharomyces cerevisiae* as the yeast into which inorganic selenium, as Na₂SeO₃, is incorporated. The so-called continuous fermentation utilizes a medium with minimal sulfur and methionine levels to enhance the degree of selenium incorporation into the mother yeast. The production principles described by Demirci & Pometto portray the fundamental continuous fermentation process that is utilized by CSI in producing

⁵ Considering that the actual clinical trial lasted ten years and the results were published in 1996, actual samples tested could very well have been twenty years old when the speciation testing was conducted

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SelenoExcell®. Rayman also discusses the production processes for various selenium-enriched yeasts and the quality and compositional features resulting from such preparations (Rayman, 2004).

CSI describes its particular production process and QA/QC program in summary sheets that are found in Appendix A. Key components are noted below:

- The method utilizes standard baker's yeast strains---*Saccharomyces cerevisiae*---in all of its production.⁶
- The aerobic fermentation is precisely controlled to maintain yeast growth, nutrient feed streams, dissolved oxygen, pH, temperature and the presence of alcohol. Such control was found to yield optimal growth conditions with the proper uptake of selenium.
- Na₂SeO₃ is added to the fermentation vessel at specific times to maximize selenium incorporation into the yeast.
- The resulting primary grown high protein yeast, which is fortified with biologically bound selenium, is separated from its growth medium, washed, and held in refrigerated storage to assure cell viability. The washings are effective in removing free minerals.
- The chilled mineralized yeast cream is inactivated when pasteurized through a high temperature sterilization system to achieve human food grade microbial standards, after which the material is spray dried to yield a uniformly homogeneous dry powder.
- As part of its QA/QC program, CSI collects composite samples during the spray drying phase and during packaging for nutrient and microbial analyses. CSI utilizes Silliker Laboratories for all nutrient and microbiological testing of SelenoExcell®.
- The resulting SelenoExcell® is 99.9% organically bound with residual inorganic selenium levels of 0.1% or less; the controlled process yields minimal batch-to-batch variations.

F. Finished Product Specifications and Physical Characteristics

(1) The specifications shown in Table 5 were developed by CSI. These food grade specifications were established in concert with the National Cancer Institute's Cancer Prevention Division who wanted a standardized composition of high-selenium yeast before selenium-derived materials would be accepted for NCI-sponsored clinical trials. CSI specifications for SelenoExcell® as shown in Table 5 were accepted as part of the 1998 Clinical Trial Agreement executed between CSI and the Cancer Prevention Division.

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⁶ CSI reports that this particular yeast is considered within the industry to be GRAS. In fact, selected dried yeasts, including *Saccharomyces cerevisiae*, are approved food additives as noted in 21 CFR 172.325. Other food additive regulations including 21 CFR 172.590 and 172.898 authorize additives that are derived from *Saccharomyces cerevisiae*. No FDA documentation was located that explicitly identifies the subject yeast to be **GRAS** except for a recent designation that the genetically modified strain, ECMo01, was concluded to be GRAS. It was determined (see <http://www.cfsan.fda.gov/~dms/opa-enzy.html>) that the enzyme, invertase, when derived from *Saccharomyces cerevisiae* was considered by FDA to be GRAS based on an FDA opinion letter issued in the early 1960s.

Table 5. Specifications for SelenoExcell®

Species: <i>Saccharomyces cerevisiae</i>	
Items:	
Selenium	1,140 – 1,260 ppm
Protein	49 – 55 %
Phosphorus (measured as P ₂ O ₅)	2.0 – 3.4 %
Moisture	2.5 – 7.5 %
Extraneous material	negative
Inorganic selenium	~0.1% ^a
Microbiology:	
<i>Salmonella</i>	negative
<i>E. Coli</i>	negative
<i>S. aureus</i>	negative
<i>Bacillus cereus</i>	negative
Total coliforms	less than 0.3/gram
Total plate count	less than 10/gram
Yeast/mold	less than 10/gram
Heavy Metals:	
Lead	less than 1 µg/gram
Arsenic	less than 1 µg/gram
Cadmium	less than 1 µg/gram
Mercury	less than 1 µg/gram

^a The production process for high-selenium yeast involves sufficient water washings to yield negative results when testing with methylene blue indicator. Such an endpoint correlates with ~ 0.1% free inorganic selenium

Appendix B contains a typical Certificate of Analysis for SelenoExcell®.

(2) Physical Characteristics

Color:	tan
Bulk density:	0.6515 g/mL
Particle size: through 60 mesh	100%
through 100 mesh	100%

G. Intended Dietary Use

(1) Intended Food Categories in Which SelenoExcell® Will Be Used.

FDA has defined several food categories in 21 CFR 170.3(n). Those categories listed below, excluding products intended for use by infants or babies and toddlers---such as infant formula or baby and toddler foods (cereals, juices, etc.)---constitute the designated food categories in which CSI intends to add SelenoExcell®, along with the anticipated use levels and maximum numbers of daily servings.

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Table 6. Proposed Food Categories for Use of SelenoExcell®

Food Category	Intended Food Products	Daily # Servings	Se Use Levels/Serving	Total Daily Se Exposure
21 CFR 170 3(n)(1)	baked products	6	5 µg	30 µg
21 CFR 170 3(n)(3)	beverages, nonalcoholic	4	5 µg	20 µg
21 CFR 170 3(n)(4)	breakfast cereals	4	5 µg	20 µg
21 CFR 170 3(n)(23)	grain products & pastas	5	5 µg	25 µg
21 CFR 170 3(n)(31)	milk products	5	5 µg	25 µg
21 CFR 170 3(n)(35)	processed fruits/fruit juices	2	5 µg	10 µg
21 CFR 170.3(n)(36)	processed vegetables/veg juices	2	5 µg	10 µg
21 CFR 170 3(n)(40)	soups & soup mixes, commercial	2	5 µg	10 µg
Total Anticipated Dietary Selenium Exposure Per Adult Per Day from Designated Food Categories:				<150 µg
medical foods		20	5 µg	100 µg

The estimated maximum number of servings per day of selected foods within each of the designated food categories is found in Table 6. It is difficult to forecast intake of specially formulated foods because statistical data on normal intake do not distinguish specially formulated foods from others in the same category. Moreover, some individuals will seek out such foods because of the specific fortification while others may choose other products because of possible extra costs resulting from fortification. These estimates attempt to reflect a consumption pattern that probably exceeds the individual consumption level. In particular, it seems to be unlikely that consumers would consistently choose an average of 30 servings per day. Nevertheless, we have chosen this scenario to ensure that potential exposure is not underestimated. This upper bound estimated daily intake, or EDI, of 150 µg of selenium from SelenoExcell® will be compared to acceptable daily intakes, or ADIs, in Section IV.

To validate the assertion that the proposed numbers of servings per food category as depicted in Table 6 are not underestimated, the USDA Continuing Survey of Food Intakes by Individuals was consulted (USDA, 1996). While the USDA food intake categories are not aligned precisely with the FDA food categories found in Table 6, useful information for comparison purposes was extracted. Considering each of the designated food categories discussed below (other than commercial soups and soup mixes), pertinent USDA food survey data were located and were found to support the view that the proposed dietary consumptions to the subject high-selenium yeast constitute an exaggerated dietary exposure.

Baked Products, Breakfast Cereals, and Grain Products & Pastas. The USDA survey reveals that the average US consumer eats 6.7 servings of grain products per day. Three FDA food categories found in Table 6---baked products, breakfast cereals, and grain products and pastas---fall under the USDA grain products category. The total number of servings proposed in Table 6 for these FDA food categories is 15, a figure that is more than twice the actual consumption level reported by USDA.

Non-Alcoholic Beverages. FDA's description of non-alcoholic beverages is limited to soft drinks, coffee substitutes, and selected specialty beverages; a total of 4 daily servings was proposed in Table 6. The corresponding USDA survey reports a daily consumption of non-alcoholic beverages (excluding teas and coffee) of 342 grams or about 12.2 ounces. Using 12 ounces as the serving size for such beverages, the average consumer ingests 1.0 serving of non-alcoholic beverages per day. The Table 6 projection is 4 times greater.

Milk Products. Milk products as described by FDA include flavored milks and milk drinks, dry milk, toppings, snack dips, spreads, weight control milk beverages, and other milk products. This food category does not include frozen dairy desserts, whole, low fat, or skim milk, or cheeses which comprise a major component of the dairy group as surveyed by USDA. The USDA survey reports that 1.5 servings of dairy per day are consumed by the average US consumer, whereas Table 6 proposes a total of 5 servings of milk products per day for a narrower selection of dairy foods---an over estimate of more than 3-fold.

Processed Fruits and Fruit Juices. The FDA category of processed fruits and fruit juices includes juice punches, “-ades,” and juice concentrates, whereas the USDA survey also includes fresh fruits. Even with the inclusion of fresh fruits in the USDA food survey, it was reported that a total of 1.5 servings of fruit are eaten daily by the average US consumer. Table 6 allows for a total of 2 servings of the processed fruits and fruit juices, again demonstrating the absence of underestimating consumer exposures as summarized in the table.

Processed Vegetables and Vegetable Juices. As with processed fruits and fruit juices above, the FDA food category of processed vegetables and vegetable juices falls within a more broadly defined USDA food category of vegetables since the USDA survey, which reports a daily consumption of 3.3 servings per person, includes all vegetables and vegetable juices---fresh and processed. The estimated daily number of servings of processed vegetables and vegetable juices found in Table 6 is 2. Thus, the proposed consumption of processed vegetables and vegetable juices probably constitutes an exaggerated consumption level if one were to factor out the fresh vegetables and vegetable juices.

Commercial Soups and Soup Mixes. USDA survey data on likely daily exposure to commercial soups and soup mixes could not be located for a comparative analysis of consumption as suggested in Table 6. Nonetheless, the estimated consumption of 2 servings of soup on a daily basis would likely be an overestimate for the average consumer since soups do not commonly seem to be consumed on a day in and day out basis by most individuals.

Medical Foods. If those individuals on a medical foods diet were to typically consume 20 food servings of medical foods per day with the use level/serving of SelenoExcell® providing 5 µg of selenium, the total daily dietary exposure of selenium would be 100 µg---an amount that is less than the highest amount considered to be generally recognized as safe. This estimate would allow for a total of 10 servings of foods from other identified non-medical food categories while remaining at or below the EDI of 150 µg. This estimate assumes that the medical foods would functionally replace 20 servings of traditional foods from the diets of those requiring medical foods. Because dietary management of such individuals is under the supervision of a physician, intake of SelenoExcell® would be monitored to ensure safe use.

(2) Intended Technical Effect to be Achieved in Foods

SelenoExcell®, when added into the foods listed in Section II.G.(1), is to function as a nutrient supplement as defined by FDA in 21 CFR 170.3(o)(20).

It is intended that the addition of SelenoExcell® into food categories described above would provide health benefits through avoidance of selenium deficiency while promoting potential health enhancements through elevated dietary exposures to this essential micronutrient.

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III. SCIENTIFIC EVIDENCE OF SELENOEXCELL® SAFETY

A. Introduction

In addressing selenium toxicities, Reid, et al., reference accounts of toxicities due to selenium ingestion dating to the time of Marco Polo (Reid, et al., 2004). The earlier reports of physiological manifestations of selenium in the mid-1900s focused on animal toxicities (Combs, 1997), and it was not until 1957 that the essential role of selenium in maintaining health was first documented (Hawkes, et al., 2003, & Combs, 1997). Epidemiological data that surfaced in 1969 first suggested an inverse correlation between cancer mortality and geographic distribution of selenium in forage crops (Combs, 1997). Interest in the health consequences of selenium in animals and humans accelerated since the 1970s, and we now have an extensive collection of scientific and medical information to draw upon as the topic of safety and toxicity is considered further

An intriguing aspect of selenium ingestion, as with other essential micronutrients, is the fact that there are negative health consequences associated with both selenium deficiencies and excesses, whereas there is a range of intermediate selenium ingestion levels that is deemed essential for maintaining good health.⁷ Man has consumed selenium as part of the normal diet dating to antiquity because of the natural presence of selenium in various plant and animal foods. The intake levels have historically been highly variable since the natural presence of selenium in soils around the world is known to be highly variable. Hence, we note both the existence of selenium deficiencies and excesses.

CSI has compiled a collection of pre-2000 summaries of scientific publications that address the role of selenium with several health conditions. The topics include:

- Selenium and overall cancer;
- Selenium's effect on prostate cancer;
- Selenium and lung cancer;
- Selenium and colon cancer;
- Selenium and thyroid regulation;
- Heart disease and its association to selenium;
- Selenium and bioavailability;
- HIV; and
- Male sperm motility.

This summary focuses principally on the favorable role played by selenium on multiple health conditions. Of particular significance is the observation that selenium intake levels that are 2-4 times the US Reference Dietary Intake reduce the incidence of selected types of cancers.

With the increased awareness of the health benefits linked with dietary selenium, Schrauzer points out that selenium supplementation, including the use of high-selenium yeasts, became increasingly available in the mid-1970s (Schrauzer, 2001). This trend of selenium supplementation has continued with several selenium supplements presently in the marketplace. From a historical perspective, we see that selenium has been a

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⁷ Section II A summarizes the variable consumption levels of selenium from many countries around the world, note that several official governmental assessments have designated recommended daily levels intended to prevent deficiencies.

natural part of man's diet---albeit in variable and only semi-quantified amounts (see Table 2)---and that supplementation has increasingly become part of man's diet.

What are the clinical manifestations of selenium toxicity or selenosis? Symptoms of selenosis include: gastrointestinal upset, hair loss; dermatitis; mottled teeth, hypersalivation; white, blotchy and brittle nails; garlic breath; fatigue; irritability; changes in selected biochemical parameters; and neurological damage (National Institutes of Health, 2006, European Commission, 2000, & Expert Committee, 2003).

It has been reported that a selenium intake of 250,000 µg as a single dose, or multiple doses of 27,000-31,000 µg results in acute toxicity as demonstrated by the known selenosis symptoms (European Commission, 2000).

According to FDA regulations,⁸ safety assessments that yield GRAS determinations can be based on scientific procedures or such determinations can be established through experience with common use in food prior to January 1, 1958. While we have unequivocal evidence regarding the long-term consumption of selenium by man that pre-dates 1958, this assessment of selenium safety relies primarily on scientific procedures and associated animal and human studies conducted over the past 40+ years. Furthermore, a large body of information dealing directly with human experiences diminishes the need to rely as heavily on the animal testing which would trigger the need for extrapolation with uncertainties to human experience. Those studies and reviews addressing the safety and toxicity manifestations of selenium, especially the high selenium yeasts and SelenoExcell®, are discussed below.

B. Human Experience & Testing

A number of individuals and organizations, including two European groups and the US Environmental Protection Agency, have undertaken detailed evaluations of the safety of selenium as a dietary component. The published reviews have addressed safety and toxicity of selenium, including high-selenium yeast forms, based on generally available primary scientific literature. The original studies that are commonly cited in considering selenium safety in humans include the works of Yang and coworkers, Longnecker and coworkers, and Clark and coworkers (Yang, et al., 1983; Yang, et al, 1989; Yang & Zhou, 1994; Longnecker, et al., 1991; & Clark, et al., 1996)

European Commission. In 2000, the Scientific Committee on Food, working under the auspices of The European Commission's Health & Consumer Protection Directorate-General, issued a report that addressed the tolerable upper intake level of selenium (European Commission, 2000). This evaluation included determining the actual intake levels of selenium in their various forms for various European countries while also considering key scientific parameters that have an impact on overall safety considerations. Metabolism with bioavailability and physiological functions of selenium were addressed in the context of ascertaining daily requirements for the subject mineral. The report also acknowledged that selenium deficiency was a particular concern for many populations, including several European populations. The evaluation focused principally on adverse and toxic effects linked with selenium intake.

Acute toxicity was noted with the inorganic salts of selenium and with selenomethionine. At doses of 250,000 µg as a single dose or multiple doses of 27,000-31,000 µg, acute toxicity was noted with classical symptoms of selenosis. However, no serious cases of selenium toxicity were recorded.

⁸ See 21 CFR 170.30(a).

Human exposures to selenium in different forms were discussed, and the results from several of the original studies have been compiled into Table 7. Selected studies will be discussed more fully below.

Daily dosages ranged from a low of 32 µg to nearly 6700 µg. More commonly, the daily dosages considered tended to fall around 200 to 600 µg. The exposures were as short as 6 weeks while others lasted for years. Evidence of selenosis or selenium intoxication was absent except for the highest exposure groups.

The following conclusions were offered:

- no data exist to suggest that selenium forms used in foods are carcinogenic;
- genotoxicity was detected in *in vitro* and *in vivo* systems but only at toxic doses that do not reflect nutritionally appropriate intakes; and
- no evidence was found for teratogenicity in humans (or macaque monkeys).

It was also concluded that the minimum daily dietary intake sufficient to cause selenosis is about 1200 µg. In fact, there were no clinical signs of selenosis in humans with a daily selenium intake of 850 µg. Interestingly, individuals with symptoms of selenosis when consuming 913 µg/day recovered from selenosis when their mean intakes were reduced to 819 µg/day. Studies where daily Se intakes were found to be 239 µg and 290 µg revealed no signs of toxicity.

Upon considering the accumulated information, the Commission indicated that the Lowest Observed Adverse Effect Level (LOAEL) for selenium would be 900-1000 µg/day since no clinical signs of selenosis were reported for individuals with a daily intake of 850 µg. The Commission determined the No Observed Adverse Effect Level (NOAEL) to be 850 µg based principally on the work of Yang and colleagues (Yang, et al, 1983; Yang, et al., 1989; & Yang & Zhou, 1994). The NOAEL of 850 µg/day was reduced by an uncertainty factor of 3 in yielding a Tolerable Upper Intake Level (UL) of 300 µg.

The Committee, in making this determination, reported that the 300 µg/day figure covered selenium intake from all sources of food, including supplements. This particular Se level is compatible with the findings of Clark, et al, who failed to observe any signs of selenosis over the course of a 10+ year study with 200 µg of high-selenium yeast supplementation, along with about 100 µg of selenium coming from the diet (Clark, et al., 1996).

The Committee stated that the UL of 300 µg/day also applies to pregnant and lactating women since no data suggest that other life-stage groups have increased susceptibilities to this selenium intake. Furthermore, children were not found to be at increased risk. Consequently, the UL was adjusted downward for children in direct proportion to their body weights.

The following conclusion was offered by the Committee:

“The Committee found sodium selenate, sodium selenite, and sodium hydrogen selenite acceptable for use in food for particular nutritional uses, but did not find other forms of selenium acceptable on the basis of current data. Therefore, the UL of this report relates only to the selenium compounds found acceptable and, in addition, to selenium naturally present in food.”

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The Committee did not extend its conclusion that the UL of 300 µg/day would apply to high-selenium yeasts.

Rayman, 2004. Rayman undertook a thorough review of the literature on high-selenium yeasts to assess its overall human safety. This was undertaken because of the findings by the European Committee that did not extend the conclusions of safety of selenium at a level of 300 µg/day beyond the selenate and selenite forms to the high-selenium yeast forms. The Rayman evaluation took into consideration known levels of selenium consumption, biosynthesis and metabolism of the selenium-enriched yeasts, manufacturing methods with quality control procedures, speciation of the subject yeasts, toxicity studies, and human intervention studies. Many of the studies considered are listed in Table 7.

In her review of the various studies, Rayman points out that the individual studies are consistent with a NOAEL of 819 µg/day, the agreed-upon figure that was embraced by the European Committee and by the Expert Group as outlined below. Other conclusions were offered:

- the selenium-yeast supplement is without toxic effects even after chronic dosages at 300 µg/day;
- there is no evidence that the high-selenium yeast supplementation causes a continuing rise in tissue selenium as had been hypothesized;
- selenium-yeast used at 200, 300, 400, and even 800 µg/day for lengthy periods of time (up to 12 years at the 200 µg/day dosage) were without indication of toxic effects; and
- high-selenium yeast is a safe, bioavailable form of selenium that mimics foods of selenium which is useful as a precursor for selenoprotein synthesis and as a human anticancer agent.

Food and Nutrition Board, 2000. Under the umbrella of the US National Academies of Science, the Institute of Medicine's Food and Nutrition Board, as part of its broader mission of providing quantitative assessments of various nutrients to benefit the health and well-being of Americans and Canadians, has undertaken its review of pertinent scientific literature of selenium to provide its recommendation for Dietary Reference Intake (DRI), and the Tolerable Upper Intake Levels (UL).

As seen in Table 3, the selenium DRI for adults is 55 µg/day and the UL was determined to be 400 µg/day.

Environmental Protection Agency, 2006. As part of its Integrated Risk Information System (IRIS), EPA evaluated the available health information on selenium. The assessment provides an oral Reference Dose (RfD) which is an estimate 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.

EPA reported the LOAEL to be 1261 µg/day with the NOAEL of 853 µg/day, figures that are consistent with the conclusions by others. The RfD was calculated by applying an uncertainty factor of 3 to the NOAEL to account for sensitive individuals, yielding 5 µg/kg of body weight/day or about 300 µg/day for a 60 kg adult.

Expert Group on Vitamins and Minerals, 2003. The Department of Health in the United Kingdom, working through the Medicines and Healthcare Products Regulatory Agency, convened an expert committee of independent experts to assess the Safe Upper Levels for various vitamins and minerals. Selenium was one of the minerals considered.

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Along with a summary of pertinent background information on selenium's natural occurrence in foods, its chemistry, physiological functions, and pharmacokinetic characteristics, the safety and toxicity aspects were addressed in some detail. Animal testing data will be presented in Section III.C.

Human exposures to selenium in various forms served as the principal focus of this Committee, and those individual studies that were considered by the Committee are incorporated in Table 7 and are summarized elsewhere in Section III. As was done by the European Commission, the dietary selenium exposures were reviewed in an attempt to ascertain the LOAEL and NOAEL that would serve as the basis to establish a Safe Upper Level for selenium.

Predictably, and as was the case with the European Commission, studies published by Yang and colleagues, along with Longnecker, et al., and Clark, et al., were viewed as pivotal (Yang, et al., 1989, Yang & Zhou, 1994, Longnecker, et al., 1991, & Clark, et al., 1996).

The Expert Group calculated the estimated maximum selenium intake value from food and supplements together to be 400 µg/day.

Selenosis is thought to develop when selenium intakes exceed 850 µg/day (or 14 µg/kg body weight for a 60 kg adult). Selenium supplementation at a daily level of 300 µg is not associated with overt adverse effects over a short period of time.

Marginal selenium toxicity was concluded to be present with daily intakes of 910 µg, and this figure was considered to be the LOAEL. An uncertainty factor of 2 was applied to the LOAEL to yield the NOAEL of 450 µg/day. If one considers the daily selenium intake from foods to be 100 µg, supplementing with an additional 200–250 µg falls within the calculated NOAEL of 450 µg/day. This conclusion was reinforced by the findings reported by Clark and colleagues and Longnecker and colleagues who noted no adverse effects following long-term selenium exposure at comparable levels (Clark, et al., 1996 & Longnecker, et al., 1991).

As was the case with the European Commission, the Expert Group did not identify any specific vulnerable groups.

Yang, et al., 1983. Yang and colleagues investigated endemic selenium intoxications due to high selenium in soils in China. When considering 248 individuals from five villages with a daily selenium intake of approximately 5,000 µg, 49% morbidity was detected. Classical symptoms of selenosis that affected hair, nails, and skin on feet, hands, and outer sides of the legs, forearms, and neck were observed, and neurological disturbances were particularly evident in one of the five villages. At a later stage, numbness, convulsions, paralysis, and motor impairment developed.

The daily selenium intake level with those who exhibited clinical signs of selenosis was estimated to range from 3,200-6,690 µg with an average of 4,990 µg. The afflicted residents did recover from selenosis as soon as the diets were modified with a downward adjustment in selenium to 240-1510 µg with a mean intake of 750 µg. The principal form of selenium consumed from the diet of rice and maize was established to be selenomethionine.

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Table 7. Summary of Selected Human Testing Studies With SelenoExcell®, Other High-Selenium Yeast Products or Selenomethionine⁹

Reference	No. of Subjects	Estimated Daily Dosage (µg)	Duration	Comments
(a)	2	350 & 600	18 m	Marginal hematological changes; borderline increase in serum alanine amino transferase
(a)	4 M per group	324, 206, & 388	?	No adverse effects reported
(a)	6 M per group	200	6 w	No adverse effects reported
(a)	32 F	450-500	3 m	Half subjects experienced depression & extreme tiredness following termination of study
(a)	125 F/lactating	90-350, 170-500, or 250-980	?	No evidence of selenosis
(b)	248	3200-6690 (4990 average)	long-term (?)	Selenium intoxication in 49% of subjects, observed skin, hair, nail, abnormalities & neurological & motor disturbances, exposures to 750 µg did not induce adverse effects, selenosis reversed with diet changes
(c)	~400	M - 70, 195, & 1438, F - 62, 198, & 1288	long-term (?)	Marginal selenium toxicity observed at 910 µg/day but not at a daily intake levels of 853 µg or less
(d)	5	819	long-term (?)	Symptoms of overt signs of selenosis at 1270 µg/day disappeared after change in diet to 819 µg/day, NOAEL of 800 µg/day
(e)	142	68-724 (239 average)	2 y	12 subjects daily exposure exceeded 400 µg; no clinically significant observations; increased lethargy noted in some subjects
(f)	1312	290	Up to 10+ y (4.5 ave)	No clinical signs of selenium toxicity based on semiannual exams, limited patient withdrawals due to GI tract distress
(g)	226	200	4 y	Hepatitis surface-antigen positive patients, no side effects noted
(g)	500	140, 240, & 340	2 y 8 m	UK PRECISE program, no signs of selenium toxicity reported as of Jan 2003, some reports of GI discomfort
(g)	500	143, 243, & 343	4 y 8 m	Danish PRECISE program, no evidence of selenium toxicity reported as of Aug 2003, some reports of GI discomfort
(g)	Small group	200-600	3-8 m	Rheumatoid arthritis patients experience pain & morning stiffness relief without adverse effects
(g)	? lactating mothers	200	3 m	Doubling of infant intake of Se without reports of adverse effects, Se levels remain 4-5 times below upper limit for infants from Food and Nutrition Board
(g)	22	100 supplement	6 m	Elderly subjects experienced age-related decline in immune response
(g)	186	200 supplement	2 y (?)	Beneficial treatment adjuvant for HIV-positive subjects without reported adverse effects
(h)	?	200	2 y	Liver cancer preventive study using high-Se yeast without adverse effects noted
(h)	3698	50 + vitamin E + β-carotene	8 y	Modest protection against stomach cancer
(h)	3698	50 + vitamin E + β-carotene	8 y	Modest protection against stomach cancer
(h)	29,584	50 + vitamin E + β-carotene	2+ y	Cancer prevention study determined that total mortality & cancer mortality lowered when using the selenium combination
(h)	298	100 followed by 50 (combination formulation)	6 m + 6 m	Frequency of micronuclei & DNA adducts reduced by 95% & 72% in different study groups, no adverse effects noted
(h)	304	200 (combination formulation)	5 y	Reduced incidence of metachronous adenomas in large bowel by half

(a) European Commission, 2000 & references found therein, (b) Yang, et al, 1983, (c) Yang, et al, 1989, (d) Yang & Zhou, 1994, (e) Longnecker, et al, 1991, (f) Clark, et al, 1996, (g) Rayman, 2004 & references found therein, (h) Whanger, 2004 & references found therein

⁹ While two studies reported adverse effects (depression and tiredness and age-related decline in immune response), these observations were not reported in other studies and are unlikely to be related to intake of the test article

Yang, et al., 1989. Yang and colleagues continued their investigations of selenium ingestion in different regions of China, considering areas to be “low,” “medium,” or “high.” Average daily selenium intakes for adult males were found to be 70, 195, and 1438 µg, respectively; the average daily selenium intakes for adult females were 62, 198, and 1288 µg, respectively. A total of 349 adults was part of the study. Clinical selenosis was observed in the high selenium area, but no clinical signs were observed when the daily selenium intake was 853 µg or less. Five individuals who had long, persistent clinical signs of selenosis were found to have a daily intake ranging from 913-1907 µg with a mean of 1260 µg. A selenium intake level of 910 µg/day was determined to be a level of marginal selenium toxicity. No specific neurological symptoms were found and there was no evidence of birth defects in humans.

Yang & Zhou, 1994. Yang and Zhou performed a follow-up study on the 5 selenosis subjects cited in Yang, et al., 1989. Incorporating dietary changes with somewhat limited selenium content, with a daily intake of 800 µg, yielded a loss of clinical signs of selenosis. The authors determined that a daily selenium intake of 800 µg represented a NOAEL, and 400 µg/day was recommended as the maximum safe daily dietary intake.

Longnecker, et al., 1991. A total of 142 subjects residing in regions of the US where selenium levels are naturally high were followed over a 2-year period of time. The daily selenium dietary intake was assessed, and subjects were monitored for adverse health effects. Selenium measurements were taken from whole blood, serum, urine, and toenails over the course of the study.

The average selenium intake was 239 µg/day, with the range spanning 68-724 µg/day. Half of the subjects had intake levels above 200 µg/day, and 12 individuals had intake levels exceeding 400 µg/day. Although it was noted that the alanine aminotransferase levels in serum were elevated, it was concluded that the values were within the reference range and were clinically insignificant. There was, however, an increased sense of lethargy associated with increased selenium values. It was concluded that no physical characteristics of selenium toxicity had manifested, nor were there any other significant effects attributed to elevated selenium intakes

Clark, et al., 1996. Clark and colleagues conducted a randomized, double blind, placebo-controlled study on the effects of selenium supplementation on the prevention of skin cancer. 1312 patients with a history of basal cell or squamous cell carcinoma were treated with 200 µg of SelenoExcell® or placebo for up to 10 years (mean of 4.5 years). Patients were assessed semiannually for known signs of frank selenosis--no indications of dermatological or other signs of selenium toxicity were detected. A total of 35 patients, including 14 from the control group, did experience gastrointestinal upset which prompted them to withdraw from the study.

While the selenium supplementation did not have an effect in reducing non-melanoma skin cancer, the study did reveal a 50% reduction in total cancer mortality, 37% lower total cancer incidence, a 63% reduction in prostate cancer, a 58% reduction in colon cancer, and 46% fewer cases of lung cancer.

The total dietary intake of selenium from supplementation (200 µg), along with the contributions from food (90 µg) totaled 290 µg/day. Also see Clark, et al., 1998.

On-Going Selenium Clinical Trials

In addition to the selenium intake studies referenced above, other selenium supplementation investigations continue or are under development (Nutraingredients, 2006). Several studies focus on selenium prevention or inhibition of prostate cancer, and others address other forms, such as liver, colorectal, esophageal, breast,

and lung cancer. Still other investigations seek information about a possible preventive role for selenium with Alzheimer's disease, non-cancerous liver disease, and improved immune function.

A multi-center, National Cancer Institute-sponsored program, the SELECT program (Selenium and Vitamin E Cancer Prevention Trial) involving many thousands of subjects will continue through 2013 (Nutraingredients, 2006). Another multi-center cancer clinical trial is underway under the auspices of the Eastern Cooperative Oncology Group (ECOG) with support from NCI (ECOG, 2007). In this investigation, the potential role of orally administered selenium in preventing the development of a second primary lung tumor in patients who previously underwent surgery to remove stage 1 non-small cell lung cancer is under evaluation.

The conclusions drawn from the clinical trials to date are compelling in that elevated levels of dietary selenium that are 2-4 times (or more) the US DRI level of 55 µg per day per adult impart health benefits, such as cancer prevention, inhibition of genetic damage, or enhanced immune system performance (Whanger, 2004). To expand the current state of knowledge and gain greater depth of understanding, scientists and health care professionals in the US and around the world are actively engaged in the design and execution of clinical trials involving selenium supplementation.

Long-term selenium supplement investigations continue at the Arizona Cancer Center, University of Arizona, the Cancer Institute at the Chinese Academy of Medical Science in Beijing, in the UK as part of the PRECISE (Prevention of Cancer by Intervention With Selenium) program, and in Denmark as part of the PRECISE program. The studies that are in process through the PRECISE program are considered to be pilot studies with the hope to expand the studies to 14,500 subjects covering 7 years.

Several prostate cancer chemoprevention studies are in process at the University of Arizona as a result of the profound results reported by Clark, et al. (Clark, et al., 1996 & Clark, et al., 1998). According to Marshall, the study designs capture a continuum ranging from short-term effects on healthy and cancerous prostatic tissues in men with diagnosed cancer, to long-term effects on healthy and premalignant tissue in men with high-grade prostatic intraepithelial neoplasia, to long-term effects on healthy tissue in high-risk men with negative biopsy, to long-term effects on cancerous tissue in men with frank cancer (Marshall, 2001). Marshall has described the four studies as follows:

1. Negative Biopsy Trial – selenium treatment of men who received negative results from prostate biopsies;
2. Selenium treatment of men with high-grade prostatic intraepithelial neoplasia;
3. Preprostatectomy Trial - selenium treatment of men with localized prostate cancer before prostatectomy; and
4. Watchful Waiting Trial - use of selenium as a chemotherapeutic agent among men with confirmed prostate cancer.

Experimental design details are contained within Table 8.

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Stratton, et al., 2003a. The results of the Clark study were remarkable in the suggestion that the incidence of certain types of cancer, including prostate cancer, can be diminished as a result of high-selenium yeast supplementation at the total daily exposure of 300 µg (food and supplement) (Clark, et al., 1996). There is a need to confirm these findings to enable a more aggressive use of selenized yeast in cancer prevention, and the subject investigation, along with the studies reported in the following two summaries, are intended to do just that. 700 men considered to be at high risk for prostate cancer, but who have had a negative

prostate biopsy, were administered high-selenium yeast supplements daily at the level of 200 or 400 µg. Can these selenium doses decrease the incidence of prostate cancer in high risk men? The study design and initial results are described. In addition, the subjects are being monitored for specific serum markers that might indicate biochemical progression of prostate cancer more effectively. Measuring both alkaline phosphatase and chromagranin A levels was built into this study.

As of June, 2003, a total of 514 men were enrolled in the study. No new safety concerns were raised during the early stages of the study.

Stratton, et al., 2003b. As was the case with the above-noted Negative Biopsy Trial, the Watchful Waiting Trial is an extension of the work reported by Clark, et al. (Clark, et al., 1996). The watchful waiting approach is a more desirable option for some men who are diagnosed with prostate cancer since selenized yeast supplementation could delay the necessity for surgery, radiation treatment, or some other invasive treatment modalities.

During the watchful waiting period, monitoring key biomarkers for progression of prostate cancer would be particularly valuable so health care providers can more confidently distinguish between slow- and fast-growing prostate cancer. The study design for the Watchful Waiting Trial includes administration on a daily basis of either 200 or 800 µg high-selenium yeast to 264 men with the trial to last at least 4 years and possibly up to 5 years. Over the course of the study, certain biomarkers, such as alkaline phosphatase and chromagranin A, along with other potential biomarkers, will be measured to provide insights into the progression of prostate cancer.

As of June, 2003, a total of 191 subjects of the targeted 264 had been recruited. No safety concerns had been raised during the early stages of this trial.

Reid, et al., 2004. As part of the Watchful Waiting Trial described above by Marshall, it was hoped to gain insights into the toxicity of selenium when administered in chemoprevention in appreciably increased dosages that exceeded the NOAEL of 400 µg dosage. 24 men with biopsy-proven prostate cancer were given either 1600 or 3200 µg/day of high-selenium yeast. Selenium levels in plasma and symptoms of selenium toxicity were assessed periodically over the course of 12 months. Liver and kidney function tests and hematology were measured at 6-month intervals. The 3200 µg/day group reported more selenium-related side effects, but blood chemistry and hematology results were in normal limits for both dosage groups. No obvious selenium-related serious toxicities were observed.

This trial has presented the highest test doses of high-selenium yeast to humans over a sustained period of time, and no serious toxicities were revealed. While these findings do not establish the safety of long-term high-dose organic selenium supplementation in the general population, the observed toxicity profiles suggest that doses greater than 400 µg/day can be given in controlled situations for extended time periods without serious toxicity.

ADME & Bioavailability

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The metabolic conversions of the different selenium forms have been well-studied and are summarized by several research groups. Cereal and forage crops, as well as *Saccharomyces cerevisiae* absorb inorganic selenium which is converted into selenomethionine which, in turn, is subsequently incorporated into protein. Selenomethionine then undergoes other metabolic conversions. Excess Se is detoxified by

successive methylation of H₂Se to yield methyl selenol (CH₃SeOH), dimethyl selenide ((CH₃)₂Se) and trimethylselenonium ion (CH₃)₃Se⁺; the latter two species are excreted in the breath and urine (Rayman, 2004, Whanger, 2004, & Infante, et al., 2005).

Table 8. Summary of Present or Planned Clinical Studies With SelenoExcell® and Other High-Selenium Yeast Products

Reference	No. of Subjects	Est. Daily Dosage (µg)	Duration	Comments
(a), (b)	700 M	200 or 400	57 m	Negative Biopsy Trial, intend to assess prostate cancer status of individuals with negative prostate cancer biopsies; 514 subjects were randomized to trial as of Jun 2003
(a)	470	200	3+ y	Intend to assess prostate cancer status of men with high-grade prostatic intraepithelial neoplasia following selenomethionine supplementation.
(a)	110	200 or 400	6-8 w	Preprostatectomy Trial, evaluation during the time interval between biopsy & prostatectomy; 55 subjects recruited to trial in 2001
(a), (c), (d)	264	200, 800, 1600 or 3200	4 - 5 y	Watchful Waiting, seeking pharmacological data from selenium exposures, along with chemotherapeutic outcomes 191 subjects recruited as of Jun 1003

(a) Marshall, 2001, (b) Stratton, et al , 2003a, (c) Stratton, et al , 2003b, (d) Reid, et al., 2004

It is also known that the organoselenium forms of selenium, especially selenomethionine, are more bioavailable than the inorganic selenium salts (Burk, et al, 2006). Rayman reports that organic forms of selenium are absorbed to the extent of about 80%, although the bioavailability is affected by the nutrient status of individuals, the manufacturing process for the subject organoselenium form, and the presence of other dietary components, including sulfur. Nonetheless, it was concluded that human supplementation studies indicate that the selenium from high-selenium yeasts is more bioavailable than inorganic selenium (Rayman, 2004).

The Expert Group on Vitamins and Minerals reported that selenium compounds are readily absorbed from the small intestine, but the extent of absorption varies, depending on the nature of the specific compound. Selenium was found to be widely distributed throughout the body, and its presence has been detected in breast milk. Selenium levels are slightly higher in the liver and kidneys than in other tissues. It was also noted by Hawkes, et al., that the whole body retention of selenium is about 15 mg with 5 mg being retained in muscle tissue (Hawkes, et al, 2003). Selenium is largely excreted in the urine, with volatile metabolites being excreted in the breath. Some fecal excretion of selenium occurs following chronic Se administration (Expert Group, 2003).

Genotoxicity

The results of *in vitro* mutagenicity tests were declared to be inconsistent, and selenium compounds are largely negative in the available *in vivo* mutagenicity tests. An increase in chromosomal aberrations in hamster bone marrow was reported, but this occurred only at lethal doses with sodium selenite (Expert Group, 2003). No genotoxicity was found to occur at nutritionally adequate intakes of selenium (Expert Group, 2003).

Reproductive Effects

Although adverse effects have been reported on the reproductive systems of various animals including birds, fish, sheep, pigs, and hamsters at maternally toxic doses, such findings did not occur with primates. Macaque monkeys were fed selenomethionine at a dose of 300 µg/kg of body weight/day during

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organogenesis with no signs of terata. Reproductive toxicity was not an issue that has been investigated in detail, but there have been no reports of such effects in humans even in high selenium intake regions in China (European Commission, 2000, & Expert Group, 2003).

Allergenicity

Rayman cautions that some individuals may be allergic to the yeast that is used in the production of high-selenium yeasts. For those individuals, a non-yeast selenium supplement would be advised. No data or reports of allergic reactions were provided (Rayman, 2004)

C. Animal Testing

The animal testing results with selenium compounds take on a somewhat reduced significance in light of the extent of human experiences and clinical testing that has been conducted on selenocompounds over the past four decades. Even so, there is merit in summarizing the findings from the animal testing since it provides additional framework in which to consider the overall safety considerations for the various forms of selenium with an emphasis on those selenocompounds that are found in foods and can be utilized for nutrient purposes.

Selenium compounds exhibit moderate to high acute oral toxicities. These toxic manifestations impact the nervous system, liver and lungs. Exposures to large doses of selenium over extended periods of time result in neurological dysfunction (impaired vision, ataxia, disorientation), and respiratory distress. Grazing livestock that have fed on selenium-accumulating plants have been observed to have “blind staggers” (Environmental Protection Agency, 2006).

Rayman reports that inorganic forms of selenium are more acutely toxic than selenized yeasts and the organic forms. She states: “The LD₅₀ for Se-yeast is 37.3 mg/kg compared with 12.7 mg/kg for sodium selenite, demonstrating that Se-yeast is considerably less acutely toxic than sodium selenite.” In further support of this conclusion, an 8-week feeding study using two different selenium forms, selenized yeast compared with selenite, at identical dietary concentrations of 16 µg Se/g of diet revealed severe hepatotoxicity, cardiotoxicity, and splenomegaly in the selenite study group and no such observations with the selenized yeast (Rayman, 2004).

A daily dose of a soluble selenium compound of 500 µg/kg body weight was not associated with any adverse effects (Expert Group, 2003).

Administration of selenium compounds to animals to ascertain carcinogenic potential revealed inconclusive results. The earliest reports suggested that rats fed seleniferous wheat developed hepatic tumors, but the study was subsequently criticized as being scientifically inadequate (Environmental Protection Agency, 2006). The only studies reporting animal carcinogenesis involved administration of selenium compounds that are neither found in food, nor would they be nutrients. Experimental data do not indicate that inorganic or organic selenium compounds that are relevant to food and nutrition are carcinogenic (European Commission, 2000).

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The topic of animal carcinogenicity has triggered substantial research, with interest stemming from selenium as a causative agent and its functioning as an anticarcinogenic agent. Whanger reports that more than 100 small animal trials have been conducted since 1949 in exploring the relationship of tumor

incidence and selenium intake. The prevailing initial view was that selenium was cancer-causing, but the availability of more studies, especially since 1957 when the essential nature of selenium in humans was established, offset this conclusion. Two-thirds of the selenium animal studies conducted over the years illustrate a significant reduction in tumor incidence (Whanger, 2004) Rayman also stated that selenized yeast was found to be effective in reducing tumor yield in the animal model for breast cancer when tumor formation was induced by methylnitrosourea administration (Rayman, 2004).

Chronic exposures in animals at levels in excess of 0.03-0.4 mg/kg bw resulted in reduced growth rates and diminished weight gain, along with liver changes, anemia, pancreatic enlargement, and, in some cases with domestic animals, neurotoxicity (European Commission, 2000) It was also reported that high selenium exposures adversely affect the female estrous cycle and the sperm concentration and quality in males. Multi-generation studies suggest that elevated selenium exposures reduce post-natal survival and weights of offspring (Expert Group, 2003). As noted in Section III.B, selenite, selenate, selenocysteine, and selenomethionine are considered to be teratogenic in birds, fish, sheep, pigs, and hamsters. However, macaques did not show any signs of teratogenicity when fed selenomethionine at dosages of 25, 150, and 300 µg/kg bw during organogenesis (European Commission, 2000, & Expert Group, 2003). It was also stated that positive reproductive effects in rodents due to selenium compounds are commonly linked with overt maternal poisoning and nutritional deprivation (European Commission, 2000).

A more detailed accounting of individual selenium animal studies can be found in the EPA safety assessment of selenium (Environmental Protection Agency, 2006).

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IV. ASSESSMENT OF COMPOSITE INFORMATION FOR SELENOEXCELL® GRAS STATUS

FDA defines “safe” or “safety” as it applies to food ingredients as

“...reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance.”¹⁰

Amplification is provided in that the determination of safety is to include probable consumption of the substance in question, the cumulative effect of the substance, and appropriate safety factors. It is FDA’s operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that

“...General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.”¹¹

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called “common knowledge element,” in terms of the two following component elements:¹²

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as the National Academy of Sciences.

Considering the composite information for the intended food uses of selenium in all forms, and by relying primarily upon human experience and testing as complemented by animal testing---the so-called scientific procedures---one can conclude that SelenoExcell® is both safe within certain use limitations and is effective in addressing a multitude of human health conditions.¹³

Multiple human experience and testing results have been utilized in determining an acceptable daily intake (or ADI) of SelenoExcell®. ADIs or ULs of 300-400 µg, based on the cited studies and conclusions

¹⁰ See 21 CFR 170.3(i)

¹¹ See 21 CFR 170.30(a)

¹² See *Federal Register* 62 April 17, 1997, 18937; or <http://www.cfsan.fda.gov/~lrd/fr970417.html>.

¹³ It is intuitively obvious that selenium has historically been consumed as part of the human diet since we now recognize the essential nutrient status of selenium in humans, plus we know that selenium is a natural constituent of numerous commonly consumed foods across the globe. However, we do not have firm historical information on the specific selenocompounds consumed and the levels at which they have been ingested over time. Hence, historical usage considerations are not part of the subject GRAS evaluation

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published by competent scientists, serve as a reference point for the indicated safe usage of SelenoExcell® as an ingredient to be incorporated into certain foods. CSI has identified the intended food categories and proposed use levels (see Table 6), and the upper bound total estimated daily intake (EDI) for adults was calculated to be 150 µg as selenium. The EDI is compared to ADIs and ULs calculated from LOAELs and NOAELs as extracted from the public literature---both original, or primary, literature and review articles and expert opinions, or secondary literature, as needed to meet the “common knowledge element”---in completing the GRAS assessment for SelenoExcell®. This, when added to typical levels of Se intake is well within accepted limits.

The assessment of selenium safety and toxicity in its various chemical forms were undertaken by several knowledgeable bodies and other experts, as summarized in Sections III.B. and III.C. All of those addressing the safe levels of selenium supplementation relied extensively on the published papers by Yang and colleagues, Clark and colleagues, and Longnecker and colleagues

The central consideration was to ascertain LOAELs and NOAELs from which safe upper limits of daily selenium exposure for humans could be derived.

- The Food and Nutrition Board determined that its Tolerable Upper Intake Level, i.e., the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population, was 400 µg (Food and Nutrition Board, 2000).
- The European Commission established its LOAEL to fall within the range of 900-1000 µg, and they designated its NOAEL to be 850 µg. Applying an uncertainty factor of 3 yields a Tolerable Upper Intake Level of 300 µg (European Commission, 2000).
- Rayman reviewed the safety literature on selenized yeasts and extracted a NOAEL of 819 µg. It was also noted that selenized yeasts were safely consumed at various levels up to 800 µg per day for extended periods of time, without toxic manifestations. It was concluded that the Tolerable Upper Intake Level of 300 µg/day was conservative and should also apply to selenized yeasts, such as SelenoExcell® (Rayman, 2004)
- EPA reported its NOAEL at be 853 µg/day, from which it applied an uncertainty factor of 3 to establish its oral RfD of 300 µg/day---an exposure over the course of a lifetime that is likely to be without appreciable risk (Environmental Protection Agency, 2006).
- Combs, who worked as part of the Clark research team, contends that the EPA RfD should more correctly be 600 µg/day for men and 475 µg/day for women. He supported his position by noting that selenium supplementation trials using dosages of 400 µg (for a total daily selenium exposure of 500 µg when considering the selenium contributions from the diet) presented no toxic manifestations (Combs, 1997).
- The Expert Group on Vitamins and Minerals determined that 910 µg/day was its LOAEL, and they applied an uncertainty factor of 2 to calculate its Safe Upper Level for selenium of 450 µg/day (Expert Group, 2003).
- Schrauzer independently concluded that extradietary selenium supplementation of 200 µg/day was generally considered to be safe and adequate for adults of average weight who subsisted on the typical American diet. He estimated that the average adult would consume a total of 280-350 µg

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Se/day, a figure which compared favorably with EPA's oral RfD. Schrauzer also noted that prolonged daily selenium intakes of 750-850 µg/day do not produce adverse effects, supporting his contention that selenium supplementation of 200 µg/day provides a wide margin of safety (Schrauzer, 2001).

- Whanger's research on the selenium-cancer relationship led him to endorse the Food and Nutrition Board upper safe limit for selenium of 400 µg/day. Nonetheless, he reported that human subjects consuming up to 600 µg Se/day appear to have experienced no adverse clinical symptoms (Whanger, 2004).
- On-going clinical testing of SelenoExcell® by the University of Arizona team, with Reid, Stratton, and Marshall continuing the studies previously spearheaded by Clark, have expanded the daily human doses for the selenized yeast up to 1600 and 3200 µg. After 12 months of exposure at these high levels, no serious toxicities were observed, and it was concluded that humans can well tolerate daily doses greater than 400 µg without serious toxicity.

From the substantial body of published scientific literature, it is apparent that total daily selenium exposures to 250 µg should be well tolerated. Since the typical American adult ingests about 100 µg of selenium as part of the present daily diet, incorporation of an additional 150 µg of selenium from added SelenoExcell® in the foods targeted by CSI should produce no adverse effects and very well may contribute to enhanced human health at these levels that exceed present practices.

Such a level of selenium should be well tolerated without toxic manifestations, in light of the NOAELs and safe upper levels that have been calculated from human data with uncertainty factors of 2 or 3 applied to the NOAEL. This is further bolstered by the additional remarks of several experts who have tested larger selenium doses on humans, including some that specifically incorporate SelenoExcell® at levels more than 20 times the selenium level of 150 µg that is presently under consideration. In short, the additional usage of 150 µg/day of selenium from SelenoExcell® as an added food ingredient is considered to be a safe level when factoring in the conservative estimates applied by several knowledgeable experts.

Consideration should be given to the subpopulation that resides in geographic areas that have naturally higher soil levels of selenium. The question may arise as to whether or not this subpopulation might consume levels of Se that are above the commonly accepted ADI or UL. As noted in Section II.A, US consumers are increasingly exposed to foods that are produced and distributed nationally with a corresponding diminished reliance on locally or regionally produced foods. This practice of increased reliance on nationally produced foods serves to mitigate concern that subpopulations residing in areas with high selenium levels might ingest excess dietary selenium. In fact, some of the foods that would be fortified with SelenoExcell® would actually replace foods regionally produced from high-selenium crops. Such replacement could actually result in a reduction in dietary selenium for those living in high selenium regions.

Furthermore, in those cases where sustained, excessive selenium intake may lead to selenosis, such effects are mild, readily observable, and are reversible. Thus, in the unlikely circumstance that the high-selenium yeast would contribute to significant intake in individuals already consuming elevated amounts of selenium, self-correcting action could be taken without residual harm to the consumer. **000030**

Having tentatively established that the particular amount of added selenium---the 150 µg/day---would be GRAS, we then direct our attention to another critical component associated with the subject GRAS

evaluation. We must consider the specific selenocompounds that constitute SelenoExcell® since not all selenocompounds exhibit identical safety or toxicity profiles. In order to draw a conclusion that a particular material is safe, one must know WHAT that particular material is. It is risky to extrapolate safety or toxicity conclusions about one selenocompound to another. This conclusion would also hold when comparing one high-selenium yeast to another high-selenium yeast, even though the extent of chemical differences among such selenium yeasts would likely be lessened.

The safety or toxicity profiles of all selenium compounds that have been subjected to the testing described in this document have been considered thus far. Such data provide an overarching framework for the safety evaluation of the subject material.

An active area of selenium research over the past several years has been speciation studies where scientists attempt to elucidate the specific chemical entities that make up mixtures such as are commonly found with selenized yeasts. Table 4 summarizes the chemical composition of SelenoExcell®, and we see that about 85% of the selenium content has been identified as to its exact chemical form. This extent of characterization also applies to other selenized yeasts. What this means is that about 10-20% of the selenium is present in some chemical forms that have not yet been determined conclusively. How does this compositional uncertainty impact the safety considerations?

A narrowed focus has been directed toward the specific chemical composition of SelenoExcell® since there are unique circumstances associated with its human food and supplement uses that override the compositional issues noted above. One can conclude that supplementing the diet with SelenoExcell® to provide 150 µg of selenium per day is GRAS, even without knowing nearly 15% of the chemical composition. SelenoExcell® was utilized in the Clark cancer study which spanned over ten years, and it continues to be the test subject in follow on studies administered by Marshall and Reid (Clark, et al., 1996; Clark, et al., 1998; Stratton, et al., 2003a; & Stratton, et al., 2003b). The past clinical experience with SelenoExcell® without apparent toxicity or noted adverse effects overrides the compositional uncertainties when drawing this safety conclusion. In this regard, the designation that SelenoExcell® as GRAS at a daily intake level that provides 150 µg of selenium is justified.

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V. CONCLUSIONS¹⁴

The cumulative scientific information on selenium and SelenoExcell®, specifically considering the human experience and associated testing, along with germane supporting information, provides the basis for the conclusion that a daily SelenoExcell® exposure as a nutrient supplement that provides selenium levels up to 150 µg for adults, with proposed food usage as summarized in Table 6, is generally recognized as safe.¹⁵ SelenoExcell® must be produced in accordance with GMP procedures and must comply with appropriate food grade specifications

We have independently and collectively evaluated the above-referenced information and offer this GRAS declaration based on scientific procedures in accordance with FDA's standard for food ingredient safety, i.e., reasonable certainty of no harm under the intended conditions of use.

In conclusion, adult human exposure to SelenoExcell®, as an ingredient added to selected food categories at a combined level that provides up to 150 µg per day of selenium is considered to be generally recognized as safe (GRAS).

Robert S. McQuate, Ph D.

January 14, 2008

Date

Richard C. Kraska, Ph.D., DABT

January 14, 2008

Date

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¹⁴ The credentials for the Expert Panel members are summarized in their respective resumes which can be found in Appendix C. Both Dr. McQuate and Dr Kraska have extensive technical backgrounds in the evaluation of food ingredient safety; each worked within FDA's GRAS Review Branch earlier in their careers and subsequently continued such evaluations in the private sector

¹⁵ This GRAS conclusion **does not** take into consideration the possibility raised by Rayman (Rayman, 2004) that some individuals may experience an allergic reaction to the yeast that is present in the SelenoExcell® formulation. The use of SelenoExcell® is deemed GRAS **except** for possible allergenicity considerations.

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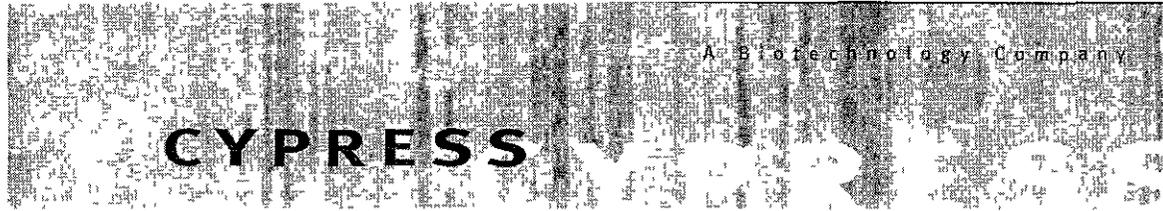
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APPENDIX A

Cypress Systems Production & Quality Procedures for SelenoExcell®

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SelenoExcell™ High Selenium Yeast Production Protocol

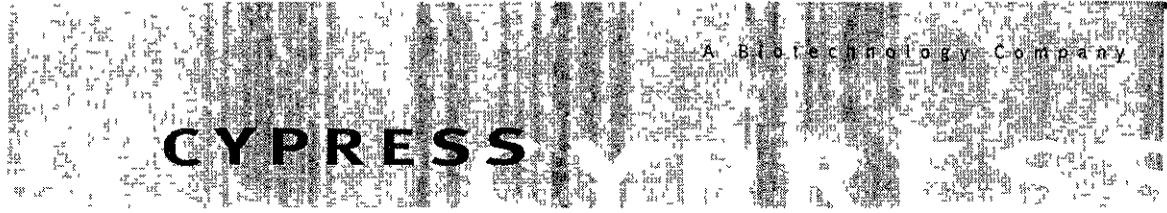
- Cypress utilizes standard baker's yeast strains (*Saccharomyces cerevisiae*) for all production.
 - ~ *These strains are recognized for food applications and are listed on the FDA GRAS list (Generally Regarded As Safe)*
- Selected strain is derived from primary grown pure culture mother stock.
 - ~ *Base stock derived from pure cultures routinely yield a higher quality and more consistent product than those utilizing secondary or waste stream yeast from the brewing of alcohol processes*
- The specific strain selected by Cypress consistently yields a high protein product ranging from 50% - 55%.
 - ~ *The majority of organic binding of the mineral composition occurs at various protein (amino acid) sites. High protein strains are required to assure maximum binding sites for optimum uptake of desired mineral*
 - Note* Low protein (30 - 35%), secondary yeast from brewing process provides minimal protein receptors for organic binding
- Fermentation is performed in precisely controlled aerobic fermentation vessels which closely maintain yeast growth, nutrient feed streams, dissolved oxygen, pH, temperature and the presence of alcohol which indicate lower than optimum growth performance.
 - ~ *Close monitoring of key fermentation and growth parameters, yields a high quality, consistent finished product*
- Selected mineral composition (selenium) is introduced at various time intervals and growth parameters to assure proper uptake and maximum utilization for organic binding.
 - ~ *This process assures that the mineral is only introduced during active growth (cell doubling) fermentation when maximum protein synthesis is occurring (i.e. maximum utilization of mineral and increased organic binding)*
 - Note* Duration of mineral yeast fermentation is 14 - 16 hours compared to a standard baker's yeast fermentation of 8 hours

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- **Following active growth fermentation, mineralized yeast cream is washed and separated four times with a doubling (2x) of clean wash water.**
 - ~ *With maximum uptake of mineral during fermentation this washing procedure assures that any remaining free mineral is properly washed away*
 - Note* Production commitment to this washing (4x with 2x clean water) requires extensive resources for equipment, processing time and wastewater treatment. This commitment is not common in other processes, but is the final assurance that SelenoExcell™ is free of inorganic forms of minerals.
- **Yeast cream is held in cold storage prior to downstream processing.**
 - ~ *Cold storage provides proper holding condition to maintain yeast viability and protect organic binding of mineral*
- **Prior to spray drying, yeast cream is pasteurized and brought to an inactive state.**
 - ~ *Enables product to achieve low micro counts required to meet or exceed established standards for human food grade products*
- **Following pasteurization, yeast cream is spray dried**
 - ~ *Spray dried mineralized yeast is uniformly blended into most dry powder formulations creating a homogenous mixture*
- **SelenoExcell™ High Selenium Yeast is produced by a highly controlled method, which provides a 100% organically bound form of selenium with minimal batch to batch variations.**
 - ~ *As demonstrated by leading health and cancer research groups, formulators and consumers can rely on the consistent quality and performance of SelenoExcell™ to deliver the full composition of organically bound selenium, which most resembles that found in nature*
- **Branded Trademark**
 - ~ *The product resulting from the original production protocol is currently trademarked as SelenoExcell. Specific labeling guidelines are available upon request*

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Quality Assurance / Quality Control Program

By establishing a critical benchmark based on consistent high quality, we can assure customers and research groups that our product will enhance their product formulation. Therefore we have developed a comprehensive Quality Assurance / Quality Control (QA / QC) Program for the testing and reporting of Microbiology and Nutrient Analysis on all of our products.

The first stage in our QA / QC program is to use leading, independent laboratories for all testing on Cypress products. This practice lends confidence to Cypress, and our customers, that our products meet or exceed USDA requirements for food grade material.

Silliker Laboratories perform all microbiology testing on Cypress products. For over 25 years Silliker has been a leading, independent food testing organization. They have grown from a single lab in 1967, to an international network of laboratories that specialize in assessing the safety, quality, and nutritional value of foods. Silliker Labs are USDA and FDA certified in Microbiology.

All Cypress products are tested by Silliker Labs for the following (included are USDA ranges for food grade materials and a typical Cypress product results)

Tested	USDA Food Range	Typical Cypress
Salmonella	Negative	Negative
E. Coli	Negative	Negative
Total Coliforms	< 10 / gram	< 1 / gram
Total Plate Count	< 7000 / gram	< 100 / gram
Yeast / Mold	< 50 / gram	< 10 / gram

In addition to the above tests, several times each year products are tested for Arsenic, Cadmium, Lead, and Mercury. Our results have been

Arsenic	Non-detectable
Cadmium	< 1 mcg / gram
Lead	< 1 mcg / gram
Mercury	< 1 mcg / gram

Analysis to document nutrient content and organic binding is conducted by a FDA and USDA certified independent laboratory. Established testing methods have produced a 99% consistency in reported results.

Routine testing by an independent laboratory certifies that our products are absent of "free" and inorganic forms of supplemented minerals.

5150 North 6th Street, Suite 156, Fresno CA 93710 2511 www.cypsystems.com Phone 559 229 7850 Fax 559 225 9007

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Test Methods

From sterile samples that are obtained during the drying process, a composite sample is created. All analyzed samples used for Nutrient and Microbial Analysis are taken from the composite sample.

Nutrient Analysis:

The following test methods are used to obtain required data on nutrient specifications prior to the sale of product.

Test	Method
Selenium Content	ICP Method
Organic Binding - Free Selenium	Methylene Blue Test
Moisture	Gas Column Chromatography

Microbial Analysis:

The following test methods are used to obtain required data on microbial specifications prior to the sale of product.

Test	Method
Coliform	MPN
E Coli	U S Pharmaceutical Method
Yeast & Mold	PDA
Total Plate Count	SMA Total Plate Count Agar
Salmonella	EIA, enriched with lactose broth in the first step of the method

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APPENDIX B

Certificate of Analysis for SelenoExcell®

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Manufacturer's Certificate of Analysis
SelenoExcell™ High Selenium Yeast

Lot Number: Se-71

Nutrient Analysis:

Total Selenium:	1,255ppm
Protein:	50.4 %
Color:	Tan
P205:	2.92
Moisture:	4.1% %
Extraneous Material:	Negative

Microbiological Assay:

Salmonella:	Negative
E. Coli:	Negative
Total Coliforms:	<0.3 /gram
Total Plate Count:	<10 /gram
Yeast/Mold:	<10 /gram
Staph aureus:	Negative
Bacillus cereus	Negative

Heavy Metals:

Arsenic:	<1 MCG/gram
Cadmium:	<1 MCG/gram
Lead:	<1 MCG/gram
Mercury:	<1 MCG/gram

Particle Size:

Bulk Density	0.6515
Through 60 mesh	100%
Through 100 mesh	100%

Organically Bound Selenium:

Positive
No Free Selenium

Manufacture Date: **October 15th, 2004**

Date of Expiration: **October 15th, 2007**

Country Of Origin: **Mexico**

PESTICIDE FREE

These results are reported by:

Quality Assurance
Fermentation Consulting, Inc.

Date: 8-11-2004

APPENDIX C

Resumes & Credentials to Provide GRAS Assessment

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ROBERT S. MCQUATE, Ph. D.

WORK HISTORY

CEO, and Co-Founder, GRAS Associates, LLC, Bend, OR
President & CEO, R. S. McQuate & Associates, Inc , Bend, OR
Chemistry Instructor, Truckee Meadows Community College, Reno, NV
Senior Vice President, Scientific & Regulatory Affairs, AminoPath Labs, LLC, Portland, OR
Board Member & Business Consultant, National Institute of Standards & Technology, Advanced Technology Program, Gaithersburg, MD
Executive Director, Advanced Science & Technology Institute, Eugene & Corvallis, OR
Adjunct Professor, Food Science & Technology, Oregon State University, Corvallis, OR
Science Director, National Soft Drink Association, Washington, DC
Senior Regulatory Scientist and Group Leader of Regulatory and Nutrition, The Dial Company, Inc , Scottsdale, AZ
Consumer Safety Officer, Food and Drug Administration, Center for Food Safety & Applied Nutrition, Division of Food and Color Additives, Washington, DC
Assistant Professor of Chemistry, Willamette University, Salem, OR

EDUCATION

Postdoctoral Research Fellow with Professor R. G. Wilkins, New Mexico State University, Las Cruces, NM
Ph.D. in Chemistry, The Ohio State University, Columbus, OH
B.S. in Chemistry with Honors, Lebanon Valley College, Annville, PA

PROFESSIONAL EXPERIENCE

CONSULTING SERVICES

CEO, GRAS Associates, LLC; President & CEO, R. S. McQuate & Associates, Inc.

- Provide food ingredient safety evaluations, focusing on independent GRAS evaluations
- Provide broad-based business consulting services to universities & companies involved in technology commercialization
- Rapid assimilation of technical and business background for use in formulating commercialization strategies
- Critically evaluate new technologies and business plans compared to competitive firms and products for economic potential
- Implement marketing activities to establish strategic alliances and/or licensing agreements
- Facilitate start-up ventures, including drafting of business plans
- Utilize negotiation skills to achieve successful execution of deals

UNIVERSITY EXPERIENCE

Executive Director, Advanced Science & Technology Institute

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- Managed industry-university interface program on behalf of University of Oregon, Oregon State University, Oregon Health Sciences University and Portland State University
- Strategic planning and program implementation, managed staff of up to 8
- Facilitated linkages between university research community and private sector, working with over 500 faculty members to yield consulting contracts, industrial research sponsorship, technology licensing and business start-ups
- Aggressively marketed faculty expertise, universities' technologies, and research capabilities through network of contacts, Internet, publications, and conferences
- Represented universities in broad-based statewide and regional economic development initiatives

Faculty, Willamette University, Oregon State University, & Truckee Meadows Community College

- Presented introductory and upper level chemistry lecture and laboratory courses
- Conducted independent research in molecular biology, enzymology, and metal ion catalysis
- Generated external grant funding to support six research students & acquire equipment.
- Provided food safety guidance to industry
- Various scientific and chemical education publications

PRIVATE SECTOR EXPERIENCE

Technical Management, The Dial Company & National Soft Drink Association

- Managed 5-person technical regulatory group with corporate responsibility for compliance with FDA, USDA, EPA, FTC, OSHA, CPSC, and NRC
- Creatively interpreted regulations to favorably impact company revenues by over 10% annually
- Special focus on product and ingredient safety, formulated regulatory strategies in anticipation of and in response to agency positions, applied quantitative risk analysis to product safety considerations.
- Provided regulatory support and training to Manufacturing and QA on Good Manufacturing Practices requirements
- Teamed with Marketing by evaluating advertising, product claims, and labeling for compliance
- Assessed university research proposals in response to industry solicitations for funding
- Served as liaison for industry interests on food ingredient safety before FDA officials
- Served as industry spokesperson with media on technical topics such as NutraSweet addition to soft drinks

GOVERNMENT EXPERIENCE

Staff, Food & Drug Administration

- FDA representative with regulated food industry officials.
- Managed safety evaluations of food and color additives and GRAS ingredients among FDA scientific divisions and with legal staff
- Generated food safety notices, proposals, and regulations.
- Evaluated complex net weight food labeling and compliance issues and formulated agency position for Commissioner
- Participated on special FDA Food Labeling Task Force to develop total food label requirements
- Formulated recommended agency policy on iron bioavailability nutritional concerns

PROFESSIONAL AFFILIATIONS

American Chemical Society
Institute of Food Technologists

Licensing Executives Society
Regulatory Affairs Professional Society

BOARD AND COMMITTEE MEMBERSHIPS

External Evaluator, Kansas Technology Enterprise Corporation, Higuchi Biosciences Center (2001)
Judge, Ohio State University Business Plan Competition (2001)
Board of Directors - Universal Pulping, Inc. (1996 - 2004)
Scientific Advisory Committee - Bainbridge Technology Group, Ltd (1991 - 2000)
Board of Directors - Regional Council of Project SBIR West (1994 - 1996)
Board of Directors - Oregon Environmental Technology Association (1994 - 1995)
Co-Director - Oregon Governor's Task Force on Technology Transfer (1991 - 1992)
Board of Directors - LEAP, Inc (1988 - 1994)
Board of Directors - Oregon Biosciences Association (1991 - 1993)
Board of Directors - BioForum (1988 - 1991)
Oregon Governor's Biotechnology Industry Advisory Council (1988)

HONORS AWARDS AND FELLOWSHIPS

Governor Barbara Roberts Certificate of Appreciation - Task Force on Technology Transfer (1993)
Governor Neil Goldschmidt Letter of Commendation - Biotechnology Industry Advisory Council (1988)
FDA Award of Merit from FDA Commissioner Jere Goyan (1980)
Letter of Commendation from FDA Commissioner Donald Kennedy (1979)
Seven Research Grants Awarded as Faculty Member at Willamette University (1974 - 1977)
National Science Foundation - Graduate Research Fellowship, The Ohio State University (1971 - 1973)
Graduated with Honors, Lebanon Valley College (1969)
Petroleum Research Fund - Undergraduate Research Fellowship, Lebanon Valley College (1967 and 1968)
Dean's List Student, Lebanon Valley College (1966 - 1969)
Salutatorian, South Lebanon High School, Lebanon, PA (1965)

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Richard C. Kraska
Chief Operating Officer and Co Founder

Curriculum Vitae

EDUCATION B S , Chemistry, Providence College
 Ph D , Pharmacology, University of Minnesota

**PROFESSIONAL
CERTIFICATION** Diplomate, American Board of Toxicology

EXPERIENCE 29 year in toxicology and regulatory affairs for industry and government in broad aspects of the chemical industry including food additives, foods, food contact materials, cosmetics, lubricants and fuels, coatings, defoamers, anti-microbial pesticides and pharmaceuticals

GRAS ASSOCIATES. LLC
Bonita Springs, FL

Chief Operating Officer and Co Founder

- Serve as Lead Scientist and Panel Chair for GRAS determinations
- Coordinate drafting and report review by chemists, toxicologists and scientists of other disciplines as needed
- Ingredients reviewed include natural antioxidants, novel sources of dietary fiber, fats and oils and extracts from exotic fruit

KRASKA CONSULTANTS, INC.
Bonita Springs, FL

Vice President and Principal

- Toxicology and Regulatory Consultant for a variety of lubricant, chemical, food processing companies and trade associations
- Offer services in Toxicology and Product Safety including FDCA, TSCA and FIFRA regulations and filings, International Hazard Communication Support, Product Stewardship, Expert Witness and Litigation Support
- Founder and Technical Consultant for the Defoamer Industry Trade Association
- Toxicology Consultant for the Independent Lubricant Manufacturers Association

THE LUBRIZOL CORPORATION
Wickliffe, OH

MANAGER OF SPECIAL TOXICOLOGY AND REGULATORY PROJECTS

- Toxicology and regulatory consultant for organic growth initiatives and new acquisitions
- Coordinating inhalation toxicology program on engines emissions with a novel diesel fuel formulation for registration with EPA under the Clean Air Act
- Coordinating world wide implementation of compliance with revised European hazard communication regulations
- Consultant to Lubrizol defoamer, coating, process chemical, metalworking and lubricant businesses on regulations and toxicology
- Team member studying and planning implementation of sustainable development at Lubrizol

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MANAGER OF TOXICOLOGY AND RISK ASSESSMENT

- Provided leadership and management for corporate toxicologists and product safety specialists
- Direct responsibility for toxicology testing and evaluation of all Company specialty chemicals and products
- Manage annual toxicology and environmental testing budget for regulatory approvals and product stewardship
- Lead consultant for business units on novel regulatory approvals, product stewardship and risk evaluation.
- Developed and institutionalized product risk assessment process for all Lubrizol businesses
- Provide leadership role representing Company on trade association task groups involved in legislative and regulatory advocacy
- Co-team leader for development and implementation of award -winning expert system for writing MSDSs from a product safety database

BP AMERICA INC (formerly THE STANDARD OIL CO) Cleveland, OH

MANAGER OF PRODUCT SAFETY AND REGULATORY COMPLIANCE

- Assumed responsibility for assuring all Company products complied with federal regulations (TSCA, FIFRA, FDCA, USDA)
- Coordinated and expedited all regulatory submissions for premarket approval, reporting rules and rulemaking comment
- Conscientiously developed Company Product Safety Policies and Manual
- Critically evaluated Corporate Hazard Communication Program in a decentralizing company
- Successfully initiated labeling program to comply with OSHA Hazard Communication Standard

AMERICAN CYANAMID COMPANY, CHEMICALS GROUP Wayne, NJ

MANAGER OF TOXICOLOGY PROGRAMS

- Wide range of responsibility for recommending, contracting, monitoring and evaluating mammalian, genetic and aquatic toxicology studies for chemical products
- Responsible for total contract value for testing, quality assurance and consultants
- Effectively guided regulatory staff in strategy and data requirements for premarket approvals
- Successfully orchestrated targeted research programs for mechanistic studies on key chemicals for aquatic and mammalian toxicity
- Actively represented Company in a wide spectrum of trade association activities

FOOD AND DRUG ADMINISTRATION Washington, DC

GRAS Review Branch Division of Food and Color Additives

SUPERVISORY CONSUMER SAFETY OFFICER

- Successfully managed group of 3-4 professionals in regulatory program to implement expert panel reviews of GRAS list food ingredients
- Projects of responsibility included salt, caffeine, BHA, BHT, cellulose, enzymes, rapeseed oil, vitamins, iron, manganese and zinc salts
- Co-directed agency expertise on toxicology, chemistry, law and policy to propose regulatory action on food uses of DSS Negotiated consistency with Bureau of Drugs proposal on OTC and Rx uses
- Advised Branch Chief in matters of policy, consistency and personnel
- Interacted with industry regarding regulatory opinions and new product approvals

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**Petitions Control Branch
Division of Food and Color Additives**

CONSUMER SAFETY OFFICER

- Coordinated scientific review and regulatory response to review food additive petitions submitted by industry for direct additives and food packaging materials
- Scientific and historical expert for General Counsel, U S Attorney and Department of Justice for legal proceedings on cyclamate
- Expert on food/drug interface of vitamins and dietary supplements
- Analyzed quality of critical studies on aspartame and served on GLP review committee
- Served as Bureau representative in Interagency Regulatory Liaison Group on phthalate plasticizers
- Assistant to Bureau Director on advocacy activities on behalf of U S industry for WHO programs

PUBLICATIONS

Reed, MD, Blair LF, Burling K, Daly I, Gigliotti AP, Gudi R, Mercieca MD McDonald JD, O'callaghan JP, Seilkop, SK, Ronsko NL, Wagner VO, Kraska RC Health effects of subchronic exposure to diesel-water-methanol emulsion emissions *Toxicology & Industrial Health* Vol 22 In Press

Reed, MD, Blair LF, Burling K, Daly I, Gigliotti AP, Gudi R, Mercieca MD. McDonald JD, Naas DJ, O'callaghan JP, Seilkop, SK, Ronsko NL, Wagner VO, Kraska RC Health effects of subchronic exposure to diesel-water emulsion emissions *Inhal Toxicol* 17 851-70 (2005)

Kraska, RC , Industrial Chemicals Regulation of new and existing chemicals In Gad S C editor *Regulatory Toxicology* Taylor and Francis Ltd London 2001

Kraska, RC and Hooper DH, Industrial Chemicals Hazard Communication, exposure limits, labeling and other workplace and transportation requirements under OSHA, DOT, and similar authorities around the world In Gad S C editor *Regulatory Toxicology* Taylor and Francis Ltd London 2001

Strother, DE, Mast RW, Kraska RC, Frankos V Acrylonitrile as a carcinogen Research needs for better risk assessment *Ann NY Acad Sci* 534 169-78 (1988)

Petersen DW, Kleinow KM, Kraska RC, Lech JJ Uptake, disposition and elimination of acrylamide in rainbow trout *Toxicol Appl Pharmacol* 80 58-65 (1985)

Mast RW, Jeffcoat AR, Sadler BM, Kraska RC and Friedman MA Metabolism, disposition and excretion of [C14] melamine in male Fischer 344 rats *Food Chem Toxicol* 21 807-810 (1983)

SPEAKER

Talks given on following topics at national meetings, seminars and workshops
GRAS Criteria
REACH and GHS Regulations
HPV Toxicology Testing
Risk Assessment and Risk Management
Lubricant Additive Safety
Trade Association Environmental Activism
Product Deselection Lists
MSDS Expert Systems
Confidential Business Information under TSCA
TSCA Section 12(b) Compliance

TRAINING COURSES

Training courses given to business, research and legal groups at Lubrizol
General Regulatory Overview
TSCA New Chemicals
FDA Food Additive Requirements
Product Regulatory Law Course (TSCA, FDCA, OSHA)
Trainer, Toxicology Module, Metalworking Fluids Certificate Course

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**TRADE
ASSOCIATION
ACTIVITIES**

Chemical Reporting Task Group
Chemical Manufacturers Association
Chairperson

Safety, Health, Environmental and Regulatory Affairs Committee, Independent Lubricant
Manufacturers Association
Vice chairperson (
Chairperson
Toxicology consultant

Oversight Committee, Metalworking Fluid Product Stewardship Group, Independent
Lubricant Manufacturers Association)

Health Environmental and Regulatory Task Group, Petroleum Additives Panel
Chairperson, Sensitization Work Group

Biocides Panel, AEATF II Protocol Committee and Technical Committee Team
Leader for Metalworking Study

Defoamer Industry Trade Association, Founder and Technical Consultant

**PROFESSIONAL
SOCIETY
MEMBERSHIPS**

Society of Toxicology (SOT)
American Standards and Testing Methods (ASTM)
Society of Tribology and Lubrication Engineers (STLE)
Regulatory Affairs Professionals Society (RAPS)
Roundtable of Toxicology Consultants (RTC)

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APPENDIX D

Key Publications Addressing the Safety of Selenium & SelenoExcell®

Clark, L. C., Combs, Jr., G. F., Turnbull, B. W., Slate, E. H., Chalker, D. K., Chow, J., Davis, L. S., Glover, R. A., Graham, G. F., Gross, E. G., Kronrad, A., Leshner, Jr., J. L., Park, H. K., Sanders, Jr., B. B., Smith, C. L., & Taylor, J. R., (1996), "Effects of Selenium Supplementation for Cancer Prevention in Patients with Carcinoma of the Skin," *JAMA*, 276(24), 1957-1963

European Commission, Health & Consumer Protection Directorate-General, (2000), "Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium," 2-18.

Expert Group on Vitamins and Minerals, Medicines and Healthcare Products Regulatory Agency, UK Department of Health, (2003), "Safe Upper Levels for Vitamins and Minerals Part 3 Trace Elements Selenium," Food Standards Agency, 232-239

Longnecker, M. P., Taylor, P. R., Levander, O. A., Howe, M., Veillon, C., McAdam, P. A., Patterson, K. Y., Holden, J. M., Stampfer, J. J., Morris, J. S., & Willett, W. C., (1991), "Selenium in Diet, Blood, and Toenails in Relation to Human Health in a Seleniferous Area," *Am J Clin Nutr*, 53, 1288-1294.

Marshall, J. R., (2001), "Larry Clark's Legacy: Randomized Controlled, Selenium-Based Prostate Cancer Chemoprevention Trials," *Nutrition and Cancer*, 40(1), 74-77

Rayman, M. P., (2004), "The Use of High-Selenium Yeast to Raise Selenium Status: How Does it Measure Up?" *British Journal of Nutrition*, 92 557-573.

Reid, M. E., Stratton, M. S., Lillico, A. J., Fakh, M., Natarajan, R., Clark, L. C., & Marshall, J. R., (2004), "A Report of High-Dose Selenium Supplementation. Response and Toxicities," *Journal of Trace Elements in Medicine and Biology*, 18, 69-74

Schrauzer, G. N., (2001), "Nutritional Selenium Supplements: Product Types, Quality, and Safety," *Journal of the American College of Nutrition*, 20(1), 1-4.

Uden, P. C., Boakye, H. T., Kahakachchi, C., Hafezi, R., Nolibos, P., Block, E., Johnson, S., & Tyson, J. F., (2004), "Element Selective Characterization of Stability and Reactivity of Selenium Species in Selenized Yeast," *J Anal At Spectrom*, 19, 65-73

Whanger, P. D., (2004), "Selenium and Its Relationship to Cancer. An Update," *British Journal of Nutrition*, 91, 11-28

Yang, G., Wang, S., Zhou, R., & Sun, S., (1983), "Endemic Selenium Intoxication of Humans in China," *Am J Clin Nutr*, 37, 872-881

Yang, G., Yin S., Zhou, R., Gu, L., Yan, B., Liu, Y. & Liu, Y., (1989), "Studies of Safe Maximal Daily Selenium Intake in a Seleniferous Area in China. II. Relation Between Selenium Intake and the Manifestation of Clinical Signs and Certain Biochemical Alterations in Blood and Urine," *Journal of Trace Elements and Electrolytes in Health and Disease*, 3, 123-130

Yang, G. and Zhou, R., (1994), "Further Observations on the Human Maximum Safe Dietary Selenium Intake in a Seleniferous Area in China," *Journal of Trace Elements and Electrolytes in Health and Disease*, 8, 159-165.

000050

Pages 000051 - 000057 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

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Pages 000173 - 000179 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

SUBMISSION END

000180

Reference List for Industry Submission, GRN 000241

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000051 - 000057	Clark, Larry C.; Combs, Gerald F.; Turnbul, Bruce W.; Slate, Elizabeth H.; Chalker, Dan K.; Chow, James; Davis, Loretta S.; Glover, Renee A.; Graham, Gloria F.; Gross, Earl G.; Krongrad, Arnon; Leshner, Jack L.; Park, H. Kim; Sanders, Beverly B; Smith, Cameron L.; Taylor, J. Richard	Effects of Selenium Supplementation for Cancer Prevention in Patients With Carcinoma of the Skin: A Randomized Controlled Trial	December 25, 1996	JAMA	Volume 276, Number 24, pgs1957-1963
000058 - 000075	NA	Opinion of the Scientific Committee on Food the Tolerable Upper Intake Level of Selenium	November 28, 2000	European Commission Health & Consumer Protection Directorate- General - Scientific Committee on Food	Volume 25, pgs 2-18
000076 - 000089	NA	Safe Upper Levels for Vitamins and Minerals	May 2003	Expert Group on Vitamins and Minerals	pgs 5-8, 232- 239
000090 - 000096	Longnecker, Matthew P.; Taylor, Philip R.; Levander, Orville A.; Howe, Sister M.; Veillon, Claude; McAdam, Patricia, A.; Patterson, Kristine Y.; Holden, Joanne M.; Stampfer, Meir J.; Morris, J. Steven; Willett, Walter C.	Selenium in diet, blood, and toenails in relation to human health in a seleniferous area	1991	The American Journal of Clinical Nutrition	Volume 53, pgs 1288-1294
000097 - 000100	Marshall, James R.	Larry Clarks Legacy: Randomized Controlled, Selenium-Based Prostate Cancer Chemoprevention Trials	2001	Nutrition And Cancer	Volume 40, Number 1, pgs 74-77
000101 - 000117	Rayman, Margaret P.	The use of high-selenium yeast to raise selenium status: how does it measure up?	2004	British Journal of Nutrition	Volume 92, pgs 557-573

NA- Not applicable

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000118 - 000123	Reid, Mary E.; Stratton, M. Suzanne; Lillico, Anna J.; Fakh, Marwan; Natarajan, Raj; Clark, Larry C.; Marshall, James R.	A report of high-dose selenium supplementation: response and toxicities	2004	Journal of Trace Elements in Medicine and Biology	Volume 18, pgs 69-74
000124 - 000127	NA	Nutritional Selenium Supplements: Product Types, Quality, and Safety	2001	Journal of the American College of Nutrition	Volume 20, Number 1, pgs 1-4
000128 - 000136	Uden, Peter C.; Boakye, Harriet Totoe; Kahakachchi, Chethaka; Hafezi, Rameh; Nolibos, Paula; Block, Eric; Johnson, Sherida; Tyson, Julian F.	Element selective characterization of stability and reactivity of selenium species in selenized yeast	2004	J Anal At Spectrom	Volume 19, pgs 65-73
000137 - 000154	Whanger, P.D.	Selenium and its relationship to cancer: an update	2004	British Journal of Nutrition	Volume 91, pgs 11-28
000155 - 000164	Yang, Guangqi; Wang, Shuzhen; Zhou, Ruihua; Sun, Shuzhuang	Endemic selenium intoxication of humans in China	1983	The American Journal of Clinical Nutrition	Volume 37, pgs 872-881
000165 - 000172	Yang, G.; Yin, S.; Zhou, R.; Gu, L.; Yan, B.; Liu, Y.; Liu, Y.	Studies of Safe Maximal Daily Se-Intake in a Seleniferous Area in China. Part II: Relation Between Se-Intake and the Manifestation of Clinical Signs and Certain Biochemical Alterations in Blood and Urine	1989	J Trace Elem Electrolytes Health Dis	Volume 3, Number 3, pgs 123-130
000173 - 000179	Yang, G.; Zhou, R.	Further Observations on the Human Maximum Safe Dietary Selenium Intake in a Seleniferous Area of China	1994	J Trace Elem Electrolytes Health Dis	Volume 8, pgs 159-165

NA- Not applicable

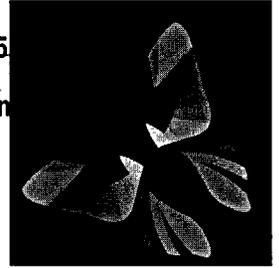
(b)(5)

GRAS ASSOCIATES, LLC

Generally Recognized As Safe

20482 Jacklight Lane Bend, OR 97702-3074 541 678-5522

mcquate@gras-associates.com www.gras-associates.com



April 9, 2008

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

Re: GRAS Notification 241 --- High-Selenium Yeast

Dear Dr. Martin:

On behalf of Cypress Systems, Inc, we request that you cease the evaluation of the above-referenced GRAS notice addressing High-Selenium Yeast.

We may elect to resubmit a modified notification at a future date.

Thank you.

Sincerely,

(b)(6)

Robert S. McQuate, Ph.D.
CEO & Co-Founder
GRAS Associates, LLC
20482 Jacklight Lane
Bend, OR 97702-3074
541-678-5522
mcquate@gras-associates.com
www.gras-associates.com