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June 22, 2023

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Dr.
College Park, MD 20740

Attention: Dr. Susan Carlson
Re: GRAS Notification – SelenoExcell® High Selenium Yeast Use in Infant Formula

Dear Dr. Carlson:

GRAS Associates, LLC, acting as the Agent for Cypress Systems, Inc. (United States), is submitting for FDA review, Form 3667 and the enclosed CD, free of viruses, containing a GRAS Notification for SelenoExcell® High Selenium Yeast Use in Infant Formula. Along with Cypress Systems, Inc.'s determination of safety, an Expert Panel of qualified persons was assembled to assess the composite safety information of the subject substance with the intended use in non-exempt infant formula for term infants as a nutrient as defined by 21 CFR 170.3(o)(20) at use levels intended to comply with the range for selenium as established in 21 CFR 107.100(a) (2.0 – 7.0 µg Se/100 kcal). The intended effect is as a nutrient necessary for the body's nutritional and metabolic processes. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS guidance document.

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. I also authorize Amy Mozingo (amozingo@gras-associates.com), VP US Nutra Regulatory Sciences, GRAS Associates LLC to lead communications related to this submission.

We look forward to your feedback.

Sincerely,

William J. Rowe

GRAS ASSOCIATES

Food Safety Regulatory Services,
A Nutrasource Company

nutrasource
Pharmaceutical and Nutraceutical Services

GRAS Conclusion

of

SelenoExcell® High Selenium Yeast Use in Infant Formula

Food Usage Conditions for General Recognition of Safety

on behalf of

Cypress
40365 Brickyard Drive, Suite 101
Madera, CA 93636

6/19/23

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FOREWORD

Cypress Systems, Inc. (“Cypress”) based our Generally Recognized as Safe (GRAS) assessment of SelenoExcell®, on the composite safety information, i.e., scientific procedures with corroboration from history of use. The safety/toxicity of SelenoExcell®, history of use of SelenoExcell®, and compositional details, specifications, and method of preparation of the subject ingredient were reviewed. In addition, a search of the scientific and regulatory literature was conducted through May 12, 2023, with particular attention paid to adverse reports, as well as those that supported conclusions of safety. Those references that were deemed pertinent to this review are listed in Part 7. The composite safety/toxicity studies, in concert with dietary exposure information, ultimately provide the specific scientific foundation for the GRAS conclusion.

At Cypress’s request, GRAS Associates, LLC (GA) convened an Expert Panel to complete an independent safety evaluation of Cypress’s SelenoExcell® product. Cypress’s SelenoExcell® preparation is manufactured by aerobic fermentation of a selected *Saccharomyces cerevisiae* yeast strain in the presence of sodium selenite (Na_2SeO_3) which results in organically bound selenium in the SelenoExcell® finished product. The purpose of the evaluation is to ascertain whether Cypress’s SelenoExcell® is generally recognized as safe, i.e., GRAS, under the intended conditions of use. In addition, Cypress has asked GA to act as Agent for the submission of this GRAS notification.

PART 1. SIGNED STATEMENTS AND CERTIFICATION

Cypress has concluded that SelenoExcell® which meets the specifications described below, is GRAS in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This determination was made in concert with an appropriately convened panel of experts who are qualified by scientific training and experience. The GRAS determination is based on scientific procedures as described in the following sections. The evaluation accurately reflects the intended conditions of food use for the designated SelenoExcell® preparation.

This signed statement and certification has been prepared in accordance with the requirements of 21 CFR 170.225.

(a) This certification is signed by a responsible official of GRAS Associates, LLC acting as agent for Cypress.

(b) This Part 1 of this GRAS notification does not include any confidential information.

(c) (1) This Independent GRAS Assessment was conducted in accordance with Subpart E of 21 CFR Part 170.

(c) (2) Names and addresses of organizations;

Sponsoring Party:
Cypress Systems, Inc.
40365 Brickyard Drive, Suite 101
Madera, CA. 93636

As the Responsible Party, Cypress accepts responsibility for the GRAS conclusion that has been made for SelenoExcell® preparation as described in the subject safety evaluation.

Agent:
GRAS Associates, LLC
11810 Grand Park Avenue
Suite 500
North Bethesda, MD 20852

(c) (3) The name of the ingredient is SelenoExcell® High Selenium Yeast.

(c) (4) SelenoExcell® is intended for use in non-exempt infant formula for term infants as a nutrient as defined by 21 CFR 170.3(o)(20) at use levels intended to comply with the range for selenium as established in 21 CFR 107.100(a) (2.0 – 7.0 µg Se/100 kcal). The intended effect is as a nutrient necessary for the body's nutritional and metabolic processes.

(c) (5) The statutory basis for our conclusion of GRAS status is through scientific procedures in accordance with § 170.30(a) and (b).

(c) (6) It is our view that the ingredient is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

(c) (7) If FDA were to ask to see the data and information that are the basis for our conclusion of GRAS status, either during or after FDA evaluation of this notice, we agree to:

(i) make the data and information available to FDA; and

(ii) agree to both of the following procedures for making the data and information available to FDA:

(A) Upon FDA's request, we will allow FDA to review and copy the data and information during customary business hours at our address specified where these data and information will be available; and

(B) Upon request by FDA, we will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for their evaluation or on paper.

(c) (8) None of the data and information in Parts Part 2 through Part 7 of this GRAS notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552 (e.g., as trade secret or as commercial or financial information that is privileged or confidential).

(c) (9) We certify that, to the best of our knowledge, this GRAS Assessment is a complete, representative, and balanced review that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

(c) (10) Cypress does not intend to add SelenoExcell® to any meat and/or poultry products that come under FSIS/USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

(c) (11) Signature

Agent for Cypress Systems, Inc.

William J. Rowe
President
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

Date: June 19, 2023

PART 2. IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

A. Chemical Identity of Ingredient

High-selenium yeast (from *Saccharomyces cerevisiae*) is the common or usual name of SelenoExcell®. The compositional features of the SelenoExcell® are described in more detail in this section. The ingredient is marketed as SelenoExcell®.

Common Names: High Selenium Yeast, Selenized Yeast, Selenium Enriched Yeast
Commercial Name: SelenoExcell® High Selenium Yeast 1200

1. Chemistry

SelenoExcell® is a selenium rich, dried cellular product derived from aerobic fermentation of a selected *Saccharomyces cerevisiae* (Baker's yeast) strain cultured in the presence of sodium selenite (Na_2SeO_3). SelenoExcell® contains 1200-1380 µg/g total organically bound selenium. The selenium content is a mixture of organoselenium forms with selenomethionine as the predominant form in the mixture. Uden et al. (2003) reported SelenoExcell® contained 84% selenomethionine (Figure 1) and positively identified selenite (0.1%), γ-glutamyl-Se-methyl-seleno- cysteine (0.5%) and Se-adenosylselenohomocysteine (0.5%). Unaccounted selenium has been attributed to the inherent analytical limitations, including extraction procedures (Rayman, 2004; Amoako et al., 2009). However, analysis of other high-selenium yeast products has reported trace levels of other organic selenium species such as selenium-cysteine, selenium cystine, selenium-methyl-selenium-cysteine, selenium-methionine selenoxide, selenium-cystathionine, and selenium-lanthionine (Uden et al., 2003; Rayman, 2004).

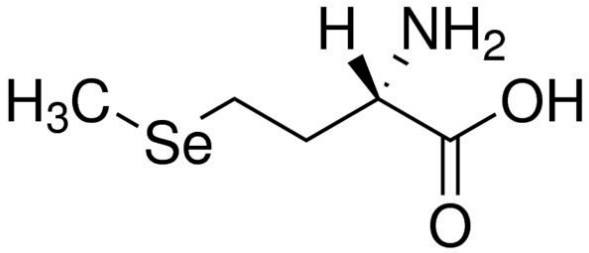

Figure 1. Structure of Selenomethionine [a]
[a] Sigma-Aldrich (2022)

B. Manufacturing Processes

The scientific principles fundamental to the manufacturing process for producing organically-bound selenium yeast via aerobic fermentation are described in detail in Cypress's previous GRAS

Notification (GRN 260) for SelenoExcell® (Cypress Systems Inc, 2008) and incorporated herein by reference. Briefly, the process utilizes *Saccharomyces cerevisiae* as the yeast into which inorganic selenium, as Na_2SeO_3, is incorporated. Continuous fermentation utilizes a medium with minimal sulfur and methionine levels to enhance the degree of selenium incorporation into the mother yeast. Cypress describes its production process and the Quality Assurance/Quality Control (QA/QC) program in summary sheets that are found in Appendix 1**.**

Key components are noted below:

- The method utilizes standard, non-GMO, Baker's yeast strain (*Saccharomyces cerevisiae)*.
- Aerobic fermentation is precisely controlled to maintain yeast growth, nutrient feed streams, dissolved oxygen, pH, temperature, and the presence of alcohol to yield optimal growth conditions with the proper uptake of selenium.
- Na_2SeO_3 is added to the fermentation vessel at specific times to maximize selenium incorporation into the yeast's natural protein matrix.
- The resulting primary grown high protein yeast, which is fortified with biologically bound selenium, is separated from its growth medium, washed twice with fresh water, 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, Cypress collects composite samples during the spray drying phase and during packaging for nutrient and microbial analyses by external, independent and certified laboratories.
- The resulting SelenoExcell® is 100% organically bound with no residual non-organic selenium.

The manufacturing process is summarized in a flow chart provided in Figure 2. All materials used in the manufacturing process (fermentation media, processing aids and food contact substances) are food grade and comply with any applicable regulations per 21 CFR. A food-grade, pure culture of a *Saccharomyces cerevisiae* strain is the starting material for fermentation. This yeast strain is overseen under strict controls by our manufacturing partner (specification found in Appendix 2). A statement detailing ingredients used in fermentation/culture media, confirming food grade status and compliance to applicable US regulation is provided in Appendix 2.

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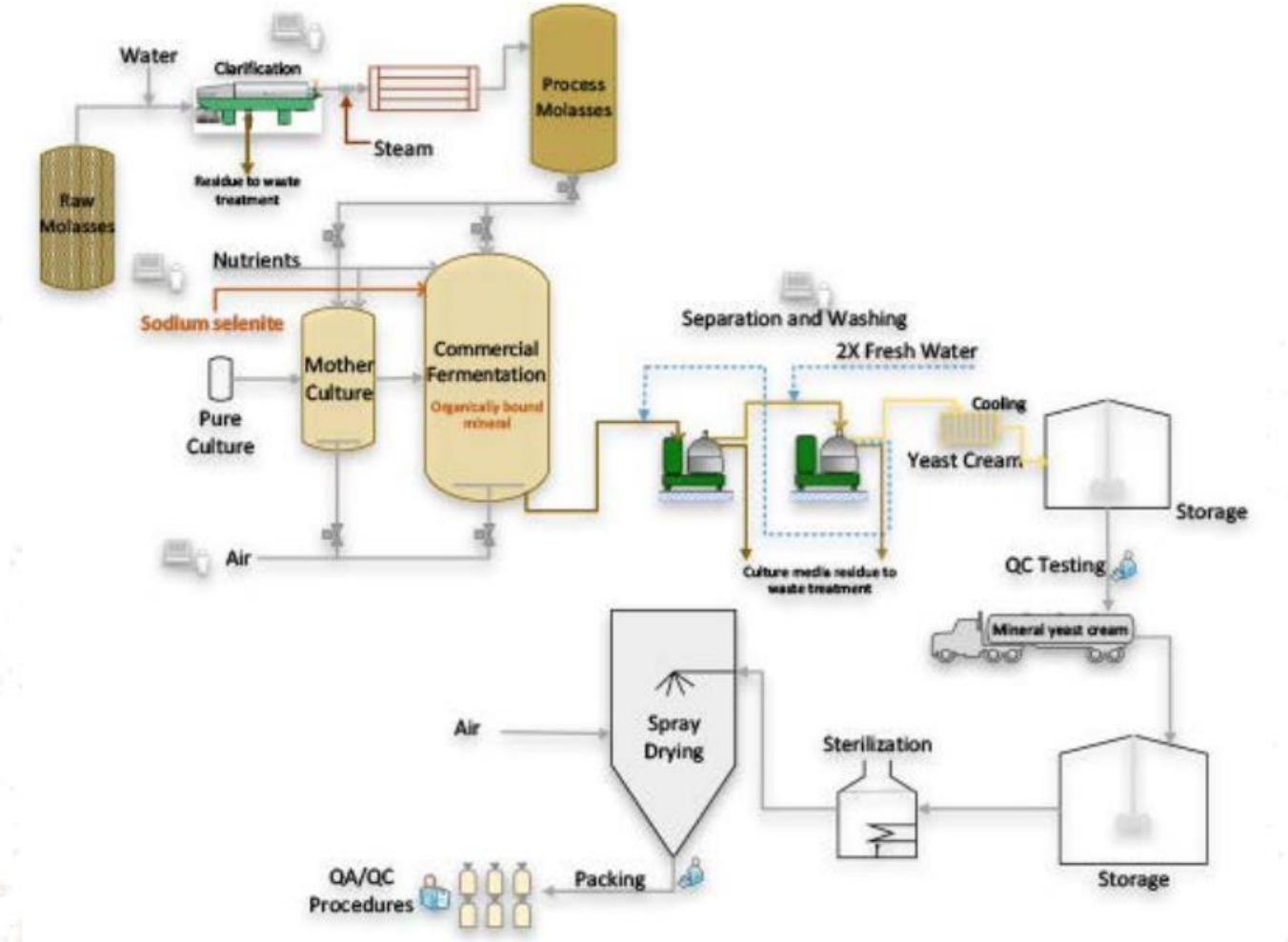

Figure 2. Flow Chart of Manufacturing Process for SelenoExcell®

C. Specifications for Cypress's SelenoExcell® Preparation and Supporting Methods

Cypress has adopted product specifications for its SelenoExcell® preparation. The compositions of five non-consecutive lots of Cypress's SelenoExcell® are shown in Table 1. Cypress's specification/product data sheet and information from four non-consecutive lots for SelenoExcell® are found in Appendix 3. The Certificates of Analysis (COA) included in Appendix 3 include higher standard limits on heavy metals. As shown in Table 1, Cypress has adopted lower limits on heavy metals as the test results support that lower limits can be consistently achieved. The specifications for SelenoExcell® for use in infant formula contain an absence specification for *Cronobacter sakazakii* spp.

Table 1. Specifications for Cypress's SelenoExcell® for Infant Formula

Physical & Chemical Parameters	Cypress's Specifications for SelenoExcell®	Analytical Method	SelenoExcell® Representative Lots			
			Lot # SE-127	Lot # SE-128	Lot# SE-130	Lot # SE-131
Total Selenium (µg/g)	1,200 -1,380	ICP-MS	1360	1220	1238	1222
Organically Bound Selenium	100%	MBRT Method	100%	100%	100%	100%
Moisture (%)	2.5-7.5	AOAC 927.05	5.05	5.09	5.04	4.53
Color	Tan to light brown	Visual	Tan	Tan	Tan	Tan
Extraneous Material	Negative	HACCP	Negative	Negative	Negative	Negative
Salmonella spp.	Negative/60g	AOAC 2004.03	Negative	Negative	Negative	Negative
E. Coli	Negative/10g	Current USP-/NF<62>	Negative	Negative	Negative	Negative
Staphylococcus aureus	Negative/10g	Current USP/NF<62>	Negative	Negative	Negative	Negative
Cronobacter sakazakii*	Negative/10g*	ISO22964	Negative	Negative	Negative	Negative
Listeria monocytogenes*	Negative/25g*	FDA-BAM 7th Ed.	Negative	Negative	Negative	Negative
Total Coliforms (MPN/g)	< 3	AOAC 966.24	< 0.3	< 0.3	< 0.3	< 0.3
Total Plate Count (CFU/g)	< 150	AOAC 966.23	20	<10	<10	<10
Yeast (CFU/g)	< 50	FDA-BAM 7th Ed.	< 10	< 10	< 10	< 10
Mold (CFU/g)	< 50	FDA-BAM 7th Ed.	< 10	< 10	< 10	< 10
Arsenic (µg/g)	< 0.5	ICP-MS	< 0.5	< 0.5	< 0.5	< 0.5
Cadmium (µg/g)	< 0.3	ICP-MS	< 0.25	< 0.25	< 0.25	< 0.25
Mercury (µg/g)	< 0.1	ICP-MS	< 0.05	< 0.10	< 0.10	< 0.10
Lead (µg/g)	< 0.1	ICP-MS	< 0.10	< 0.10	< 0.10	< 0.10
Particle Size (through 60 mesh)	98% Minimum	ASTA 10.0 (Ro-Tap Sieve)	100	100	100	100%
Particle Size (through 100 mesh)	95% Minimum	ASTA 10.0 (Ro-Tap Sieve)	98	99	98	98%

Physical & Chemical Parameters	Cypress's Specifications for SelenoExcell®	Analytical Method	SelenoExcell® Representative Lots			
			Lot # SE-127	Lot # SE-128	Lot# SE-130	Lot # SE-131
Bulk Density (g/mL)	0.6 – 0.9	Internal Methods (ASTA 25.0)	0.72	0.73	0.69	0.69

*These parameters are guaranteed for each lot, and every lot designated for use in infant formula will be tested.
AOAC – AOAC International; ASTA – American Spice Trade Association; CFU – Colony forming units; FDA-BAM – U.S. Food and Drug Administration Bacteriological Analytical Manual; g – Grams; HACCP – Hazard analysis and critical control points; ICP-MS – Inducively-coupled plasma mass specometry; µg - Micrograms; MBRT – Methylene Blue Reduction Test; mL – Milliliters; MPN – Most probable number; USP-NF - United States Pharmacopeia-National Formulary

D. Physical or Technical Effect

SelenoExcell® will be added as a source of the required nutrient selenium to non-exempt infant formula for term infants within the permitted use levels of 2.0 – 7.0 µg selenium/100 kcal of infant formula. The intended effect is as a nutrient necessary for the body's nutritional and metabolic processes.

E. Stability

SelenoExcell® has been shown to be stable after storage over a four-year period in multiple batches as shown in Appendix 4. Samples were selected from batches manufactured between 1998 and 2010. Selenium levels were analyzed at the time of manufacture and reanalyzed in 2010 and 2014. The selenium content of all the samples remained within 5% variance on the Inductively Coupled Plasma - Optical Emission Spectrometry (ICP-OES) technique.

As stated in GRN 260 "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 raised by Uden et al. (2003) who conducted compositional testing of the test materials that had been used in a 10+ year cancer clinical testing by Clark et al. (1996). This clinical trial utilized SelenoExcell® as the administered form of selenium that yielded favorable clinical results. According to Uden et al. (2003), the tableted form of SelenoExcell® was stored at room temperature for more than ten years, and further testing by Uden and colleagues using proteolytic digestion followed by High Performance Liquid Chromatography-Mass Spectroscopy (HPLC-ICP-MS) Gas Chromatography-Atomic Emission Detection (GC-AED), and Nuclear Magnetic Resonance (NMR) 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. However, there is no reason to expect that this has any significant relation to safety."

Amoako et al. (2007) further characterized the yeast tablets from the Clark et al. (1996) trial and reported that all initial selenium was present and no increase in the inorganic forms of selenium was observed. Amoako et al. (2009) evaluated selenium yeast samples, including SelenoExcell®, and reported they formed S-(methylseleno) cysteine and selenocysteine at 100 °C for 7 days.

F. Genetically-Modified Organism (GMO) Status

SelenoExcell® is manufactured using a culture *Saccharomyces cerevisiae* from a pure strain that is tested for identity, purity, and viability through morphological characterization and physiological evaluation. The strain is maintained at the ATCC and has not been genetically modified (GM) and no GM materials are introduced during any stage of the process. A Non-GMO Statement for SelenoExcell® is found in Appendix 5.

G. Allergens

Allergenic substances are not included at any step of the manufacturing process of SelenoExcell® or in the fermentation medium (except for yeast, see Appendix 6). The potential for an allergenic response to SelenoExcell® has been reviewed in detail in GRN260 (Cypress Systems Inc, 2008). A comprehensive review of the published literature did not identify reports of allergenicity associated

with ingestion of either *Saccharomyces cerevisiae* or high-selenium yeast. Outreach to the American Academy of Allergy, Asthma and Immunology, The Food Allergy Network, the American Academy of Pediatrics and the American College of Allergy, Asthma and Immunology confirmed the absence of reports of food allergies linked with *Saccharomyces cerevisiae* and the European Food Safety Authority (EFSA) Panel on food additives concluded that "food uses of the selenium-enriched yeast were unlikely to present an allergenic risk to consumers" (EFSA, 2008).

PART 3. DIETARY EXPOSURE

A. Current Dietary Exposure

1. Estimates of SelenoExcell® Daily Intake

SelenoExcell® is intended for use as a source of selenium in non-exempt infant formula (in currently available protein bases (e.g., soy, milk, whey)) for term infants at use levels to comply with the range of selenium established in 21 CFR 107.100(a) (2.0 – 7.0 µg Se/100 kcal).

The dietary exposure distributions were calculated using the Creme Food Safety® model, a scientific cloud-based software service designed and developed to calculate dietary intakes of foods, chemicals, and nutrients in populations of consumers. This is achieved by linking food consumption data from the What We Eat In America (WWEIA) portion of the 2017-2018 National Health and Nutrition Examination Survey (NHANES) (NHANES, 2017-2018) to the appropriate food composition and chemical occurrence data using a number of validated and published models, available upon request from Crème Global (https://www.cremeglobal.com/). Calculations for this intake analysis were completed using deterministic (single points) input data. Output calculation types include daily average intakes, acute exposures, as well as population statistics such as mean, percentiles, standard errors, and confidence intervals. Results are output for "Consumers Only" (i.e., consumers of the food / substance of interest), and Total Population (consumers and non-consumers). Results of the exposure assessment are given in absolute terms (mg/day) as well as relative to the consumer's body weight (mg/kg bw/day). The per unit of body weight exposure is calculated on a subject level using the bodyweight recorded by the NHANES data.

According to the intake analysis of total formula consumption in infants up to 12 months (Categories: Formula, prepared from concentrate; Formula, prepared from powder; Formula, ready-to-feed), the highest intake is in 0–6-month-old infants (Table 2). The highest 90th percentile intake, in males, is 207.3 g/kg bw/day. Female infants 0–6-months-old consume 200.4 g/kg bw/day and the genders combined 90th percentile intake is 206 g/kg bw/day.

According to the FAO Codex Alimentarius (FAO, 2007), infant formula prepared ready for consumption shall contain not less than 60 kcal (250 kJ) and not more than 70 kcal (295 kJ) per 100 mL. This equates to approximately 143-167 mL infant formula to provide 100 kcal.

Several recent GRAS notifications (GRN 990; GRN 915; GRN 993; GRN 1013; GRN 1041) for ingredients for use in infant formula have reported a caloric value for standard infant formula ranging from 67-68 kcal/100 mL (FDA, 2021b; FDA, 2021a; FDA, 2021c; FDA, 2021d; FDA, 2022b; FDA, 2022a).

Using a caloric value of 68 kcal/100 mL (the high end of range), this would be equivalent to a 90th percentile energy intake of 140 kcal/kg bw/day based on the present intake analysis results for 0–6-month-old male and female infants.

This is in line with previous GRAS notifications that have assumed typical formula consumption ranging from 100 to 120 kcal/kg bw/day (FDA, 2022a), or have reported 90th percentile energy intakes as high as 141.3 kcal/kg bw/day for males and 138.9 kcal/kg bw/day for females (FDA, 2021b).

For the purpose of this analysis, 1 g is equivalent to 1 mL, thus consumption of infant formula (for both sexes) at the 90th percentile is considered to be 206 mL/kg bw/day.

Intake of formula by infants 0-6 months on a body weight basis is higher than for infants 7-12 months, as foods other than infant formula are typically introduced after 6 months. Table 2 provides data on formula intake by consumer only infants by age group and gender.

Table 2. Summary of Formula Intake (Consumers Only) by Volume in Infants 0 to 1 year of Age

Gender	Age (Years)	Age (Months)	Mean Consumption (mL/kg bw/day)	90th Percentile Total Consumption (mL/kg bw/day)
Male	0 – 0.5	0-6	133.41	207.29
Female	0 – 0.5	0-6	113.08	200.44
Both genders	0 – 0.5	0-6	124.26	205.95
Male	0.58 – 1	7-12	72.96	128.21
Female	0.58 – 1	7-12	72.60	120.35
Both genders	0.58 – 1	7-12	72.80	124.75

bw – Body weight; kg – Kilograms; mL - Milliliters

Basing the intake on 68 kcal per 100 mL, Table 3 shows the amount of caloric intake by age group and gender.

Table 3. Summary of Caloric Intake in Infants (Consumer Only) 0 to 1 Year of Age (Calculated as 68 kcal per 100 mL Formula)

Gender	Age (Years)	Age (Months)	Total Mean Intake (kcal/kg bw/day)	90th Percentile Intake (kcal/kg bw/day)
Male	0 – 0.5	0-6	90.72	140.96
Female	0 – 0.5	0-6	76.90	136.30
Both genders	0 – 0.5	0-6	84.50	140.05
Male	0.583 – 1	7-12	49.61	87.18
Female	0.583 – 1	7-12	49.36	81.84
Both genders	0.583 – 1	7-12	49.50	84.83

bw – Body weight; kcal – Kilocalories; kg – Kilograms; mL - Milliliters

Based on specifications range of 1200-1380 µg selenium per gram of SelenoExcell® in Part 2, and the intake of infant formula at the 90th percentile and infant weight-for age charts (CDC, 2001), addition of SelenoExcell® will be added to infant formula intended for infants 0-6 months of age at a maximum of 1.8 mg/100 kcal, providing approximately 2.5 µg selenium per 100 kcal of formula.[1] The maximum estimated daily intake of selenium from the proposed use in non-exempt term infant formula for 0-6 month-old infants is approximately 31 µg per day,[2] well below the tolerable upper limit (UL) of 45 µg established by the IOM for infants 0-6 months of age (IOM, 2000).

Older infants have a lower intake of formula compared to 0–6-month-old infants. The highest 90th percentile consumer is male infants with an intake of 128.21 mL formula/kg body weight (equating to 87.18 kcal/kg bw/day). The 90th percentile body weight of 11.5 month-old infants is 11.72 kg (CDC, 2001). Under this scenario, a 6–12-month-old infant would consume 1,022 calories from formula intake (calculated as 87.18 kcal/kg bw/day x 11.72 kg). This equates to 10.2 100 kcal servings. A use level of 2.5 mg of SelenoExcell® per 100 kcal of infant formula provides 3.5 µg selenium[3] and the daily selenium intake from addition of SelenoExcell® to infant formula would be 35.7 µg. Utilizing the IOM calculation of average selenium from complementary foods for 7 to 12-month-old infants at 11 µg/day, the maximum estimated daily intake of selenium would be approximately 47 µg per day, well below the ULs established by the IOM (60 µg) and EFSA (55 µg) for this age group .

While there is evidence of higher bioavailability of selenium from selenium-enriched yeast and/or selenomethionine (Hadrup and Ravn-Haren, 2021; Ravn-Haren et al., 2008b), there is no evidence that selenium-enriched yeast poses a higher risk of selenosis than inorganic selenium species; on the contrary there is evidence it may present a lower risk (Rayman, 2004; Spallholz and Raftery, 1987; Vinceti et al., 2017). To account for the potential of higher bioavailability, the maximum proposed use of SelenoExcell® in non-exempt term infant formula is at the lower end of the range of selenium established in 21 CFR 107.100(a).

B. Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food

This section is not applicable to Cypress's SelenoExcell® product, which would be chemically stable under the proposed conditions of use.

C. Dietary Exposure to Contaminants or Byproducts

Potential contaminants of Cypress's SelenoExcell® include microbes and heavy metals. The specifications set for Cypress's SelenoExcell® place limits on the maximum permissible levels of these impurities to assure an acceptable final product. The batch data for four nonconsecutive lots of SelenoExcell® document quality control of the final product such that it meets these specifications (Table 1).

PART 4. SELF-LIMITING LEVELS OF USE

The intended use of SelenoExcell® is not self-limiting.

[1] 2.5 µg Se /1380 µg Se/g = 0.0018 g (1.8 mg).
[2] 12.5 100 kcal servings per day * 2.5 µg Se = 31.25 µg Se per day
[3] 3.5 µg/1380 µg Se/g = 0.0025 g (2.5 mg).

PART 5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

The statutory basis for the conclusion of GRAS status of SelenoExcell® in this document is based on scientific procedures in accordance with 21 CFR 170.30(a)(b). Therefore, experience based on common use in food before 1958 does not apply. A discussion of the history of safe consumption of SelenoExcell® is discussed in Part 6.

PART 6. NARRATIVE

A. Introduction

A search of scientific and regulatory literature was conducted through May 14, 2023. Databases searched include PubMed and Google Scholar using search terms including “selenium yeast”, “selenium-enriched yeast” and “selenomethionine”, with particular attention paid to those relevant to the safety of selenium-enriched yeast and/or selenium in infants.

B. History of Safe Consumption in Breast Milk and Infant Formula

Selenium is a trace element that is a necessary component of proteins and enzymes required for a variety of functions, including antioxidant defense, modulation of the inflammatory response, and production of thyroid hormones (Lonnerdal et al., 2017). A detailed description of the history of selenium in human diet is reviewed in GRN 260 (Cypress Systems Inc, 2008) and incorporated here by reference.

In the growing infant, selenium is essential for optimal health and development. In breast-fed infants, selenium stores are dependent on the selenium content of the mother’s diet. In formula-fed infants, selenium levels are correlated to the level and type of selenium fortification used in the formula and to the residual selenium reserves accumulated *in utero.* Selenium reserves are considerably lower in preterm infants than in full term infants. However, even in full term infants, plasma concentrations of selenium are only half of those observed in adults and these reserves are quickly depleted in growing infants; therefore, infants depend on dietary sources of selenium as they mature (Lonnerdal et al., 2017).

There is no history of consumption for high-selenium yeast in infant formulas in the U.S or internationally. In most countries, inorganic forms of selenium are used to fortify infant formula (He et al., 2018). Selenium is found in human milk, the majority of which is bound to proteins. Selenium concentrations in breast milk depend on selenium consumed in natural foods, which reflects the selenium content of the soils where they are grown. Selenium in breast milk occurs as glutathione peroxidase (4-32%) followed by selenocystamine, selenocystine, and selenomethionine. Breast milk does not contain appreciable levels of inorganic selenium. Breast milk selenium concentrations range from 10 to 30 µg/L (1.5 to 4.5 µg/100 kcal), while values as high as 283 µg/L (42.5 µg/100 kcal) have been reported with no apparent adverse effects on the breast-fed infant (Dorea, 2002; Vanek, 2015; Keshan Disease Research, 1979; Lonnerdal et al., 2017; Michalke and Schramel, 1998; Michalke and Schramel, 1997).

While breast milk is the preferred form of nutrition for infants, it is not always available for all infants or all mothers. However, it wasn’t until 1998 that standards for selenium fortification for infant formula were established and not until 2007 that actual minimum and maximum levels were recommended. In

2015, the FDA issued a final rule mandating selenium fortification in infant formula of 2.0 -7.0 µg/100 kcal (He et al., 2018).

C. Regulatory History of Selenium and High Selenium Yeast

1. United States

a. Foods

A search of FDA's GRAS Notice Inventory website[4] using the search term "selenium" identified 3 notifications. In 2008, Cypress notified the FDA of its conclusion that SelenoExcell® was GRAS for use in foods (GRN 241). However, the notification was withdrawn, and FDA ceased to evaluate the notice. Cypress refiled their notification which FDA filed as GRN 260 (Cypress Systems Inc, 2008), and received a "no questions" response from the FDA (FDA, 2009). The intended use was as an ingredient in baked products, non-alcoholic beverages, breakfast cereals, grain products and pastas, milk products, processed fruits/fruit juices, processed vegetables/ vegetables juices, commercial soups and soup mixes and medical foods at a level of 5 µg selenium/serving. The anticipated total daily selenium exposure due to use in the designated food categories was estimated to be less than 100 µg selenium. The anticipated daily medical food use would provide 100 µg selenium. The notification was based on scientific procedures and excluded infant formula and foods intended for babies and toddlers.

Alltech submitted a GRAS notification (GRN 353) for Sel-Plex®, a high-selenium yeast (Alltech, 2010) and received a "no questions" response from the FDA (FDA, 2011). The intended uses described in GRN353 are as an ingredient providing a source of selenium for use in yogurts, breads, instant cereals, breakfast and granola-type bars, soups, pastas, crackers, salty snacks, pretzels, popcorn, and beverages, at use levels to provide selenium up to 19.2 µg/day. Sel-Plex® may also be used as an ingredient in medical foods such that the aggregate amount of selenium consumed in the diet will not exceed 38.4 µg/day.

A search for "selenium" in FDAs Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System for adverse events reported from January 2004 to March 2022 resulted in 132 occurrences related to selenium containing products for oral intake. Of these, all but one product were dietary supplements. One adverse event was reported for a food product (orange juice) containing 20% of the recommended daily amount of selenium per serving (or 14 µg under the daily values in place in 2002). The adverse event reported on the food product (reported in 2002) included anxiety, distractibility, panic attack, malaise, insomnia and paranoia in a 48 year-old male (CFSAN, 2022).

b. Infant Formula

The Food and Nutrition Board of the National Research Council established a Recommended Dietary Allowance for selenium for infants 0 to 6 months of age of 10.0 µg/day based on extrapolation from adult values on the basis of body weight and a growth factor (National Research Council, 1989). In 1989, the Life Sciences Research Office recommended a selenium range of 1.5 - 5 µg/100 kcal for term infant formulas (Raiten et al., 1998). The Institute of Medicine (IOM) established an Adequate Intake (AI) for selenium of 15 µg/day (2.1 µg/kg bw) for infants 0 to 6 months of age and 20 µg/day

[4] https://www.fda.gov/food/generally-recognized-safe-gras/gras-notice-inventory

(2.2 µg/kg bw) for infants 7 to 12 months of age based on the average concentration of selenium in human milk (IOM, 2000). The IOM review calculated the intake of selenium from complementary foods for 7 to 12-month-old infants at 11 µg/day. Available formulas at the time of the IOM review report a range of 15 to 20 µg selenium/L.

The IOM set the tolerable upper intake level (UL) for selenium in infants at 45 µg/day for infants 0-6 months of age and 60 µg/day for infants 7-12 months of age (IOM, 2000). The IOM selected this level as the concentration in human milk that is not associated with known adverse effects.

In the Federal Register of April 16, 2013 (78 FR 22442), FDA proposed to amend the nutrient specifications for infant formula to include selenium as a required nutrient in 21 CFR § 107.100(a). The FDA proposed to establish minimum and maximum levels for selenium in infant formulas because evidence exists for both deficiency and toxicity of selenium. FDA identified and reviewed three relevant technical reports which recommended nutrient levels for formulas for term infants and nutrient needs of healthy term infants: (1) The Life Sciences Research Office (LSRO) report "Assessment of Nutrient Requirements for Infant Formulas" (Raiten et al., 1998), (2) "Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids" (IOM, 2000) and (3) "Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group" (Koletzko et al., 2005).

The FDA selected 7.0 µg/100 kcal based on the tolerable upper limit set by the Food and Nutrition Board of the Institute of Medicine (IOM). The IOM selected this level as the concentration in human milk that is not associated with known adverse effects. This is below the maximum level set by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) which recommended a maximum level of 9 µg/100 kcal based on scientific evidence regarding the absence of adverse effects, when such information was available. When scientific information was lacking, an established history of apparent safe use was considered (Koletzko et al., 2005). The ESPGHAN report was prepared at the request of the Codex Committee on Nutrition and Foods for Special Dietary Uses for use in revising the Codex standard 72-1982.

In the final rule, FDA selected 2.0 µg selenium per 100 kilocalories (/100 kcal) as the minimum level of selenium in infant formulas and 7.0 µg/100 kcal as the maximum level of selenium in infant formulas (FDA, 2013; FDA, 2015).

2. Other Countries

a. Foods

The European Food Safety Authority (EFSA) published a scientific opinion on the safety and bioavailability of high selenium yeast as a source for selenium in foods and nutritional supplements for the general population (EFSA, 2008). This opinion, specific to the safety and bioavailability of selenium-enriched yeast for use in foods for particular nutritional uses and in foods (including food supplements) for the general population, does not cover use in infant formula. The EFSA committee's opinion related only to selenium-rich yeasts that were produced in culture utilizing sodium selenite as the selenium source and containing, in the dried form as marketed, not more than 2.5 mg selenium/g. The predominant organic selenium species present in the yeast must be selenomethionine, constituting 60-85% of the total selenium in the product. The content of other organic selenium compounds including selenocysteine cannot exceed 10%. The EFSA committee noted that selenomethionine is readily bioavailable and that organic selenium species tend to be 1.5 – 2 times

more bioavailable than the inorganic forms of selenium. EFSA observed that the increased bioavailability of selenium from organic sources of selenium as with the high-selenium yeasts did not translate to increased toxicity for the organic selenium species. The EFSA panel concluded that high selenium yeast, when used in foods and consumed at levels of 30-200 µg/day, providing 50-200 µg selenium per day (although the majority of food products provide only 100 µg selenium/day), "does not present a safety concern" (EFSA, 2008).

b. Infant Formula

The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommended a maximum level of 9 µg selenium/100 kcal in infant formula based on scientific evidence regarding the absence of adverse effects (Koletzko et al., 2005). This was subsequently adopted by the Codex Alimentarius Commission (CAC) for its CODEX STAN 72-1981 (Revision 2007) and has not been changed to date (He et al., 2018). Sodium selenite, sodium selenate, and sodium hydrogen selenite are permitted to be added into infant formula milk.

Following the CAC, the European Union, Australia and New Zealand, and China set selenium supplementation in infant formula at 1-9 µg, 1.05-4.98 µg and 2.01-7.95 µg/kcal, respectively. Only inorganic selenium is permitted as supplementation in infant formulas in most countries and regions, except for Australia and New Zealand, which allows for the use of selenomethionine in infant formula (He et al., 2018).

In 2014, EFSA issued a scientific opinion on the essential composition of infant and follow-on formula in which EFSA recommended a minimum selenium content in formula of 3 µg/100 kcal (EFSA NDA Panel, 2014).

EFSA recently updated the scientific opinion on the tolerable upper intake level for selenium (EFSA NDA Panel et al., 2023) and noted that the published literature does not indicate that infants are more susceptible than adults to selenium toxicity. As such, the UL for adults was used to extrapolate the UL for infants 4-6 months of age and 7-11 months of age based on allometric scaling (body weight 0.75) and rounding to the nearest 5 µg. Established ULs for male and female infants 4-6 months of age and 7-11 months of age are 45 and 55 µg per day, respectively. The Panel also noted that exclusively formula fed infants consuming formula with the highest permitted concentration of selenium may exceed the established ULs.

The National Health and Medical Research Council of Australia and New Zealand has set ULs for selenium at 45 and 60 µg per day for infants 0-6 months and 7-12 months, respectively (NHMRC, 2006).

D. Absorption, Distribution, Metabolism & Excretion (ADME) Studies

In humans, selenium absorption occurs in the lower part of the small intestines via different mechanisms often along with sulfur, via sodium dependent processes (Roman et al., 2013). Although there are differences in absorption and use of selenium between organic and inorganic sources, about 70-90% is absorbed (Fairweather-Tait et al., 2010). Selenium in the form of selenite or selenate is well absorbed but less retained in the body compared to organic forms such as selenomethionine and selenocysteine (Burk et al., 2006). Several studies report higher bioavailability of selenium from yeast than from inorganic sources (Ravn-Haren et al., 2008a; Ravn-Haren et al., 2008b). It should be

noted that blood levels are the most used indicator of absorption and bioavailability allowing for comparison across studies (Hadrup and Ravn-Haren, 2021).

Selenomethionine, selenocysteine, selenate, and selenite enter the selenide pool. Then selenium is either used for selenoprotein synthesis or excreted in the urine. Selenomethionine can also be incorporated directly into proteins by replacing methionine (Fairweather-Tait et al., 2010). Selenium is reduced to hydrogen selenide. From there, the selenium is either utilized or excreted. If it is in excess and therefore excreted it goes through methylation to become dimethylselenide which is excreted in the breath or selenosugars and trimethylselenide which are excreted in the urine (Roman et al., 2014). Selenium is distributed to tissues and organs as selenocysteine in selenoproteins or as selenomethionine in the protein pool. Figure 3 provides the metabolism of selenium.

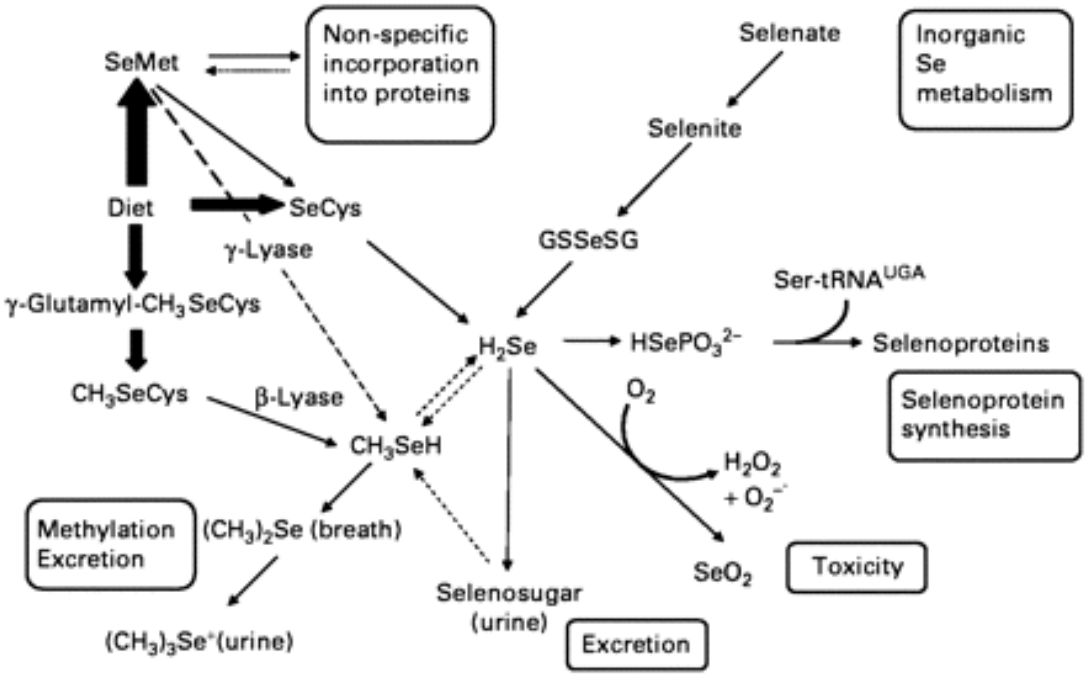

Figure 3. Metabolism of Selenium [a]

[a] Fairweather-Tait et al. (2010)

E. Safety Studies

Additional publications were identified for use of selenium yeast in livestock and poultry; however, the studies were designed to assess production performance endpoints therefore summaries and discussions of these are not included herein with exception of swine reproduction/gestation studies. The European Food Safety Authority (EFSA) Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has evaluated the safety and efficacy of various selenium-enriched yeast products, and has approved many for all animal species. Multiple scientific opinions on the safety and efficacy have been published since 2017 based on modification of the terms of authorization of the additive or for renewal of authorization (Bampidis et al., 2021; Bampidis et al., 2020; Bampidis et al., 2018; Bampidis et al., 2019; Rychen et al., 2017). In all cases, the FEEDAP Panel cited there was no

new evidence that would make the Panel reconsider previous conclusions for the safety of selenium-enriched yeast in target species, consumers, and the environment.

No new safety studies on selenium yeast were located in the published literature since GRN 260. One study was identified in which various safety assays were conducted for comparison of "bioselenium" obtained from yeast to sodium selenite (Wang et al., 2017). It is unclear if these studies were conducted under good laboratory practice or standard guidelines. Additional details of these studies are provided below.

1. Acute Toxicity Studies

Wang et al. (2017) evaluated the acute oral toxicity of selenium obtained from *S. cerevisiae* D254 fermented with addition of sodium selenite. The "bioselenium" was purified by lysing the selenium rich *S. cerevisiae* cells and the contents dialyzed against distilled water with 1 mL cysteine solution. The water was changed during dialysis until the solution did not fade within one minute after addition of methylene blue, which indicated that all the inorganic selenium was eliminated. The bioselenium was then digested with mixed acids. The authors stated that selenium incorporation in the extract was measured but they did not report the results. In this study bioselenium obtained from cultures with various fermentation times (1, 3, and 6 months) was compared with sodium selenite. Kunming mice (6-8 weeks old, 5 males and 5 females per group, with average bw of 18-20 g) were provided sodium selenite (5.56, 8.33, 12.50, 18.75, 28.12, and 42.19 mg/kg bw) or bioselenium from each fermentation time batch at doses of 5240, 7860, 11790, and 17685 mg/kg bw. Mice were fasted for 8 hours prior to administration. The LD_{50}[5] of the sodium selenite was calculated to be 21.17 mg/kg while the LD_{50} for bioselenium was calculated 7401.2, 915.3 and 1179 mg/kg for the 1-, 3-, and 6-month fermentation time, respectively.

2. Subchronic Toxicity Studies

Wang et al. (2017) also evaluated the repeat dose oral toxicity of bioselenium made from yeast in a 30-day test in Kunming mice (6 weeks old, average bw 16-20 g, 10 males and 10 females per group). The control group received distilled water and the test groups were comprised of three dose groups each for sodium selenite (1.41, 2.12, and 3.16 mg/kg bw/day) and bioselenium (786.3, 1179.5, and 1769.3 mg/kg bw/day). Animals were observed daily and weighed weekly during the study period. Animals were fasted 12 hours overnight prior to termination by cervical dislocation. Hearts, liver, spleen and kidney were excised and weighed for calculation of the organ to body weight ratio. Mice in the high dose sodium selenite group had decreased activity compared with the control group. Lower body weights were also observed in the sodium selenite group compared to control starting at week two, with all groups showing statistically significant differences at week three. In the bioselenium groups, only the high dose group had statistically significant differences in weight compared to the control group at weeks three and four. The organ to body weight ratios for the bioselenium groups showed no statistically significant differences compared to the control while the sodium selenite groups showed significant differences in low, mid and high-dose groups with the high-dose group having highly significant ($P<0.01$) differences compared with control for the heart, spleen and kidney in the high dose group (Wang et al., 2017).

[5] LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals.

3. Micronucleus Test

Wang et al. (2017) evaluated genetic toxicity of sodium selenite and bioselenium in mice using a bone marrow micronucleus test.

The bone marrow micronucleus test utilized 80 healthy 6–8-week-old male and female Kunming mice (5/sex/group). Positive (40 mg/kg bw cyclophosphamide) and negative (distilled water) control groups were included in the study. The test material included sodium selenite (2.65, 5.29, and 10.59 mg/kg bw), and bioselenium from yeast fermented for six months (589, 2950, and 1470 mg/kg bw). Animals were euthanized by cervical dislocation 6 hours after the second test (test materials were administered orally within 30 hours- the interval between the first and second test was 24 hours). Bone marrow cells were collected from both femurs into fetal calf serum, centrifuged and cells smeared on glass slides, coded, air-dried, and fixed with methanol at room temperature for five minutes. The smears were stained (Giemsa, dibasic sodium phosphate and monobasic sodium phosphate) and 1000 polychromatic erythrocytes were viewed using light microscopy to determine the micronucleus rate and polychromatic erythrocyte/normochromatic erythrocyte (PCE/NCE) ratio. The negative control showed a low micronucleus rate level, and the positive control group had a significantly higher ($P<0.05$) micronucleus rate compared to the negative control. All doses of sodium selenite tested resulted in significant higher ($P<0.05$) increase in the micronucleus rate and PCE/NCE ratio compared to the negative control. The micronucleus rates and the ratio of PCE/NCE of the bioselenium groups was not significantly different from the negative control (Wang et al., 2017).

4. Sperm Aberration Test

Wang et al. (2017) also evaluated sperm aberration in male Kunming mice administered sodium selenite (2.65, 5.29, and 10.59 mg/kg bw), bioselenium from yeast fermented for six months (589, 2950, and 1470 mg/kg bw), 40 mg/kg bw cyclophosphamide (positive control) and distilled water (negative control) by gavage for 5 consecutive days. Animals were euthanized by cervical dislocation 35 days after the first administration and the bilateral epididymis was collected, sectioned, and stained for microscopic evaluation. One thousand sperm were evaluated per mouse for numbers of aberrated sperm. The positive control had significantly ($P<0.05$) higher sperm aberration rate compared to the negative control as had the three dose groups of sodium selenite. Sperm from the bioselenium test groups had no significant differences in aberration rates compared with the negative control (Wang et al., 2017).

5. Studies in Swine

Mahan and Peters (2004) investigated the effect of organic (Se-yeast) and inorganic (selenite) Se supplementation in a swine model following from juvenile stage (grower phase) through to reproductive performance. Yorkshire x Landrace gilts (total n=126) were assigned to one of six treatments – control diet (basal Se concentration from 0.055 – 0.085 mg Se/kg diet), control diet plus 0.15 mg inorganic Se/kg diet, control diet plus 0.30 mg inorganic Se/kg diet, control diet plus 0.15 mg organic Se/kg diet, control diet plus 0.30 mg organic Se/kg diet, or control diet plus 0.15 mg inorganic Se plus 0.15 mg organic Se/ kg diet. Feeding amount post grower phase until animals reached breeding weight of approximately 135 kg was reported to be variable but the minimum amount was 1.82 kg feed per animal per day. This equates to 0.27 and 0.55 mg daily supplementation of Se over the control diet (or 0.002 and 0.004 mg/kg bw/day). Se supplementation did not affect performance measures, but Se supplementation from either organic or inorganic sources increased Se serum concentration and glutathione peroxidase activity. Higher levels of supplementation resulted in higher

serum values for both. Se concentration in liver, loin, kidney and pancreatic tissue was greatest for organic> inorganic> basal diets. Supplementation with organic Se reduced the number of still born piglets and Se supplementation in general increased the total number and number of live pigs born. Other measures of reproductive performance had statistically significant differences between the treatment groups but no strong pattern for one treatment type. Serum Se concentrations were similar between the 0.3 mg Se/kg diet treatment groups, and serum GSH-Px activity was similar across all treatment groups. Se concentration in milk and colostrum increased with Se supplementation, with a more profound effect from the organic Se supplementation. Piglets from sows supplemented with organic Se had higher loin and liver Se concentrations, and total body Se was higher for piglets from the organic Se supplement than the inorganic supplement when comparing the 0.3 mg Se/kg diet treatment groups. The authors concluded that supplemental Se from both organic and inorganic sources increased litter size, but more Se was transferred to the piglets when sows were fed organic sources of Se. Sows supplemented with both inorganic and organic Se in the diet showed similar results to the same level of organic Se supplement only. No adverse effects were reported in the publication.

Yoon and McMillan (2006) investigated the effect of feeding sows Se supplementation above the NRC recommendation of 0.15 mg Se/kg feed. Yorkshire x Landrace sows (total n=52) were assigned to one of three treatments – control diet (basal Se amount 0.20 – 0.23 mg Se/kg diet), control diet plus 0.3 mg Se/kg diet from sodium selenite or control diet plus 0.3 mg Se/kg diet from Se-enriched yeast from 60 days pre-partum to 14 days post-partum. Reproductive performance, Se concentration in the colostrum, milk, and serum from sows, and Se concentration, Immunoglobulin G, and glutathione peroxidase (GPX-1) from the serum of piglets were measured. Organic and inorganic Se supplements reduced the number of still born piglets but did not impact other measures of reproductive performance. At farrowing, sow serum Se concentrations were highest for the organic Se treatment group. Piglet serum Se concentration at birth was highest for the sows from the organic Se treatment group compared to the control, however, at weaning there was no statistical difference between the treatment groups. Serum immunoglobulin, GPX-1 did not differ significantly in piglets from the different treatment groups. Se concentration in milk and colostrum was higher in sows fed organic Se supplements compared to the inorganic Se supplements or control diets. The authors concluded that diet supplementation for sows of 0.3 mg Se/kg diet of from an organic source was beneficial, even with adequate Se in the basal diet. No adverse effects were noted in the publication.

Zhan et al (2011) investigated the effect of maternal selenomethionine intake on offspring in a swine model. Six sows (Landrace x Yorkshire) per treatment group (in six replicates) were given either sodium selenite (0.3 mg Se/kg diet) or selenomethionine (0.3 mg Se/kg diet). The base diet contained 0.4 mg Se/kg diet. The diet was fed from 32 days pre-partum to 28 days post-partum (weaning). Diets were fed three times per day and restricted to 1.3 kg per animal for gestation and 2.0 kg per animal for lactation. Se concentration was measured in the colostrum and weekly in the milk from sows. Piglets were weighed weekly starting at birth, and one piglet from each litter was sacrificed at weaning. Se concentration was measured in the serum, liver, kidney, pancreas, muscle, thymus, and thyroid gland. Se concentration was higher in the colostrum and milk from sows supplemented with selenomethionine, and Se concentration in all measured tissues was higher for piglets from these sows. Overall, piglets from sows supplemented with selenomethionine were 12.2% larger at weaning ($P<0.05$). Enzymes indicative of antioxidant status were also higher in piglets from sows fed selenomethionine, although magnitude of the increase varied across tissue type (liver, kidney, pancreas, muscle and serum). The authors concluded that supplemental feeding of sows increased bioavailability of Se for piglets. No adverse effects were reported in the publication.

Jin et al. (2022) investigated the supplementation of maternal diets with inorganic (sodium selenite) and organic Se (Se-enriched yeast) at two concentrations in a swine model. Yorkshire x Landrace sows (total n=54; average body weight 229.5 kg) were assigned to one of five treatment groups – control diet, control with 0.3 mg inorganic Se/kg diet; control with 0.5 mg inorganic Se/kg diet; control with 0.3 mg organic Se/kg diet; or control with 0.5 mg organic Se/kg diet. The sows were fed 2.4 kg per day during gestation (providing 0.003 – 0.005 mg supplemental Se per kg bw/day) and the gestation diet was decreased 0.2 kg/day for 5 days before farrowing. After farrowing, the lactation diet consisted of 1, 2, 3, 4, and 5 kg/day as lactating age increased, and the sows were then fed *ad libitum* until weaning. The performance of the sows, reproductive performance, litter performance, milk composition, and serum Se concentration in sows and piglets were measured. None of the treatments had an effect on sow performance or reproductive performance. Treatment with organic Se at both concentrations resulted in higher piglet weight and weight gain at day 21 of lactation compared to the inorganic treatment. Colostrum from sows fed 0.5 mg inorganic Se/kg diet and both concentrations of organic Se had higher Se levels, whereas Se concentration of milk at day 21 of lactation was higher for the organic Se supplement (highest at the highest supplement level). Serum Se concentration for both sows and their piglets were highest for organic Se supplementation and increased with the level of supplementation. The authors concluded that maternal supplementation with organic Se or 0.5 mg Se/kg diet of inorganic Se can improve piglet performance and Se status. No adverse effects were reported in the publication.

Kim et al. (2022) investigated the supplementation of maternal diets with sodium selenite (inorganic Se) and Se-enriched yeast (organic Se) in a swine model. Yorkshire x Landrace sows (total n=45; average body weight 241.8 kg) were assigned one of three treatments – control diet, control plus 0.15 mg Se/kg diet from each inorganic and organic source (ISOS15) and control diet plus 0.25 mg Se/kg diet from each inorganic and organic source (ISOS25). Each sow was fed 2.4 kg once daily during gestation (then decreased 0.2 kg per day for 5 days before farrowing. Following farrowing, sows were fed 1-5 kg/day for 5 days postpartum and them *ad libitum* until weaning. Colostrum, milk, and serum samples were collected from the sows and analyzed for Se concentration. Serum and tissue samples were collected from the piglets at 24 hours post-partum (n=4), day 7 of lactation (n=3) and day 21 of lactation (n=3). Supplementation had no effect on the body weight or backfat thickness of sows, or the litter size, litter weight, or litter weight gain. There was no significant difference between the treatment groups in the selenium concentration of the colostrum or milk of the sows. Sows fed supplemented diets (ISOS15 and ISOS25) and their offspring had significantly higher serum Se concentrations, and piglet kidney and muscle Se concentration at day 21, compared to the control. The authors concluded that maternal supplementation of mixed inorganic and organic Se can improve Se status for both sows and piglets. No adverse effects were reported in the publication.

6. Clinical Studies

There is a large volume of published scientific literature pertaining to selenium supplementation. The following section describes meta-analyses and systematic reviews, and randomized controlled trials (RCT) published since GRN 260 in which selenium supplementation was investigated in adults and infants.

a. Reviews

Vinceti et al. (2017) reviewed studies in populations (adult and children) with abnormally high or low environmental selenium intakes in order to assess the health risk of environmental selenium. The analysis also included high-quality and large randomized controlled trials of selenium

supplementation in cancer protection. However, this was a literature review rather than a systematic review or meta-analysis. The authors concluded that toxic effects of environmental selenium are found at intakes as low as 260 µg/day for organic bound selenium and 16 µg/day for inorganic selenium. The authors state that "high selenium intake may have unfavorable effects on the endocrine system, particularly on the thyroid status (1 study), and increase the risk of type 2 diabetes (3 studies), some specific cancers such as melanoma and lymphoid cancers (3 studies), nervous system disturbances (2 studies), and risk of amyotrophic lateral sclerosis (1 study)". Based on their review, the authors concluded that selenium intake should not exceed 90 µg/day.

Wichman et al. (2016) conducted a systematic review and meta-analysis of controlled trials comparing selenium supplementation's effect on thyroid autoantibodies (with or without Levothyroxine) to a placebo in patients with autoimmune thyroiditis. Assessed outcomes were serum thyroid peroxidase and thyroglobulin autoantibody levels, and immunomodulatory effects. Sixteen trials met the inclusion criteria (1,494 patients). Only one study used high-selenium yeast at 100 µg/day and 5 studies used selenomethionine at 200 µg/day. The longest durations were 12 months. No negative effects were reported in the assessed outcomes. Analysis of the reported adverse effects in the included studies showed a relative risk[6] of 4.96 ([CI 1.12–22.21], p = 0.036). Gastric discomfort was the adverse effect most reported (seven patients in the selenium-treated groups). Other adverse effects were headache (selenium group), hair loss (equally in selenium and placebo groups), and skin rash (selenium group). There were no reports of serious adverse effects or signs of acute toxicity or hospitalizations.

A Cochrane systematic review and random-effects meta-analysis evaluated 10 RCTs and 70 observational trials (27,232 participants, 200 µg/day for up to 3 years) which addressed the effect of selenium supplementation (including selenium-rich yeast) on the relationship between selenium exposure and cancer risk in humans (Vinceti et al., 2018). The summary risk ratio (RR) for estimated cancer mortality was 1.02 (95% confidence interval (CI) 0.80 to 1.30; 1 study, 17,448 participants). For the most frequently investigated site-specific cancers, investigators provided little evidence of any effect of selenium supplementation. Two RCTs with 19,009 participants indicated that colorectal cancer was unaffected by selenium administration (RR 0.99, 95% CI 0.69 to 1.43), as were non-melanoma skin cancer (RR 1.16, 95% CI 0.30 to 4.42; 2 studies, 2027 participants), lung cancer (RR 1.16, 95% CI 0.89 to 1.50; 2 studies, 19,009 participants), breast cancer (RR 2.04, 95% CI 0.44 to 9.55; 1 study, 802 participants), bladder cancer (RR 1.07, 95% CI 0.76 to 1.52; 2 studies, 19,009 participants), and prostate cancer (RR 1.01, 95% CI 0.90 to 1.14; 4 studies, 18,942 participants). None of the risk ratios mentioned here are statistically significant at P <0.05 because the CI range contains the value 1 (Tan and Tan, 2010).

While this review and the included studies focused on the efficacy of selenium supplementation and/or the prevention of cancer, the authors also addressed the potential for increased risk of other diseases including Type 2 Diabetes (T2D). The authors reported "RCTs showed a slightly increased risk of T2D associated with supplementation" but no meta-analysis was conducted on this effect (Vinceti et al., 2018).

Muzembo et al. (2019) completed a systematic review of RCTs in patients with HIV infection by measuring its effect on viral load and cluster of differentiation 4 cell count (CD4). Six out of the 507 retrieved articles that met the inclusion criteria were used in this review. Dosages in all six studies

[6] Calculated as the probability of an adverse effect occurring in the selenium group compared to the placebo or no treatment group.

were 200 µg selenium/day. The source of selenium was selenomethionine in 4 studies and two studies did not report the source of selenium. The duration of selenium supplementation and follow-up varied from 9 to 24 months. The authors reported no negative effects on outcome measures and stated that supplements were well tolerated in all reviewed studies.

A systematic review and meta-analysis were performed which assessed the effect of selenium supplementation on antioxidant markers. Thirteen studies were included (2790 patients). The daily selenium dose was 200 µg/day in seven trials, one trial used 300 µg/day, one trial used 50 µg/day, and one study used 60 and 960 µg/day. The source of selenium was not reported. There were no adverse effects on any antioxidant markers assessed. There was no evidence of adverse events (Hasani et al., 2019).

Fernandez-Lazaro et al. (2020) systematically searched for published studies to evaluate the effectiveness of selenium supplementation on antioxidant defense system, muscle performance, testosterone hormone response, and athletic performance among physically active individuals. Six studies (132 participants) met the inclusion criteria and were included in the systematic review. The studies administered selenium at 180 µg/day or 240 µg/day (from selenomethionine) and 200 µg/day (from sodium selenite). There were no adverse effects of selenium on any measured parameters and no side effects of selenium supplementation were reported in any of the studies included in this systematic review. The authors conclude “it seems that daily doses of selenium supplementation of 180 µg/day or 240 µg/day are apparently safe”.

In a systematic review and meta-analysis, Kelishadi et al. (2022) assessed the effect of selenium supplementation on lipid profile and blood pressure. Twenty-one studies were included (2984 participants) with dosages ranging from 100 to 300 µg selenium per day and durations ranging from 2 to 260 weeks. The source of selenium in most of the studies was high-selenium yeast. The data showed that selenium supplementation did not significantly affect triglyceride levels, low-density lipoprotein (LDL), or high-density lipoprotein (HDL). Results of a subgroup analysis showed that when baseline levels of LDL were in the normal range (< 130 mg/dL), selenium supplementation elicited a statistically significant increase in LDL (weighted mean differences: 2.89 mg/dL; 95 % CI: 0.26, 5.51, P = 0.031. Selenium supplementation also had a small but statistically significant effect on increasing systolic blood pressure (weighted mean differences: 2.02 mm Hg; 95 % CI: 0.50, 3.55, p = 0.009, while it had no significant effect on diastolic blood pressure. No other safety parameters or adverse events were discussed.

Several other systematic reviews and/or meta-analyses have been published assessing efficacy or protective effects of selenium supplementation in a number of diseases. None of these discuss adverse effects or adverse events. These include selenium supplementation’s effect on patients with Alzheimer’s Disease and mild cognitive impairment (Pereira et al., 2022), Graves’ disease (Zheng et al., 2018), metabolic disease (Djalalinia et al., 2021), Kashin-beck disease (Xie et al., 2018), Keshan disease (Zhou et al., 2018), thyroid disease (Zuo et al., 2021), female infertility (Lima et al., 2022), polycystic ovary syndrome (Hajizadeh-Sharafabad et al., 2019), and depression (Sajjadi et al., 2022).

None of the information stated in the review articles is contrary to the IOM’s conclusion that the tolerable upper limit for selenium in infants is 45 µg/day or 60 µg/day (for infants aged 0-6 months or 7-12 months, respectively).

b. Studies and Reviews Related to Type 2 Diabetes

GRN 260 reviewed in detail the effects of long-term selenium supplementation and risk of T2D. Of note is a letter authored by Dr. G.F. Combs, an author of several studies investigating the potential linkage between selenium supplementation and onset of T2D (Appendix C, GRN 260). In the letter, Dr. Combs concludes that their study results “do not indicate a relationship of Se status and diabetes risk. While we recognize the inferential limitations inherent in a small study such as this, it is also the case that these are the most robust data relevant to the question of whether selenium status may be related to diabetes risk. Thus, it is our plan to continue to address this hypothesis in further studies; but for the moment, I consider the supporting evidence very weak.” Subsequent published studies assessing the association between selenium status and diabetes risk are discussed below.

A systematic review and meta-analysis of RCTs was conducted by Mao et al. (2014) that assessed the association between selenium supplementation and the risk of T2D. Four RCTs involving 20,294 participants met the inclusion criteria. The combined relative risks compared with the control group (95% confidence limits) were 1.09 (0.99, 1.20, P=0.085). The authors concluded that these findings “do not support the routine application of selenium supplementation for T2D prevention in Caucasians.” However, the authors also state that several limitations within their review merit attention including differences of age, selenium status at baseline and study, study length, and study population.

In a systematic review and non-linear dose-response meta-analysis of observational studies, Wang et al. (2015) reported on the association between serum selenium levels and T2D. Five studies involving 13,460 participants met the inclusion criteria. The pooled odds ratios (95% CI) for the prevalence of T2D was 1.63 (1.04, 2.56) (P=0.033) comparing the highest (>132.50 µg/L) to the lowest (<97.5 µg/L) categories of selenium serum levels. In trials, a dose of 100 µg selenium/day increased blood selenium from 82 to 122 µg/L, whereas a dose of 200 µg/day increased blood selenium from 67 to 190 µg/L (Flores-Mateo et al., 2006). Therefore, the estimated intake of selenium in the highest category was 100-200 µg/day. The analysis reported “a positive association between serum selenium levels and T2D existed in populations with both relatively low levels and high levels of serum selenium, indicating a likely U-shaped non-linear dose–response relationship between serum selenium and T2D”. The effect of selenium supplementation or high selenium yeast was not analyzed in this report. This non-linear effect is consistent with a previous epidemiological study (Rayman and Stranges, 2013) and an RCT which assessed the risk of T2D from selenium supplementation (Rayman et al., 2012) which is discussed in detail below.

A systematic review and meta-analysis by Kong et al. (2016) reported on the association between serum selenium levels and gestational diabetes mellitus (GDM). Out of 44 references reviewed, 7 studies involving 569 patients met the inclusion criteria. Plasma selenium was significantly lower in women with GDM than in women without GDM. This effect was stronger in non-Caucasian women and those in the third trimester. The effect of selenium supplementation or high selenium yeast was not analyzed in this report.

Strozyk et al. (2019) completed a systematic review of RCTs assessing the effectiveness and safety of selenium supplementation in adults with T2D. Four RCTs (241 participants) met the inclusion criteria. In two of the RCTs (n=120 total, 200 µg/day selenium), selenium supplementation significantly reduced fasting insulin levels, homeostasis model of assessment-estimated insulin resistance (HOMA-IR), and homeostasis model of assessment-estimated ß cell function (HOMA-B). Mortality, diabetes-related complications, non-high-density lipoprotein (non-HDL), blood pressure and

health-related quality of life were not assessed in any of the RCTs. Only one adverse event (nausea) was reported as a reason for discontinuing the intervention. However, the authors state that the reporting of side effects was not adequate in three out of four RCTs.

Three studies based on the randomized, double-blinded, placebo-controlled Selenium Trial reported on T2D-related outcomes in subjects receiving high-selenium yeast. In the original study (described in more detail in subsequent section), a modest increase was found in the risk of new-onset T2D but only in the older Selenium Trial cohort (Thompson et al., 2016). Kohler et al. (2018a) later performed a subsequent cross-sectional analysis on the Selenium Trial study and reported a higher prevalence of T2D, with odds ratios (95% CIs) of 1.25 (0.80, 1.95) and 1.77 (1.16, 2.71), for the second or third tertiles of baseline plasma selenium levels (135.4 ± 5.9 ng/mL and 1687 ± 23.4 ng/mL). Based on the previously cited reference by Tan (2010), only the value for the third tertile is statistically significant at $P< 0.05$. Further, based on data from Flores-Mateo et al. (2006), the estimated intake of selenium in the third tertile would have been higher than 200 µg/day the (the level associated with a plasma selenium level of 190 µg/L).

Kohler et al. (2018b) conducted a systematic review and meta-analysis investigating the evidence of any association between Se and T2D. Sixteen studies from 15 published papers met inclusion criteria. Of the 13 observational studies (total number of participants not calculated) included, 8 demonstrated a statistically significant positive association between concentrations of blood selenium and odds for T2D, with odds ratios (95% CI) ranging from 1.52 (1.01–2.28) to 7.64 (3.34–17.46), and a summary odds ratio (OR) (95% CI) of 2.03 (1.51–2.72). In contrast, among three randomized clinical trials (N=20,290) of selenium supplementation (200 µg selenium/day from either selenized yeast or L-selenomethionine, duration ranging from 3 years to 16 years), a higher risk of T2D was not observed for those who received selenium compared to a placebo (OR = 1.18, 95% CI 0.95–1.47). The authors note that the results for the relationship between selenium and T2D differ between observational studies and randomized clinical trials and that “it remains unclear whether these differences are the result of uncontrolled confounding in the observational studies, or whether there is a modest effect of selenium on the risk for T2D that may vary by duration of exposure.” They conclude these findings meta- indicate consistent moderate associations only between high levels of dietary or serum selenium (“high” levels not defined) and prevalent T2D and inconsistent results among studies aimed at assessing incident T2D and that there is no consistent evidence that selenium supplementation plays a role in T2D development among adults.

The Hortega study evaluated the cross-sectional and prospective associations of plasma selenium concentrations with T2D, and the interaction of selenium concentrations with genetic variation in candidate polymorphisms. The study included 1452 Spanish men and women aged 18-85 years. The multivariable adjusted odds ratios (95% CI) for the prevalence of T2D in the second (76.3-94.2 µg/L) and third ($\geq$94.2 µg/L) tertiles of plasma selenium were 1.80 (1.03, 3.14) and 1.97 (1.14, 3.41), respectively. The hazard ratios for the incidence of diabetes for the upper tertiles were 1.76 (0.96, 3.22) and 1.80 (0.98, 3.31), respectively. The median follow-up time was 13.2 yr. The overall geometric mean concentration of plasma selenium was 84.2 µg/L. The authors reported significant interactions between selenium and polymorphisms of several genes and concluded that “plasma selenium was positively associated with prevalent and incident diabetes.” The selenium source in this study was dietary, and intake of selenium supplements or intake of high selenium yeast was not reported (Galan-Chilet et al., 2017). This is the only study identified by the literature search which indicated that an intake of < 100 µg/day selenium (which increased blood selenium from 82 to 122 µg/L in the Flores-Mateo et al., (2006) study) could increase the odds of T2D.

Rayman et al. (2012) reported on the effect of selenium supplementation on the risk of T2D in a population of relatively low selenium status as part of the UK PRECISE pilot study. In this randomized parallel arm trial, 512 elderly subjects received either 0, 100, 200, or 300 µg selenium/day from high selenium yeast (SelenoPrecise) daily for 6 months. The mean baseline plasma selenium concentration was 88.5 ng/g and rose after selenium supplementation. Selenium supplementation had no effect on plasma adiponectin concentration, an independent predictor of T2D. The authors concluded the results "did not show a diabetogenic effect of selenium".

Although there is some variability in the results, there is evidence from observational studies that blood Se concentrations are positively associated with the risk of T2D. This association may be non-linear, increasing both below and above the normal physiological Se concentrations. Further, an increased risk of T2D was observed in several large randomized clinical trials of Se supplementation. Overall, the data indicates that plasma levels of selenium that are associated with increased risk of T2D are consistent with selenium intakes > 100 µg/day.

c. Clinical Trials in Infants

Two clinical trials with infants reported on supplementation with high-selenium yeast (Bogye et al., 1998a; Bogye et al., 1998b; Bogye et al., 1998c). In one study, 28 very low birth weight preterm infants (mean birth weight 962 ± 129 g and gestational age 27 ± 1 week) living in a low selenium area of Hungary were randomized into two groups, one supplemented with 5 µg/day selenium from 4.8 mg of "yeast-selenium" (n=14) and a non-supplemented reference group (n=14). Within two weeks, in the selenium yeast supplemented group the serum selenium concentration increased from 32.1 ± 8.5 µg/L to 41.5 ± 6.5 µg/L and in the nonsupplemented group the selenium concentration decreased. The serum glutathione peroxidase activity increased in the supplemented group, and it did not change significantly in the nonsupplemented group. There were no observed complications or side effects in connection with enteral yeast-selenium supplementation. The authors concluded that selenium-enriched yeast is "a safe and an effective form of short term enteral selenium supplementation for preterm infants" (Bogye et al., 1998b).

In a second study, 36 very low birth weight preterm infants (mean birthweight 975 ± 122 g and gestational age 27 ± 1 wk) were randomly allocated into a supplemented group (n=18) , which received 4.8 mg selenium-rich yeast (5 µg selenium) or a control group (n=18), which received 4.8 mg yeast daily via nasogastric drip for the first 14 postnatal days. In the supplemented group the serum selenium concentration increased from 36.1 (±12.8) µg/L to 43.5 (7.9) µg/l and in the non-supplemented group it decreased from 34.4 (20.4) µg/L to 26.1 (16.6) µg/L from birth in two weeks. No complications or side effects as a result of supplementation were observed. The authors concluded that it is "a safe and an effective means of short term enteral selenium supplementation in preterm infants" (Bogye et al., 1998c). The selenium yeast was obtained from Buszesz Co., Hungary. It contained 50% selenomethionine and inorganic selenium (as selenite) was "estimated on the order of a few percent"(Alfthan et al., 1991).

d. Clinical Trials with Adults

GRN260 described clinical trials in which SelenoExcell® was administered to adults at doses as high as 3200 µg selenium per day. There were no serious toxicities reported in these studies (Clark et al., 1996; Clark et al., 1998; Stratton et al., 2003a; Stratton et al., 2003b; Reid et al., 2008; Reid et al., 2006; Reid et al., 2004; Marshall, 2001).

Of note are the studies with highest dose of SelenoExcell® (Reid et al., 2004) and the longest duration (Clark et al., 1996). In the Reid et al. (2004) study, SelenoExcell® was administered to 24 men with prostate cancer at 1600 or 3200 µg selenium/day. The 3200 µg selenium/day group reported more selenium-related side effects such as garlic breath, brittle nails, brittle hair, stomach upset, and dizziness. Plasma selenium levels of both groups were well below the upper tolerated limit of 1000 ng/mL and the adverse symptoms did not correlate with peaks in plasma Se levels. The authors reported “no obvious selenium-related serious toxicities”.

Clark et al. (1996) investigated the effects of selenium supplementation on the prevention of skin cancer. In this a double blind, placebo-controlled trial, 1312 patients were treated with 200 µg selenium/day from 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. In a secondary analysis of the Clark et al. (1996) study by Stranges et al. (2007), the authors stated that “selenium supplementation does not seem to prevent type 2 diabetes, and it may increase risk for the disease.” The authors note the study limitations include reliance on a limited subpopulation and on self-reporting of the type 2 diabetes diagnosis. Additional secondary analyses reported no safety-related parameters (Stranges et al., 2006; Reid et al., 2006).

Since GRN 260, 38 additional clinical trials have been published in which adults were administered high-selenium yeast. SelenoExcell® was the subject of 3 of those trials and these trials are described in detail below.

A Phase 2 randomized; double-blind, placebo-controlled clinical trial was conducted in men with localized non-metastatic prostate cancer. A total of 140 men (mean age 72.8) were randomized to placebo (n=46), 200 µg/day (n=47) or 800 µg/day (n=47) selenium from SelenoExcell® and monitored every 3 months for up to 5 years. Prostate-specific antigen (PSA) velocity was used as a marker of prostate cancer progression. Supplementation with high dose selenium (800 µg/day) was observed to be a risk factor for increased PSA velocity in men with highest quartile baseline plasma selenium concentrations (mean level of 134.5 ng/mL, standard deviation 41.5, quartiles not defined). Adverse events were also monitored. None of the serious adverse events were study related. The only events that were concluded to “possibly, probably or definitely” be related to intervention were brittle hair and brittle nail [10 in placebo group (21.7%), 6 in 200 µg/day group (12.8%) and 8 in 800 µg/day group (17.0%) (p = 0.51)], garlic breath and liver/kidney function test abnormalities (tests and values not defined) [5 in the placebo group (10.9%), 0 (0.0%) in the 200 µg/day group and 4 in the 800 µg/day group (8.5%) (p=0.05)] (Stratton et al., 2010).

Thompson et al. (2016) completed a randomized, double-blinded, placebo-controlled, parallel arm clinical trial (the Selenium Trial) on the effect of high selenium yeast (SelenoExcell®) alone and together with Celecoxib on colorectal cancer prevention. In this study, 1681 adult men and women aged 40 – 80 years of age following colonoscopic removal of colorectal adenomas received 200 µg high selenium yeast (SelenoExcell®) and/or 400 mg Celecoxib daily for 33 months. The Celecoxib treatment was suspended mid trial because of the risk of cardiovascular toxicity. Of the total of 1621 participants were enrolled in the selenium (n=685) and placebo (n=689) arms, 1374 were available for analysis. Serious adverse events and known selenium-associated adverse events were monitored, including Type 2 Diabetes, brittle hair and nails, and squamous cell skin cancer. There was a modestly increased risk for new-onset T2D (HR=1.25, 95% CI 1.04, 4.67, p=0.03) only among

participants over 63 years. There were no other significant differences reported between the treatment groups for all other adverse events. In a follow up study, Jacobs et al. (2019) reported on the effect of 200 µg selenium supplementation on pancreatic β-cell function and insulin sensitivity in a subset of 400 adult men and women recovering from colonoscopic removal of colorectal adenomas participating in the Selenium Trial. The authors concluded "These findings do not support a significant adverse effect of daily selenium supplementation with 200 µg/day of selenized yeast on β-cell function or insulin sensitivity as an explanation for previously reported associations between selenium and Type 2 Diabetes." In a cross-sectional analysis of the participants from the Selenium Trial, Kohler et al. (2018a) reported on the association between baseline plasma selenium and the prevalence of T2D. After adjustment for confounding, higher plasma selenium concentrations were associated with a higher prevalence of T2D. Compared to the first tertile of baseline plasma selenium (113.5 ± 9.7 ng/mL), the Odds Ratios (OR) for the second (135.4 ±5.9 ng/mL) and third tertiles (168.7 ± 23,4 ng/mL) were OR=1.25, 95% CI 0.80,1.95) and OR=1.77, 95% CI 1.16, 2.71, p-trend = 0.007). No significant effect was observed for age, sex, body mass index, smoking, or ethnicity. Based on the previously cited reference by Tan and Tan (2010), only the value for the third tertile is statistically significant at $p< 0.05$. Based on data from Flores-Mateo et al. (2006), the estimated intake of selenium in the third tertile would have been higher than 100-200 µg/day.

A randomized double-blind, placebo-controlled trial compared the effects of SelenoExcell® (200 or 285 µg/day) and selenomethionine (200 µg/day) on prostate cancer relevant biomarkers in men. For a period of 9 months, 69 healthy men received either selenium from SelenoExcell®, synthetic selenomethione or a placebo. Primary endpoints included blood levels of selenium-containing compounds and oxidative stress biomarkers (urine 8-hydroxy-2'-deoxyguanosine [8-OHdG] and 8-iso-prostaglandin-F2α [8-iso- PGF2α] and blood glutathione (GSH)). Secondary endpoints included plasma glucose and PSA levels. No negative effects on oxidative stress biomarkers, PSA or glucose were reported. Among the participants that completed the study, no serious adverse effects were reported regardless of arm. All potential adverse events reported were minor and none were attributed to treatment protocol (Richie et al., 2014).

Thirty additional randomized, placebo-controlled clinical trails with other forms of high-selenium yeast (total of 7,784 participants) published since GRN 260 are summarized in Table 4 below. Eleven studies did not discuss adverse events. In the nineteen trials that monitored adverse events, only one reported a side effect (minor rash) that was possibly related to selenium administration (Rayman et al., 2014) while the rest reported no significant differences in adverse events compared to placebo or observed no adverse effects. These trials were efficacy trials and unless noted in the table, there were no negative effects of selenium supplementation on outcome measures.

The highest daily dosage of these studies was 400 µg selenium (Algotar et al., 2013; Algotar et al., 2011), of which one of these studies (n=699) also had longest duration (5 years) and reported that there was no significant differences in adverse events between treatment groups. The authors of the largest study (n=1561) reported that 200 µg selenium/day from selenium-enriched yeast taken for 48 months "was safe" (Karp et al., 2013).

Table 4 is limited to trials with high-selenium yeast and any safety data (tolerability or adverse events) reported in the trials are provided, as well as any negative impacts on the endpoints measured.

Table 4. Summary Clinical Studies with High-Selenium Yeast

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
Studies in Pregnant and/or Lactating/Breastfeeding Women					
Selenium yeast	200 µg selenium	36 patients with gestational diabetes mellitus	Randomized, double-blind, placebo-controlled trial – 6 weeks	Adverse events not discussed. Endpoints measured included gene expression of peroxisome proliferator-activated receptor gamma and glucose transporter 1 in lymphocytes, gene expression of low-density lipoprotein receptor and lipoprotein(a), incidence of newborns' hyperbilirubinemia and newborns' hospitalization expression. No negative impacts were noted in the Se-treated group.	Karamali et al. (2020)
Selenium-enriched yeast	60 µg selenium	230 primiparous pregnant women	Randomized, double-blind, placebo-controlled trial – 12-14 weeks	One participant reported rash which was possibly associated with treatment. Endpoints measured included soluble vascular endothelial growth factor receptor-1, placental growth factor and soluble endoglin, Inhibin A and activin A, E-selectin and vascular cell adhesion molecule-1. 3-Nitrotyrosine, C-reactive protein and Pentraxin-3. No negative impacts were noted in the Se-treated group.	Rayman et al. (2014)
Selenium yeast	100 µg selenium	166 primigravid pregnant women in the first trimester of pregnancy	Randomized double-blind placebo-controlled trial – 6 months	Adverse events not discussed. Endpoints measured included symptoms of post-natal depression as measured by Edinburgh Postnatal Depression Scale. No negative impacts were noted in the Se-treated group.	Mokhber et al. (2011)
Selenomethionine	200 µg selenium	915 HIV-infected pregnant women between 12 and 27 weeks of gestation	Randomized, double-blind, placebo-controlled clinical trial – from recruitment until 6 months post delivery	Morbidity data collected during monthly clinic visits showed selenium supplemented group had reduced diarrheal morbidity risk by 40% (RR = 0.60; 95% CI). There was no effect on other morbidity endpoints measured.	Kupka et al. (2009)
Studies in Non-Pregnant/Non-Lactating Adults					

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
High-selenium yeast	300 µg selenium	42 healthy men (aged 18-45)	Randomized, double-blind, placebo-controlled clinical trial – 48 weeks	Adverse events not discussed. Endpoints measured included serum thyroxine, T3, thyrotropin, body weight, body fat, energy intake, voluntary activity, brachial artery responsiveness to transient occlusion, and arterial diameter or blood flow rate. No negative impacts were noted in the Se-treated group.	Hawkes et al. (2008a), Hawkes and Laslett (2009), Hawkes et al. (2008b)
Selenium-enriched yeast	200 µg selenium	179 plasma transplant recipients (aged 18-60)	Randomized, double-blind, placebo-controlled clinical trial – 3 years	Adverse events not discussed. Endpoint measured included Se concentration in plasma. Se plasma levels were significantly higher in the Se-supplemented group ($p = <0.01$) and were significantly lower in cases of liver transplant compared to kidney and heart transplant ($p = 0.03$). Increased Se concentration was not linked to sex and age but to area of residence although the number of subjects was insufficient to draw conclusions.	Bost and Blouin (2009)
Selenium-rich yeast, selenium-rich onions	50, 100 or 200 µg selenium	119 healthy volunteers (aged 50-64)	Randomized, double-blind, placebo-controlled trial using a parallel design – 12 weeks	Adverse events not discussed. Endpoints measured included changes in platelet glutathione peroxidase activity. No negative impacts were noted in the Se-treated group.	Hurst et al. (2010)
Selenium-rich yeast	200 µg selenium	42 patients with chronic kidney disease (aged 42-70)	Randomized, double-blind, placebo-controlled clinical trial – 12 weeks	Adverse events not discussed. Endpoints measured included DNA damage in white blood cells expressed as the tail moment, single-strand breaks, and oxidative bases lesion in DNA, using formamidopyrimidine glycosylase. No negative impacts were noted in the Se-treated group.	Zachara et al. (2011)
Selenized yeast	200 or 400 µg selenium	53 men who had undergone open radical	Phase 2 Randomized, double-blind, placebo-	Adverse events not discussed. Serum and prostate tissue selenium levels were measured.	Algotar et al. (2011)

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
		prostectomies (mean age 62.4)	controlled clinical trial – 6 weeks	Both Se-supplemented groups had statistically higher selenium in prostate tissue compared to placebo. The 400 µg Se group had significantly higher levels than the 200 µg Se group.	
High-selenium yeast (SelenoPrecise®)	100, 200 or 300 µg selenium	501 volunteers (aged 60-74)	Randomized, placebo-controlled, parallel-group study – 6 months	No significant differences in adverse events between treatment groups. Endpoints measured included total and high-density lipoprotein (HDL) cholesterol concentrations. No negative impacts were noted in the Se-treated group.	Rayman et al. (2011)
Selenium-enriched yeast	50, 100, or 200 µg selenium	119 subjects with low plasma selenium	Randomized, double-blind, placebo-controlled clinical trial – 12 weeks	Adverse events not discussed. Endpoints measured included red cell count, white cell count, Hb, hematocrit, mean cell Hb platelet count, Se-dependent GPx1 activity in red blood cells and platelets, and gene expression of selenoproteins in response to influenza vaccine. No negative impacts were noted in the Se-treated group.	Goldson et al. (2011)
Selenium-yeast + CoEnzyme Q10	200 µg selenium + 200 mg CoEnzyme Q10	443 elderly individuals (aged 70-88)	Randomized, double-blind, placebo-controlled trial – 48 months	No adverse events attributed to treatment. Endpoints measured included cardiac biomarker N-terminal proBNP (NT-proBNP), echocardiographic changes and cardiac mortality. No negative impacts were noted in the Se-treated group.	Alehagen et al. (2013)
High-selenium yeast	200 or 400 µg selenium	699 men at high risk of prostate cancer	Phase 3 randomized, double-blind, placebo-controlled clinical trial – 5 years	No significant differences in adverse events between treatment groups. Endpoints measured included time to diagnosis of prostate cancer and PSA velocity. No negative impacts were noted in the Se-treated group.	Algotar et al. (2013)

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
Selenized yeast	200 µg selenium	1561 adult patients with resected stage 1 non-small-cell lung cancer (medium age 66)	Randomized, Double-Blind, Placebo-Controlled, Phase III Chemopreventi on Trial – 48 months	"Selenium was safe." Endpoint measured included incidence of second primary tumors and disease-free survival. At the final analysis, the incidence rates second primary tumors were not significantly different.	Karp et al. (2013)
Selenium-enriched yeast	100, 200 or 300 µg selenium	468 elderly subjects (aged 60-74)	Randomized, double-blinded, placebo-controlled trial with four groups – 5 years	No significant differences in adverse events between treatment groups. Endpoints measured included total cholesterol, HDL-cholesterol, non-HDL-cholesterol and total: HDL-cholesterol ratio. No negative impacts were noted in the Se-treated group.	Cold et al. (2015)
Selenium yeast	200 µg selenium	58 women diagnosed with cervical intraepithelial neoplasia (aged 18-55)	Randomized, double-blind, placebo-controlled trial – 6 months	"No side-effects throughout the study" Endpoints measured included fasting plasma glucose levels, serum insulin levels, homeostatic model assessment of insulin resistance values, quantitative insulin sensitivity check index, serum triacylglycerol, HDL-cholesterol levels plasma total antioxidant capacity, glutathione levels and malondialdehyde levels. No negative impacts were noted in the Se-treated group.	Karamali et al. (2015)
High-selenium yeast + zinc	200 µg selenium	68 female hypothyroid patients (aged 25-65)	Randomized, double-blind, placebo-controlled trial – 9 months	Adverse events not discussed. Endpoints measured included free and total triodothyronine, free and total thyroxine, thyroid-stimulating hormone and anthropometric parameters. No negative impacts were noted in the Se-treated group.	Mahmoodia nfard et al. (2015)
High-selenium yeast (SelenoPrecise®)	100, 200 or 300 µg selenium	492 subjects (aged 60-74)	Randomized, double-blind, placebo-controlled clinical trial – 5 years	No significant differences in adverse events between treatment groups. Endpoints measured included thyroid stimulating hormone, free triiodothyronine, and free	Winther et al. (2015)

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
				thyroxine. No negative impacts were noted in the Se-treated group.	
Selenium yeast	200 µg selenium	60 patients with diabetic nephrology (aged 40-85)	Randomized, double-blind, placebo-controlled trial – 12 weeks	"No side effects were observed." Endpoints measured included C-reactive protein, matrix metalloproteinase-2, plasma malondialdehyde concentrations, plasma total antioxidant capacity, serum protein carbonyl plasma nitric oxide levels glutathione, transforming growth factor β, and advanced glycation end products. No negative impacts were noted in the Se-treated group.	Bahmani et al. (2016)
Selenium-enriched yeast	200 µg selenium	139 healthy subjects aged 50–64	Randomized, double-blind, placebo-controlled trial – 12 weeks	Adverse events not discussed. Endpoints measured included changes in cellular and humoral immune responses. Authors concluded "Se-supplementation in healthy human adults with marginal Se status resulted in both beneficial and detrimental effects on cellular immunity…".	Ivory et al. (2017)
Selenium yeast tablets	200 µg selenium	160 patients with stenosis (aged 35-65)	Single-center, double blind, placebo-controlled, randomized clinical trial. – 60 days	No adverse events discussed. Endpoints measured included expression of SEPP1 in mRNA and protein levels. No negative impacts were noted in the Se-treated group.	Gharipour et al. (2018)
Selenium-rich yeast (SelenoPrecise®)	100, 200 or 300 µg selenium	491 male and female volunteers (aged 60–74)	10 year follow up extension of single-center, randomized, double-blinded, placebo-controlled, multi-arm, parallel clinical trial – 5 years (Cold et al., 2015)	No significant differences in adverse events between treatment groups 300 µg/d of selenium (as high-selenium yeast) vs. placebo-yeast taken for 5 years resulted in a significant absolute excess risk of all-cause mortality of 11.3% (95% CI 0.0, 22.6%) 10 years later in a country of moderately low selenium status.	Rayman et al. (2018)
Selenium yeast	200 µg selenium	33 patients undergoing coronary artery	Randomized, double-blind, placebo-	No side effects were reported after selenium supplementation throughout the study.	Kamali et al. (2019)

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
		bypass grafting surgery (aged 40-85)	controlled trial – 4 weeks	Endpoints measured included fasting plasma glucose, insulin, homeostasis model of assessment-estimated insulin resistance, total-/HDL-cholesterol ratio, HDL-cholesterol, high- sensitivity C-reactive protein, malondialdehyde glutathione levels. No negative impacts were noted in the Se-treated group.	
Selenium yeast	200 µg selenium	53 subjects with congestive heart failure (aged 45-85)	Randomized, double-blind, placebo-controlled trial – 12 weeks	No side effects were reported after Se supplementation throughout the study. Endpoints measured included serum insulin, homoeostatic model of assessment for insulin, quantitative insulin sensitivity check index, LDL-and HDL-cholesterol, total/HDL-cholesterol ratio, high-sensitivity C-reactive protein, plasma total antioxidant capacity and total glutathione levels. No negative impacts were noted in the Se-treated group.	Raygan et al. (2018)
Selenium yeast	200 µg selenium	36 patients with gestational diabetes mellitus	Randomized, double-blind, placebo-controlled trial – 6 weeks	Adverse events not discussed. Endpoints measured included gene expression of peroxisome proliferator-activated receptor gamma and glucose transporter 1 in lymphocytes, gene expression of low-density lipoprotein receptor and lipoprotein(a), incidence of newborns' hyperbilirubinemia and newborns' hospitalization expression. No negative impacts were noted in the Se-treated group.	Karamali et al. (2020)
Beta-glucan complex with selenium and zinc enriched yeast (ABB C1®)	100 µg selenium	72 volunteers (≥ 60 years)	Randomized, double-blind, placebo-controlled trial – 30-35 days	No serious adverse events related to ABB C1® or tolerance issues were reported	Rodriguez et al. (2021)
Selenious yeast tablet	200 µg selenium	90 patients with Hashimoto's thyroiditis (mean	Prospective, single-center, open-label,	No adverse events reported. Endpoints measured included thyroid peroxidase antibody,	Hu et al. (2021)

Substance Tested	Total Daily Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
		age 38.6), 26 healthy individuals (mean age 36.2)	randomized, parallel controlled trial – 6 months	thyroglobulin antibody, thyroid function, urinary iodine, selenium, glutathione peroxidase3, and selenoprotein P1. No negative impacts were noted in the Se-treated group.	
Selenium-enriched yeast or sodium selenite	200 µg selenium	50 patients (aged 18-80) diagnosed with atherosclerosis	Randomized, double-blind, placebo-controlled trial - 6 months	Adverse events not discussed. Se supplementation had no negative impact on any endpoints measured. No significant changes in total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, insulin and homeostatic model was found within or between groups. No negative impacts were noted in the Se-treated group.	Khabbaz Koche Ghazi et al. (2021)
Selenium-rich yeast	200 µg selenium	60 patients with atherosclerosis (aged 18-80)	Randomized, double-blind, placebo-controlled trial – 8 weeks	No side effects. Endpoints measured included mRNA expression in peripheral blood mononuclear cells, levels of antioxidant enzymes and indices of oxidative stress, relative expression levels of transcription factors. No negative impacts were noted in the Se-treated group.	Roshanravan et al. (2022)
Selenium-rich yeast	100, 200, 300 µg selenium	481 Danish men and women (60-74 years)	Randomized, double-blind, placebo-controlled trial -5 years (60 months)	Secondary analysis of bone turnover marker data from a 5-year trial. Adverse events for the full study reported previously and consisted of grooved nails, hair loss and skin reactions.	Perri et al. (2022)
Selenium-rich yeast	200 µg selenium	111 women with elevated risk of breast cancer (22-78 years; mean 49 years)	Randomized, double-blind, placebo controlled trial – 1 year	Compliance was high (assessed by pill count and plasma selenium). Eleven subjects reported 14 adverse events, 12 mild and 2 moderate. There was no direct link with the selenium supplementation.	Thompson et al. (2022)

CI – Confidence interval; d – Day; Hb – Hemoglobin; HDL – High density lipoprotein; HIV – Human Immunodeficiency Virus; LDL – Low density lipoprotein; mg – Milligrams; mRNA - Messenger ribonucleic acid; NT-proBNP – N-terminal proBNP; PSA – Prostate-specific antigen; RR – Relative risk; Se – Selenium; SEPP1 - Selenoprotein P; µg - Micrograms

Sixteen trials in non-pregnant adults in which selenomethione was the source of selenium have also been published with dosages ranging from 50-200 µg selenium and durations as high as 3 years. The majority of these studies either did not discuss adverse events, found no significant difference between treatments or did not observe any significant events (Combs et al., 2012; Combs et al.,

2009; Pirola et al., 2016; Passerieux et al., 2015; Khazdouz et al., 2020; Burk et al., 2015; Esposito et al., 2017; Krysiak and Okopien, 2011; Mantovani et al., 2019; Cassano et al., 2015; de Farias et al., 2015; Miller et al., 2012; Xia et al., 2010; Krysiak et al., 2019). There were two exceptions. In the SELECT study by Lippman et al. (2009), 35,553 subjects were administered 200 µg selenium from selenomethionine with and without Vitamin E for 3 years. The only statistically significant differences in adverse events between selenomethionine treatment and placebo were alopecia and grades 1 to 2 dermatitis. In a multicenter, randomized, double-blind, placebo-controlled trial, Marshall et al. (2011) assigned 200 µg selenium from selenomethionine to 423 men with High-Grade Prostatic Intraepithelial Neoplasia. There were 21 grade-2 events (detailed data not reported) in the selenium arm and 13 in the placebo arm. There was only one grade-3 event, which was dermatologic, in the selenium arm.

A RCT analyzing the effect of selenomethione in children and adolescents with autoimmune thyroiditis (AT) was also publsihed. Seventy-one patients (aged 4.5-17.8) diagnosed with AT (antibodies against thyroid peroxidase [anti-TPO] and/or thyroglobulin [anti-Tg] ≥60 IU/mL, euthyroidism or treated hypothyroidism and goiter in thyroid gland ultrasonography) were randomized to receive 200 µg selenomethionine or placebo daily for 6 months. Blood samples were drawn for measurement of serum fT4, TSH, anti-TPO and anti-Tg levels, and thyroid gland ultrasonography was performed at the entry to the study and after 6 months of treatment.

A statistically significantly higher reduction in anti-Tg levels was observed at the end of the study in the selenium group compared to the placebo group (Δ: −70.9 ± 22.1 vs −6.7 ± 60.6 IU/mL, P = 0.021). Although anti-TPO levels were also decreased in the selenium group, this change was not significantly different from that of the control group (Δ: −116.2 ± 68.4 vs +262.8 ± 255.5 IU/mL, P = 0.219). No significant difference in thyroid gland volume was observed between the two study groups (P > 0.05). All patients completed the study without reporting any side effects, with the exception of one patient, who temporarily complained of rash which was determined not to be associated with treatment (Kyrgios et al., 2019) .

None of the information stated in the review articles for adults would revoke the GRAS status of high selenium yeast.

F. GRAS Criteria

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.”[7]

Amplification is provided in that the conclusion 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[7]:

[7] See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe.

> "…General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."
>
> "'Common knowledge' can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958."

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:

- 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 JECFA and the National Academy of Sciences.

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

The apparent imprecision of the terms "appreciable," "at the time," and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988; Renwick, 1990; Rulis and Levitt, 2009).

As noted below, this safety assessment to ascertain GRAS status for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

G. Expert Panel Findings on Safety of Cypress's SelenoExcell®

An evaluation of the safety and GRAS status of the intended use of Cypress's SelenoExcell® has been conducted by an Expert Panel convened by GRAS Associates; the Panel consisted of Bo Lönnerdal, PhD, Richard Kraska, PhD, and Laurie C. Dolan, PhD, DABT, as Panel Chair. The Expert Panel reviewed Cypress's dossier as well as other publicly available information available to them. The individuals who served as Expert Panelists are qualified to evaluate the safety of foods and food ingredients by merit of scientific training and experience.

The GRAS Expert Panel report is provided in Appendix 7.

H. Common Knowledge Elements for GRAS Conclusions

The first common knowledge element for a GRAS conclusion requires that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing studies published in peer-reviewed scientific journals. The second common knowledge element for a GRAS conclusion requires that consensus exists within the broader scientific community.

1. Public Availability of Scientific Information

The studies reviewed have been published in the scientific literature as summarized in Part 6 GRN 260 received a no questions letter from FDA for use of SelenoExcell® for use in a variety of conventional foods in 2009. Lack of reported adverse events for selenium supplementation of food at intakes < 100 µg/day supports safety in use. Results of an updated literature on the safety of selenium enriched yeast or selenium derived from yeast indicate no safety issues and two clinical studies conducted in pre-term infants are also publicly available and support safety of use of SelenoExcell® as indicated in this dossier.

2. Scientific Consensus

The second common knowledge element for a GRAS conclusion requires that there be a basis to conclude that consensus exists among qualified scientists about the safety of the substance for its intended use.

SelenoExcell® is a selenium rich, dried cellular product derived from aerobic fermentation of a selected *Saccharomyces cerevisiae* (Baker's yeast) strain which has been cultured in the presence of sodium selenite (Na_2SeO_3). The scientific principles fundamental to the manufacturing process for producing organically-bound selenium yeast via aerobic fermentation are described in detail in Cypress's previous GRAS Notification (GRN 260) for SelenoExcell® (Cypress Systems Inc, 2008). The resulting SelenoExcell® contains 1200-1380 µg/g total organically bound selenium. Selenium in breast milk is also organically-bound and contains no appreciable levels of inorganic selenium (Dorea, 2002). SelenoExcell® has been shown to be stable after storage over a four-year period.

SelenoExcell® is intended for use as a source of selenium in non-exempt infant formula for term infants at use levels to comply with the range levels established in an FDA rule (2.0 – 7.0 µg Se/100 kcal). The tolerable upper limit (UL) for selenium in infants determined by the IOM (45 µg/day for infants 0-6 months of age and 60 µg/day for infants 7-12 months of age). EFSA recently established a more conservative UL of 55 µg/day for infants 7-12 months of age (EFSA NDA Panel et al., 2023). Breast milk selenium concentrations range from 10 to 30 µg/L (1.5 to 4.5 µg/100 kcal), while values as high as 283 µg/L (42.5 µg/100 kcal) have been reported with no apparent adverse effects on the breast-fed infant.

There is no evidence that SelenoExcell® poses a higher risk of selenosis than inorganic selenium species. However, there is evidence of higher bioavailability of selenium from selenium-enriched yeast and/or selenomethionine. In order to comply with the FDA rule but avoid exceeding the UL of 45 µg for infants 0-6 months and the more conservative UL of 55 µg for infants 7-12 months, SelenoExcell® may be added to non-exempt term infant formula for 0-6 month-old infants at 1.8 mg/100 kcal, providing approximately 2.5 µg selenium per 100 kcal of formula. SelenoExcell® is intended for use in formula for 6-12 month-old infants at 2.5 mg per 100 kcal formula, providing 3.5 µg selenium per 100 kcal of formula. Estimated intake of formula fed 0-6 month-old infants is 1250 kcal

per day (calculated as 140.96 mL/kg bw*8.87 kg bw). This equates to 12.5 100 kcal servings providing approximately 31 µg selenium/day intake from addition of SelenoExcell®. Infants 6-12 months consume 10.2 100 kcal servings of infant formula daily providing approximately 36 µg selenium from addition of SelenoExcell®. Utilizing the IOM calculation of selenium from complementary foods for 7 to 12-month-old infants at 11 µg/day, the maximum daily intake of selenium would be 47 µg selenium/day, below the 60 µg UL established for this age group.

The exposure assessment confirms that the addition of 1.8 mg SlenoExcell®, providing 2.5 µg selenium per 100 kcal formula intended for 0-6 month-old infants; and the addition of 2.5 mg of SelenoExcell® providing 3.5 µg selenium per 100 kcal formula intended for 7-12 month-old infants complies with the requirements for addition of selenium to infant formula as established in 21 CFR 107.100(a) and do not exceed established tolerable upper limits.

The specifications for SelenoExcell® for use in infant formula contain an absence specification for *Cronobacter sakazakii* spp. whereas the specification for SelenoExcell® for use in conventional foods do not. Allergenic substances are not included at any step of the manufacturing process of SelenoExcell® or in the fermentation medium (except for yeast). The potential for an allergenic response to SelenoExcell® has been reviewed in detail in GRN 260 (Cypress Systems Inc, 2008). A comprehensive review of the published literature did not identify reports of allergenicity associated with ingestion of either *Saccharomyces cerevisiae* or high-selenium yeast. The European Food Safety Authority (EFSA) Panel on food additives concluded that “food uses of the selenium-enriched yeast were unlikely to present an allergenic risk to consumers” (EFSA, 2008).

There is a large volume of published scientific literature pertaining to selenium supplementation (including organic forms). For this GRAS Determination, meta-analyses and systematic reviews, and randomized controlled trials (RCT) published since GRN 260 were reviewed, in which selenium supplementation was investigated in adults and infants. Overall, the data support that up to 100 µg/day selenium from SelenoExcell® is safe (consistent with GRN 260) for adults. Two clinical trials in infants indicate that use of 5 µg/day selenium from 4.8 mg of “yeast-selenium” is safe for use in very low birth weight preterm infants. While this intake level of selenium is lower than the estimated selenium intake from use of SelenoExcell® infant formula, there is no reason to suspect that SelenoExcell® would be more toxic than other forms of selenium, which have IOM ULs of 45 µg/day for infants 0-6 months and 55 µg/day for infants 7-12 months.

PART 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.

A. References

1. List of Acronyms

µg	Microgram(s)
ADME	Absorption, Distribution, Metabolism and Excretion
AI	Adequate intake
AOAC	AOAC International
ASTA	American Spice Trade Association
AT	Autoimmune thyroiditis
ATCC	American Type Culture Collection
bw	Body weight
C	Celsius

CAC	Codex Alimentarius Commission
CD4	Cluster of differentiation 4 cell count
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CFU	Colony forming unit
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
COA	Certificate of Analysis
dL	Deciliters
EFSA	European Food Safety Authority
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FAO	Food and Agriculture Organization of the United Nations
FD&C Act	Federal Food Drug and Cosmetics Act
FDA-BAM	FDA's Bacteriological Analytical Manual
FDA	U.S. Food and Drug Administration
FEEDAP	The European Food Safety Authority (EFSA) Panel on Additives and Products or Substances used in Animal Feed
g	Gram(s)
GA	GRAS Associates
GC-AED	Gas Chromatography-Atomic Emission Detection
GDM	Gestational diabetes mellitus
GM	Genetically Modified
GMO	Genetically modified organism
GPX-1	Glutathione peroxidase
GRAS	Generally Recognized as Safe
GRN	GRAS Notifications
GSH	Blood glutathione
HACCP	Hazard analysis and critical control points
HDL	High-density lipoprotein
HOMA-B	Homeostasis model of assessment-estimated ß cell function
HOMA-IR	Homeostasis model of assessment-estimated insulin resistance
HPLC-ICP-MS	High Performance Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometry
ICP-MS	Inductively coupled plasma-mass spectrometry
ICP-OES	Inductively coupled plasma - Optical emission spectrometry
IOM	Institute of Medicine
IU	International Units
JECFA	Joint Expert Committee on Food Additives
kcal	Kilocalorie(s)
kg	Kilogram(s)
kJ	Kilojoules
L	Liters
LDL	Low-density lipoprotein
LSRO	Life Sciences Research Office
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
NHANES	National Health and Nutrition Examination Survey
NMR	Nuclear Magnetic Resonance
OR	Odds ratio
PCE/NCE	Polychromatic erythrocyte/normochromatic erythrocyte
PSA	Prostate-Specific Antigen
QA/QC	Quality Assurance/Quality Control

RCT	Randomized controlled trial
RR	Risk ratio
Se	Selenium
T2D	Type 2 diabetes
TSH	Thyroid stimulating hormone
UL	Tolerable upper intake level
USP-NF	United States Pharmacopeia-National Formulary
wk	Week(s)
WWEIA	What We Eat In America

2. References

Alehagen, U., Johansson, P., Bjornstedt, M., Rosen, A. and Dahlstrom, U. (2013) 'Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens', *Int J Cardiol,* 167(5), pp. 1860-6.

Alfthan, G., Aro, A., Arvilommi, H. and Huttunen, J. K. (1991) 'Selenium metabolism and platelet glutathione peroxidase activity in healthy Finnish men: effects of selenium yeast, selenite, and selenate', *The American Journal of Clinical Nutrition,* 53(1), pp. 120-125.

Algotar, A. M., Stratton, M. S., Ahmann, F. R., Ranger-Moore, J., Nagle, R. B., Thompson, P. A., Slate, E., Hsu, C. H., Dalkin, B. L., Sindhwani, P., Holmes, M. A., Tuckey, J. A., Graham, D. L., Parnes, H. L., Clark, L. C. and Stratton, S. P. (2013) 'Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer', *Prostate,* 73(3), pp. 328-35.

Algotar, A. M., Stratton, M. S., Xu, M. J., Dalkin, B. L., Nagle, R. B., Hsu, C. H., Ahmann, F. R., Clark, L. C. and Stratton, S. P. (2011) 'Dose-dependent effects of selenized yeast on total selenium levels in prostatic tissue of men with prostate cancer', *Nutr Cancer,* 63(1), pp. 1-5.

Alltech (2010) 'High-selenium yeast GRN 000353'. Available at: https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm267426.pdf.

Amoako, P. O., Kahakachchi, C. L., Dodova, E. N., Uden, P. C. and Tyson, J. F. (2007) 'Speciation, quantification and stability of selenomethionine, S-(methylseleno) cysteine and selenomethionine Se-oxide in yeast-based nutritional supplements', *Journal of Analytical Atomic Spectrometry,* 22(8), pp. 938-946.

Amoako, P. O., Uden, P. C. and Tyson, J. F. (2009) 'Speciation of selenium dietary supplements; formation of S-(methylseleno) cysteine and other selenium compounds', *Analytica Chimica Acta,* 652(1), pp. 315-323.

Bahmani, F., Kia, M., Soleimani, A., Mohammadi, A. A. and Asemi, Z. (2016) 'The effects of selenium supplementation on biomarkers of inflammation and oxidative stress in patients with diabetic nephropathy: a randomised, double-blind, placebo-controlled trial', *Br J Nutr,* 116(7), pp. 1222-1228.

Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Dusemund, B., Fašmon Durjava, M., Kouba, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R. E., Woutersen, R., Brozzi, R., Galobart, J., Gregoretti, L., Innocenti, M. L., Vettori, M. V. and López-Gálvez, G. (2021) 'Safety and efficacy of the feed additive consisting of selenium-enriched yeast (*Saccharomyces cerevisiae* CNCM I-3060) for all animal species (Alltech Ireland)', *EFSA Journal,* 19(12), pp. e06979.

Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Dusemund, B., Kos Durjava, M., Kouba, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R. E., Woutersen, R., Saarela, M., Anguita, M., Galobart, J., Holczknecht, O., Manini, P., Pizzo, F., Tarrés-Call, J. and Pettenati, E. (2020) 'Assessment of the application for renewal of the authorisation of Actisaf(®) Sc 47 (*Saccharomyces cerevisiae* CNCM I-4407) as a feed additive for calves for rearing', *EFSA Journal,* 18(6), pp. e06167.

Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Dusemund, B., Kouba, M., Kos Durjava, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R., Woutersen, R., Cubadda, F., Flachowsky, G., Gropp, J., Leng, L., López-Gálvez, G. and Mantovani, A. (2018) 'Assessment of the application for renewal of authorisation of selenomethionine produced by *Saccharomyces cerevisiae* CNCM I-3060 (selenised yeast inactivated) for all animal species', *EFSA Journal,* 16(7), pp. e05386.

Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Dusemund, B., Kouba, M., Kos Durjava, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R. E., Woutersen, R., Flachowsky, G., Gropp, J., Cubadda, F., López-Gálvez, G. and Mantovani, A. (2019) 'Assessment of the application

for renewal of authorisation of selenomethionine produced by *Saccharomyces cerevisiae* NCYC R397 for all animal species', *EFSA Journal,* 17(1), pp. e05539.

Bogye, G., Alfthan, G. and Machay, T. (1998a) 'Bioavailability of enteral yeast-selenium in preterm infants', *Biol Trace Elem Res,* 65(2), pp. 143-51.

Bogye, G., Alfthan, G. and Machay, T. (1998b) 'Randomized clinical trial of enteral yeast-selenium supplementation in preterm infants', *Biofactors,* 8(1-2), pp. 139-42.

Bogye, G., Alfthan, G., Machay, T. and Zubovics, L. (1998c) 'Enteral yeast-selenium supplementation in preterm infants', *Arch Dis Child Fetal Neonatal Ed,* 78(3), pp. F225-6.

Bost, M. and Blouin, E. (2009) 'Effect of supplementation with Se-enriched yeast and factors influencing Se concentration in plasma of transplant recipients', *J Trace Elem Med Biol,* 23(1), pp. 36-42.

Burk, R. F., Hill, K. E., Motley, A. K., Byrne, D. W. and Norsworthy, B. K. (2015) 'Selenium deficiency occurs in some patients with moderate-to-severe cirrhosis and can be corrected by administration of selenate but not selenomethionine: a randomized controlled trial', *Am J Clin Nutr,* 102(5), pp. 1126-33.

Burk, R. F., Norsworthy, B. K., Hill, K. E., Motley, A. K. and Byrne, D. W. (2006) 'Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial', *Cancer Epidemiol Biomarkers Prev,* 15(4), pp. 804-10.

Cassano, P. A., Guertin, K. A., Kristal, A. R., Ritchie, K. E., Bertoia, M. L., Arnold, K. B., Crowley, J. J., Hartline, J., Goodman, P. J., Tangen, C. M., Minasian, L. M., Lippman, S. M. and Klein, E. (2015) 'A randomized controlled trial of vitamin E and selenium on rate of decline in lung function', *Respir Res,* 16, pp. 35.

CDC (2001) *Data Table of Infant Weight-for-age Charts*: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Available at: https://www.cdc.gov/growthcharts/html_charts/wtageinf.htm.

CFSAN (2022) *CFSAN Adverse Event Reportingt System (CAERS)*: US Food and Drug Administration. Center for Food Safety and Applied Nutrition (CFSAN). Available at: https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers#files.

Clark, L. C., Combs, G. F., Jr., Turnbull, B. W., Slate, E. H., Chalker, D. K., Chow, J., Davis, L. S., Glover, R. A., Graham, G. F., Gross, E. G., Krongrad, A., Lesher, J. L., Jr., Park, H. K., Sanders, B. B., Jr., Smith, C. L. and Taylor, J. R. (1996) 'Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group', *JAMA,* 276(24), pp. 1957-63.

Clark, L. C., Dalkin, B., Krongrad, A., Combs, G. F., Jr., Turnbull, B. W., Slate, E. H., Witherington, R., Herlong, J. H., Janosko, E., Carpenter, D., Borosso, C., Falk, S. and Rounder, J. (1998) 'Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial', *Br J Urol,* 81(5), pp. 730-4.

Cold, F., Winther, K. H., Pastor-Barriuso, R., Rayman, M. P., Guallar, E., Nybo, M., Griffin, B. A., Stranges, S. and Cold, S. (2015) 'Randomised controlled trial of the effect of long-term selenium supplementation on plasma cholesterol in an elderly Danish population', *Br J Nutr,* 114(11), pp. 1807-18.

Combs, G. F., Jr., Jackson, M. I., Watts, J. C., Johnson, L. K., Zeng, H., Idso, J., Schomburg, L., Hoeg, A., Hoefig, C. S., Chiang, E. C., Waters, D. J., Davis, C. D. and Milner, J. A. (2012) 'Differential responses to selenomethionine supplementation by sex and genotype in healthy adults', *Br J Nutr,* 107(10), pp. 1514-25.

Combs, G. F., Jr., Midthune, D. N., Patterson, K. Y., Canfield, W. K., Hill, A. D., Levander, O. A., Taylor, P. R., Moler, J. E. and Patterson, B. H. (2009) 'Effects of selenomethionine supplementation on selenium status and thyroid hormone concentrations in healthy adults', *Am J Clin Nutr,* 89(6), pp. 1808-14.

Cypress Systems Inc (2008) *GRAS Assessment of high-selenium yeast, GRN 000260*: U.S. Food and Drug Administration (FDA). Available at: https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264257.pdf.

de Farias, C. R., Cardoso, B. R., de Oliveira, G. M., de Mello Guazzelli, I. C., Catarino, R. M., Chammas, M. C., Cozzolino, S. M. and Knobel, M. (2015) 'A randomized-controlled, double-blind study of the impact of selenium supplementation on thyroid autoimmunity and inflammation with focus on the GPx1 genotypes', *J Endocrinol Invest,* 38(10), pp. 1065-74.

Djalalinia, S., Hasani, M., Asayesh, H., Ejtahed, H. S., Malmir, H., Kasaeian, A., Zarei, M., Baygi, F., Rastad, H., Mahdavi Gorabi, A. and Qorbani, M. (2021) 'The effects of dietary selenium supplementation on inflammatory markers among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials', *J Diabetes Metab Disord,* 20(1), pp. 1051-1062.

Dorea, J. G. (2002) 'Selenium and breast-feeding', *Br J Nutr,* 88(5), pp. 443-61.

EFSA (2008) 'Scientific Opinon of the Panel of Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission on Selenium-enriched yeast as a source for selenium', *The EFSA Journal,* 766, pp. 1-43.

EFSA NDA Panel (2014) 'Scientific Opinion on the essential composition of infant and follow-on formulae. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)', *EFSA Journal,* 12(7), pp. 106.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K. I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Peláez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aggett, P., Crous Bou, M., Cubadda, F., Ciccolallo, L., de Sesmaisons Lecarré, A., Fabiani, L., Titz, A. and Naska, A. (2023) 'Scientific opinion on the tolerable upper intake level for selenium', *EFSA Journal,* 21(1), pp. e07704.

Esposito, D., Rotondi, M., Accardo, G., Vallone, G., Conzo, G., Docimo, G., Selvaggi, F., Cappelli, C., Chiovato, L., Giugliano, D. and Pasquali, D. (2017) 'Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: clinical results of a blinded placebo-controlled randomized prospective trial', *J Endocrinol Invest,* 40(1), pp. 83-89.

Fairweather-Tait, S. J., Collings, R. and Hurst, R. (2010) 'Selenium bioavailability: current knowledge and future research requirements', *Am J Clin Nutr,* 91(5), pp. 1484s-1491s.

FAO (2007) *Codex Alimentarius. Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants. CXS 72-1981*: Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). Available at: https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXS%2B72-1981%252FCXS_072e.pdf.

FDA (2009) 'Agency response letter GRAS Notice No., GRN 000260', Available: US Food and Drug Administration (FDA). Available at: https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm155153.htm.

FDA (2011) 'Agency response letter GRAS Notice No., GRN 000353', Available: US Food and Drug Administration (FDA). Available at: https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm245816.htm.

FDA (2013) 'Proposed Rule. Infant formula: The addition of minimum and maximum levels of selenium to infant formula and related labeling requirements', *Federal Register,* 78 FR 22442, pp. 22442-22451.

FDA (2015) 'Final Rule. Infant formula: The addition of minimum and maximum levels of selenium to infant formula and related labeling requirements', *Federal Register,* 80 FR 35834, pp. 35834-35841.

FDA (2021a) *GRN No. 915 Calcium L-methylfolate*. Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=915.

FDA (2021b) *GRN No. 990 Short-chain fructooligosaccharides*. Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=990.

FDA (2021c) *GRN No. 993 L-carnitine-L-tartrate*. Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=993.

FDA (2021d) *GRN No. 1013 Lactobacillus rhamnosus DSM 33156.* Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=1013.

FDA (2022a) *GRN No. 1008 Algal oil (=35% docosahexaenoic acid) from Aurantiochytrium limacinum TKD-1*. Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=1008.

FDA (2022b) *GRN No. 1041 Dry whole milk*. Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=1041.

Fernandez-Lazaro, D., Fernandez-Lazaro, C. I., Mielgo-Ayuso, J., Navascues, L. J., Cordova Martinez, A. and Seco-Calvo, J. (2020) 'The Role of Selenium Mineral Trace Element in Exercise: Antioxidant Defense System, Muscle Performance, Hormone Response, and Athletic Performance. A Systematic Review', *Nutrients,* 12(6).

Flores-Mateo, G., Navas-Acien, A., Pastor-Barriuso, R. and Guallar, E. (2006) 'Selenium and coronary heart disease: a meta-analysis', *Am J Clin Nutr,* 84(4), pp. 762-73.

Galan-Chilet, I., Grau-Perez, M., De Marco, G., Guallar, E., Martin-Escudero, J. C., Dominguez-Lucas, A., Gonzalez-Manzano, I., Lopez-Izquierdo, R., Briongos-Figuero, L. S. and Redon, J. (2017) 'A gene-environment interaction analysis of plasma selenium with prevalent and incident diabetes: The Hortega study', *Redox Biology,* 12, pp. 798-805.

Gharipour, M., Ouguerram, K., Nazih, E. H., Salehi, M., Behmanesh, M., Roohafza, H., Hosseini, S. M., Nezafati, P., Dianatkhah, M., Gharipour, A., Haghjoo, S., Sarrafzadegan, N. and Sadeghi, M. (2018) 'Effects of selenium supplementation on expression of SEPP1 in mRNA and protein levels in subjects with and without metabolic syndrome suffering from

coronary artery disease: Selenegene study a double-blind randomized controlled trial', *J Cell Biochem,* 119(10), pp. 8282-8289.

Goldson, A. J., Fairweather-Tait, S. J., Armah, C. N., Bao, Y., Broadley, M. R., Dainty, J. R., Furniss, C., Hart, D. J., Teucher, B. and Hurst, R. (2011) 'Effects of selenium supplementation on selenoprotein gene expression and response to influenza vaccine challenge: a randomised controlled trial', *PLoS One,* 6(3), pp. e14771.

Hadrup, N. and Ravn-Haren, G. (2021) 'Absorption, distribution, metabolism and excretion (ADME) of oral selenium from organic and inorganic sources: A review', *J Trace Elem Med Biol,* 67, pp. 126801.

Hajizadeh-Sharafabad, F., Moludi, J., Tutunchi, H., Taheri, E., Izadi, A. and Maleki, V. (2019) 'Selenium and Polycystic Ovary Syndrome; Current Knowledge and Future Directions: A Systematic Review', *Horm Metab Res,* 51(5), pp. 279-287.

Hasani, M., Djalalinia, S., Khazdooz, M., Asayesh, H., Zarei, M., Gorabi, A. M., Ansari, H., Qorbani, M. and Heshmat, R. (2019) 'Effect of selenium supplementation on antioxidant markers: a systematic review and meta-analysis of randomized controlled trials', *Hormones (Athens),* 18(4), pp. 451-462.

Hawkes, W. C., Keim, N. L., Diane Richter, B., Gustafson, M. B., Gale, B., Mackey, B. E. and Bonnel, E. L. (2008a) 'High-selenium yeast supplementation in free-living North American men: no effect on thyroid hormone metabolism or body composition', *J Trace Elem Med Biol,* 22(2), pp. 131-42.

Hawkes, W. C. and Laslett, L. J. (2009) 'Selenium supplementation does not improve vascular responsiveness in healthy North American men', *Am J Physiol Heart Circ Physiol,* 296(2), pp. H256-62.

Hawkes, W. C., Richter, B. D., Alkan, Z., Souza, E. C., Derricote, M., Mackey, B. E. and Bonnel, E. L. (2008b) 'Response of selenium status indicators to supplementation of healthy North American men with high-selenium yeast', *Biol Trace Elem Res,* 122(2), pp. 107-21.

He, M. J., Zhang, S. Q., Mu, W. and Huang, Z. W. (2018) 'Selenium in infant formula milk', *Asia Pac J Clin Nutr,* 27(2), pp. 284-292.

Hu, Y., Feng, W., Chen, H., Shi, H., Jiang, L., Zheng, X., Liu, X., Zhang, W., Ge, Y., Liu, Y. and Cui, D. (2021) 'Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial', *Clin Transl Sci,* 14(4), pp. 1390-1402.

Hurst, R., Armah, C. N., Dainty, J. R., Hart, D. J., Teucher, B., Goldson, A. J., Broadley, M. R., Motley, A. K. and Fairweather-Tait, S. J. (2010) 'Establishing optimal selenium status: results of a randomized, double-blind, placebo-controlled trial', *Am J Clin Nutr,* 91(4), pp. 923-31.

IOM (2000) 'Selenium. Food and Nutrition Board Institute of Medicine (IOM)', *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Washington, D.C.: The National Academies Press, pp. 284-324.

Ivory, K., Prieto, E., Spinks, C., Armah, C. N., Goldson, A. J., Dainty, J. R. and Nicoletti, C. (2017) 'Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults', *Clin Nutr,* 36(2), pp. 407-415.

Jacobs, E. T., Lance, P., Mandarino, L. J., Ellis, N. A., Chow, H. S., Foote, J., Martinez, J. A., Hsu, C. P., Batai, K., Saboda, K. and Thompson, P. A. (2019) 'Selenium supplementation and insulin resistance in a randomized, clinical trial', *BMJ Open Diabetes Res Care,* 7(1), pp. e000613.

Jin, X. H., Kim, C. S., Gim, M. J. and Kim, Y. Y. (2022) 'Effects of selenium source and level on the physiological response, reproductive performance, serum Se level and milk composition in gestating sows', *Anim Biosci,* 35(12), pp. 1948-1956.

Kamali, A., Amirani, E. and Asemi, Z. (2019) 'Effects of Selenium Supplementation on Metabolic Status in Patients Undergoing for Coronary Artery Bypass Grafting (CABG) Surgery: a Randomized, Double-Blind, Placebo-Controlled Trial', *Biol Trace Elem Res,* 191(2), pp. 331-337.

Karamali, M., Dastyar, F., Badakhsh, M. H., Aghadavood, E., Amirani, E. and Asemi, Z. (2020) 'The Effects of Selenium Supplementation on Gene Expression Related to Insulin and Lipid Metabolism, and Pregnancy Outcomes in Patients with Gestational Diabetes Mellitus: a Randomized, Double-Blind, Placebo-Controlled Trial', *Biol Trace Elem Res,* 195(1), pp. 1-8.

Karamali, M., Nourgostar, S., Zamani, A., Vahedpoor, Z. and Asemi, Z. (2015) 'The favourable effects of long-term selenium supplementation on regression of cervical tissues and metabolic profiles of patients with cervical intraepithelial neoplasia: a randomised, double-blind, placebo-controlled trial', *Br J Nutr,* 114(12), pp. 2039-45.

Karp, D. D., Lee, S. J., Keller, S. M., Wright, G. S., Aisner, S., Belinsky, S. A., Johnson, D. H., Johnston, M. R., Goodman, G., Clamon, G., Okawara, G., Marks, R., Frechette, E., McCaskill-Stevens, W., Lippman, S. M., Ruckdeschel, J. and Khuri, F. R. (2013) 'Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597', *J Clin Oncol,* 31(33), pp. 4179-87.

Kelishadi, M. R., Ashtary-Larky, D., Davoodi, S. H., Clark, C. C. T. and Asbaghi, O. (2022) 'The effects of selenium supplementation on blood lipids and blood pressure in adults: A systematic review and dose-response meta-analysis of randomized control trials', *J Trace Elem Med Biol,* 74, pp. 127046.

Keshan Disease Research, G. (1979) 'Epidemiologic studies on the etiologic relationship of selenium and Keshan disease', *Chin Med J,* 92, pp. 477-482.

Khabbaz Koche Ghazi, M., Ghaffari, S., Naemi, M., Salehi, R., Taban Sadeghi, M., Barati, M., Namazi Shabestari, A., Kafil, B., Mesri Alamdari, N., Soleimanzadeh, H., Tarighat-Esfanjani, A. and Roshanravan, N. (2021) 'Effects of sodium selenite and selenium-enriched yeast on cardiometabolic indices of patients with atherosclerosis: A double-blind randomized clinical trial study', *J Cardiovasc Thorac Res,* 13(4), pp. 314-319.

Khazdouz, M., Daryani, N. E., Alborzi, F., Jazayeri, M. H., Farsi, F., Hasani, M., Heshmati, J. and Shidfar, F. (2020) 'Effect of Selenium Supplementation on Expression of SIRT1 and PGC-1alpha Genes in Ulcerative Colitis Patients: a Double Blind Randomized Clinical Trial', *Clin Nutr Res,* 9(4), pp. 284-295.

Kim, C. S., Jin, X. H. and Kim, Y. Y. (2022) 'Effects of mixed selenium sources on the physiological responses and blood profiles of lactating sows and tissue concentration of their progeny', *Anim Biosci,* 35(11), pp. 1725-1732.

Kohler, L. N., Florea, A., Kelley, C. P., Chow, S., Hsu, P., Batai, K., Saboda, K., Lance, P. and Jacobs, E. T. (2018a) 'Higher Plasma Selenium Concentrations Are Associated with Increased Odds of Prevalent Type 2 Diabetes', *J Nutr,* 148(8), pp. 1333-1340.

Kohler, L. N., Foote, J., Kelley, C. P., Florea, A., Shelly, C., Chow, H. S., Hsu, P., Batai, K., Ellis, N., Saboda, K., Lance, P. and Jacobs, E. T. (2018b) 'Selenium and Type 2 Diabetes: Systematic Review', *Nutrients,* 10(12).

Koletzko, B., Baker, S., Cleghorn, G., Neto, U. F., Gopalan, S., Hernell, O., Hock, Q. S., Jirapinyo, P., Lonnerdal, B., Pencharz, P., Pzyrembel, H., Ramirez-Mayans, J., Shamir, R., Turck, D., Yamashiro, Y. and Zong-Yi, D. (2005) 'Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group', *J Pediatr Gastroenterol Nutr,* 41(5), pp. 584-99.

Kong, F.-J., Ma, L.-L., Chen, S.-P., Li, G. and Zhou, J.-Q. (2016) 'Serum selenium level and gestational diabetes mellitus: a systematic review and meta-analysis', *Nutrition Journal,* 15(1), pp. 94.

Krysiak, R., Kowalcze, K. and Okopien, B. (2019) 'Selenomethionine potentiates the impact of vitamin D on thyroid autoimmunity in euthyroid women with Hashimoto's thyroiditis and low vitamin D status', *Pharmacol Rep,* 71(2), pp. 367-373.

Krysiak, R. and Okopien, B. (2011) 'The effect of levothyroxine and selenomethionine on lymphocyte and monocyte cytokine release in women with Hashimoto's thyroiditis', *J Clin Endocrinol Metab,* 96(7), pp. 2206-15.

Kupka, R., Mugusi, F., Aboud, S., Hertzmark, E., Spiegelman, D. and Fawzi, W. W. (2009) 'Effect of selenium supplements on hemoglobin concentration and morbidity among HIV-1-infected Tanzanian women', *Clin Infect Dis,* 48(10), pp. 1475-8.

Kyrgios, I., Giza, S., Kotanidou, E. P., Kleisarchaki, A., Tsinopoulou, V. R., Papadopoulou, A., Markantonatou, A. M., Kanellidou, E., Giannakou, A. and Galli-Tsinopoulou, A. (2019) 'l-selenomethionine supplementation in children and adolescents with autoimmune thyroiditis: A randomized double-blind placebo-controlled clinical trial', *J Clin Pharm Ther,* 44(1), pp. 102-108.

Lima, L. G., Santos, A., Gueiber, T. D., Gomes, R. Z., Martins, C. M. and Chaikoski, A. C. (2022) 'Relation between Selenium and Female Fertility: A Systematic Review', *Rev Bras Ginecol Obstet,* 44(7), pp. 701-709.

Lippman, S. M., Klein, E. A., Goodman, P. J., Lucia, M. S., Thompson, I. M., Ford, L. G., Parnes, H. L., Minasian, L. M., Gaziano, J. M., Hartline, J. A., Parsons, J. K., Bearden, J. D., 3rd, Crawford, E. D., Goodman, G. E., Claudio, J., Winquist, E., Cook, E. D., Karp, D. D., Walther, P., Lieber, M. M., Kristal, A. R., Darke, A. K., Arnold, K. B., Ganz, P. A., Santella, R. M., Albanes, D., Taylor, P. R., Probstfield, J. L., Jagpal, T. J., Crowley, J. J., Meyskens, F. L., Jr., Baker, L. H. and Coltman, C. A., Jr. (2009) 'Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT)', *JAMA,* 301(1), pp. 39-51.

Lonnerdal, B., Vargas-Fernandez, E. and Whitacre, M. (2017) 'Selenium fortification of infant formulas: does selenium form matter?', *Food Funct*.

Lu, F. C. (1988) 'Acceptable daily intake: inception, evolution, and application', *Regulatory Toxicology and Pharmacology,* 8(1), pp. 45-60.

Mahan, D. C. and Peters, J. C. (2004) 'Long-term effects of dietary organic and inorganic selenium sources and levels on reproducing sows and their progeny', *J Anim Sci,* 82(5), pp. 1343-58.

Mahmoodianfard, S., Vafa, M., Golgiri, F., Khoshniat, M., Gohari, M., Solati, Z. and Djalali, M. (2015) 'Effects of Zinc and Selenium Supplementation on Thyroid Function in Overweight and Obese Hypothyroid Female Patients: A Randomized Double-Blind Controlled Trial', *J Am Coll Nutr,* 34(5), pp. 391-9.

Mantovani, G., Isidori, A. M., Moretti, C., Di Dato, C., Greco, E., Ciolli, P., Bonomi, M., Petrone, L., Fumarola, A., Campagna, G., Vannucchi, G., Di Sante, S., Pozza, C., Faggiano, A., Lenzi, A. and Giannetta, E. (2019) 'Selenium supplementation in the management of thyroid autoimmunity during pregnancy: results of the "SERENA study", a randomized, double-blind, placebo-controlled trial', *Endocrine,* 66(3), pp. 542-550.

Mao, S., Zhang, A. and Huang, S. (2014) 'Selenium supplementation and the risk of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials', *Endocrine,* 47(3), pp. 758-63.

Marshall, J. R. (2001) 'Larry Clark's legacy: randomized controlled, selenium-based prostate cancer chemoprevention trials', *Nutrition and cancer,* 40(1), pp. 74-77.

Marshall, J. R., Tangen, C. M., Sakr, W. A., Wood, D. P., Jr., Berry, D. L., Klein, E. A., Lippman, S. M., Parnes, H. L., Alberts, D. S., Jarrard, D. F., Lee, W. R., Gaziano, J. M., Crawford, E. D., Ely, B., Ray, M., Davis, W., Minasian, L. M. and Thompson, I. M., Jr. (2011) 'Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917', *Cancer Prev Res (Phila),* 4(11), pp. 1761-9.

Michalke, B. and Schramel, P. (1997) 'Selenium speciation in human milk with special respect to quality control', *Biol Trace Elem Res,* 59(1-3), pp. 45-56.

Michalke, B. and Schramel, P. (1998) 'Application of capillary zone electrophoresis-inductively coupled plasma mass spectrometry and capillary isoelectric focusing-inductively coupled plasma mass spectrometry for selenium speciation', *J Chromatogr A,* 807(1), pp. 71-80.

Miller, J. C., Thomson, C. D., Williams, S. M., van Havre, N., Wilkins, G. T., Morison, I. M., Ludgate, J. L. and Skeaff, C. M. (2012) 'Influence of the glutathione peroxidase 1 Pro200Leu polymorphism on the response of glutathione peroxidase activity to selenium supplementation: a randomized controlled trial', *Am J Clin Nutr,* 96(4), pp. 923-31.

Mokhber, N., Namjoo, M., Tara, F., Boskabadi, H., Rayman, M. P., Ghayour-Mobarhan, M., Sahebkar, A., Majdi, M. R., Tavallaie, S., Azimi-Nezhad, M., Shakeri, M. T., Nematy, M., Oladi, M., Mohammadi, M. and Ferns, G. (2011) 'Effect of supplementation with selenium on postpartum depression: a randomized double-blind placebo-controlled trial', *J Matern Fetal Neonatal Med,* 24(1), pp. 104-8.

Muzembo, B. A., Ngatu, N. R., Januka, K., Huang, H. L., Nattadech, C., Suzuki, T., Wada, K. and Ikeda, S. (2019) 'Selenium supplementation in HIV-infected individuals: A systematic review of randomized controlled trials', *Clin Nutr ESPEN,* 34, pp. 1-7.

National Research Council (1989) *Recommended dietary allowances.* 10 edn. Washington, DC: The National Academies Press.

NHANES (2017-2018) *National Health and Nutrition Examination Survey (NHANES): 2017-2018*. Hyattsville, MD: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS. Available at: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2017 (Accessed: June 19 2023).

NHMRC (2006) *National Health and Medical Research Council (NHMRC) Government of Australia and New Zealand. Nutrient reference values for Austarlia and New Zealand. Selenium*. Available at: https://www.eatforhealth.gov.au/nutrient-reference-values/nutrients/selenium (Accessed: June 19 2023).

Passerieux, E., Hayot, M., Jaussent, A., Carnac, G., Gouzi, F., Pillard, F., Picot, M. C., Bocker, K., Hugon, G., Pincemail, J., Defraigne, J. O., Verrips, T., Mercier, J. and Laoudj-Chenivesse, D. (2015) 'Effects of vitamin C, vitamin E, zinc gluconate, and selenomethionine supplementation on muscle function and oxidative stress biomarkers in patients with facioscapulohumeral dystrophy: a double-blind randomized controlled clinical trial', *Free Radic Biol Med,* 81, pp. 158-69.

Pereira, M. E., Souza, J. V., Galiciolli, M. E. A., Sare, F., Vieira, G. S., Kruk, I. L. and Oliveira, C. S. (2022) 'Effects of Selenium Supplementation in Patients with Mild Cognitive Impairment or Alzheimer's Disease: A Systematic Review and Meta-Analysis', *Nutrients,* 14(15).

Perri, G., Hill, T. R., Mathers, J. C., Walsh, J. S., Gossiel, F., Winther, K., Frölich, J., Folkestad, L., Cold, S. and Eastell, R. (2022) 'Long-Term Selenium-Yeast Supplementation Does Not Affect Bone Turnover Markers: A Randomized Placebo-Controlled Trial', *J Bone Miner Res,* 37(11), pp. 2165-2173.

Pirola, I., Gandossi, E., Agosti, B., Delbarba, A. and Cappelli, C. (2016) 'Selenium supplementation could restore euthyroidism in subclinical hypothyroid patients with autoimmune thyroiditis', *Endokrynol Pol,* 67(6), pp. 567-571.

Raiten, D. J., Talbot, J. M. and Waters, J. H., eds., (1998) 'Assessment of nutrient requirements for infant formulas', *J Nutrition,* 128(11S), pp. 2059S-2291S.

Ravn-Haren, G., Bügel, S., Krath, B. N., Hoac, T., Stagsted, J., Jørgensen, K., Bresson, J. R., Larsen, E. H. and Dragsted, L. O. (2008a) 'A short-term intervention trial with selenate, selenium-enriched yeast and selenium-enriched milk: effects on oxidative defence regulation', *Br J Nutr,* 99(4), pp. 883-92.

Ravn-Haren, G., Krath, B. N., Overvad, K., Cold, S., Moesgaard, S., Larsen, E. H. and Dragsted, L. O. (2008b) 'Effect of long-term selenium yeast intervention on activity and gene expression of antioxidant and xenobiotic metabolising enzymes in healthy elderly volunteers from the Danish Prevention of Cancer by Intervention by Selenium (PRECISE) pilot study', *British Journal of Nutrition* 99(6), pp. 1190-1198.

Raygan, F., Behnejad, M., Ostadmohammadi, V., Bahmani, F., Mansournia, M. A., Karamali, F. and Asemi, Z. (2018) 'Selenium supplementation lowers insulin resistance and markers of cardio-metabolic risk in patients with congestive heart failure: a randomised, double-blind, placebo-controlled trial', *Br J Nutr,* 120(1), pp. 33-40.

Rayman, M. P. (2004) 'The use of high-selenium yeast to raise selenium status: how does it measure up?', *Br J Nutr,* 92(4), pp. 557-73.

Rayman, M. P., Blundell-Pound, G., Pastor-Barriuso, R., Guallar, E., Steinbrenner, H. and Stranges, S. (2012) 'A randomized trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin', *PLoS One,* 7(9), pp. e45269.

Rayman, M. P., Searle, E., Kelly, L., Johnsen, S., Bodman-Smith, K., Bath, S. C., Mao, J. and Redman, C. W. (2014) 'Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: a randomised, controlled pilot trial', *Br J Nutr,* 112(1), pp. 99-111.

Rayman, M. P. and Stranges, S. (2013) 'Epidemiology of selenium and type 2 diabetes: can we make sense of it?', *Free Radic Biol Med,* 65, pp. 1557-64.

Rayman, M. P., Stranges, S., Griffin, B. A., Pastor-Barriuso, R. and Guallar, E. (2011) 'Effect of supplementation with high-selenium yeast on plasma lipids: a randomized trial', *Ann Intern Med,* 154(10), pp. 656-65.

Rayman, M. P., Winther, K. H., Pastor-Barriuso, R., Cold, F., Thvilum, M., Stranges, S., Guallar, E. and Cold, S. (2018) 'Effect of long-term selenium supplementation on mortality: Results from a multiple-dose, randomised controlled trial', *Free Radic Biol Med,* 127, pp. 46-54.

Reid, M. E., Duffield-Lillico, A. J., Slate, E., Natarajan, N., Turnbull, B., Jacobs, E., Combs, G. F., Jr., Alberts, D. S., Clark, L. C. and Marshall, J. R. (2008) 'The nutritional prevention of cancer: 400 mcg per day selenium treatment', *Nutr Cancer,* 60(2), pp. 155-63.

Reid, M. E., Duffield-Lillico, A. J., Sunga, A., Fakih, M., Alberts, D. S. and Marshall, J. R. (2006) 'Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial', *Int J Cancer,* 118(7), pp. 1777-81.

Reid, M. E., Stratton, M. S., Lillico, A. J., Fakih, M., Natarajan, R., Clark, L. C. and Marshall, J. R. (2004) 'A report of high-dose selenium supplementation: response and toxicities', *J Trace Elem Med Biol,* 18(1), pp. 69-74.

Renwick, A. (1990) 'Acceptable daily intake and the regulation of intense sweeteners', *Food Additives & Contaminants,* 7(4), pp. 463-475.

Richie, J. P., Jr., Das, A., Calcagnotto, A. M., Sinha, R., Neidig, W., Liao, J., Lengerich, E. J., Berg, A., Hartman, T. J., Ciccarella, A., Baker, A., Kaag, M. G., Goodin, S., DiPaola, R. S. and El-Bayoumy, K. (2014) 'Comparative effects of two different forms of selenium on oxidative stress biomarkers in healthy men: a randomized clinical trial', *Cancer Prev Res (Phila),* 7(8), pp. 796-804.

Rodriguez, J. A. M., Bifano, M., Roca Goma, E., Plasencia, C. M., Torralba, A. O., Font, M. S. and Millan, P. R. (2021) 'Effect and Tolerability of a Nutritional Supplement Based on a Synergistic Combination of beta-Glucans and Selenium- and Zinc-Enriched *Saccharomyces cerevisiae* (ABB C1((R))) in Volunteers Receiving the Influenza or the COVID-19 Vaccine: A Randomized, Double-Blind, Placebo-Controlled Study', *Nutrients,* 13(12).

Roman, M., Jitaru, P. and Barbante, C. (2013) 'Selenium biochemistry and its role for human health', *Metallomics,* 6(1), pp. 25-54.

Roman, M., Jitaru, P. and Barbante, C. (2014) 'Selenium biochemistry and its role for human health', *Metallomics,* 6(1), pp. 25-54.

Roshanravan, N., Koche Ghazi, M. K., Ghaffari, S., Naemi, M., Alamdari, N. M., Shabestari, A. N., Mosharkesh, E., Soleimanzadeh, H., Sadeghi, M. T., Alipour, S., Bastani, S. and Tarighat-Esfanjani, A. (2022) 'Sodium selenite and Se-enriched yeast supplementation in atherosclerotic patients: Effects on the expression of pyroptosis-related genes and oxidative stress status', *Nutr Metab Cardiovasc Dis,* 32(6), pp. 1528-1537.

Rulis, A. M. and Levitt, J. A. (2009) 'FDA'S food ingredient approval process: safety assurance based on scientific assessment', *Regulatory Toxicology and Pharmacology,* 53(1), pp. 20-31.

Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Chesson, A., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López-Alonso, M., López Puente, S., Mayo, B., Ramos, F., Saarela, M., Villa, R. E., Wallace,

R. J., Wester, P., Pechova, A., López-Gálvez, G. and Mantovani, A. (2017) 'Safety and efficacy of selenium-enriched yeast (*Saccharomyces cerevisiae* CNCM I-3399) for all animal species', *EFSA J,* 15(7), pp. e04937.

Sajjadi, S. S., Foshati, S., Haddadian-Khouzani, S. and Rouhani, M. H. (2022) 'The role of selenium in depression: a systematic review and meta-analysis of human observational and interventional studies', *Sci Rep,* 12(1), pp. 1045.

Sigma-Aldrich (2022). Selenomethione.

Spallholz, J. E. and Raftery, A. (1987) 'Nutritional, chemical, and toxicological evaluation of a high-selenium yeast'.

Stranges, S., Marshall, J. R., Natarajan, R., Donahue, R. P., Trevisan, M., Combs, G. F., Cappuccio, F. P., Ceriello, A. and Reid, M. E. (2007) 'Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial', *Ann Intern Med,* 147(4), pp. 217-23.

Stranges, S., Marshall, J. R., Trevisan, M., Natarajan, R., Donahue, R. P., Combs, G. F., Farinaro, E., Clark, L. C. and Reid, M. E. (2006) 'Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial', *Am J Epidemiol,* 163(8), pp. 694-9.

Stratton, M. S., Algotar, A. M., Ranger-Moore, J., Stratton, S. P., Slate, E. H., Hsu, C. H., Thompson, P. A., Clark, L. C. and Ahmann, F. R. (2010) 'Oral selenium supplementation has no effect on prostate-specific antigen velocity in men undergoing active surveillance for localized prostate cancer', *Cancer Prev Res (Phila),* 3(8), pp. 1035-43.

Stratton, M. S., Reid, M. E., Schwartzberg, G., Minter, F. E., Monroe, B. K., Alberts, D. S., Marshall, J. R. and Ahmann, F. R. (2003a) 'Selenium and inhibition of disease progression in men diagnosed with prostate carcinoma: study design and baseline characteristics of the 'Watchful Waiting' Study', *Anticancer Drugs,* 14(8), pp. 595-600.

Stratton, M. S., Reid, M. E., Schwartzberg, G., Minter, F. E., Monroe, B. K., Alberts, D. S., Marshall, J. R. and Ahmann, F. R. (2003b) 'Selenium and prevention of prostate cancer in high-risk men: the Negative Biopsy Study', *Anticancer Drugs,* 14(8), pp. 589-94.

Strozyk, A., Osica, Z., Przybylak, J. D., Kolodziej, M., Zalewski, B. M., Mrozikiewicz-Rakowska, B. and Szajewska, H. (2019) 'Effectiveness and safety of selenium supplementation for type 2 diabetes mellitus in adults: a systematic review of randomised controlled trials', *J Hum Nutr Diet,* 32(5), pp. 635-645.

Tan, S. and Tan, S. (2010) 'The Correct Interpretation of Confidence Intervals', *Proceedings of Singapore Healthcare,* 19, pp. 276-278.

Thompson, H. J., Sedlacek, S. M., Fitzgerald, V. K., Wolfe, P. and McGinley, J. N. (2022) 'A Randomized, Double-Blind, Placebo-Controlled Investigation of Selenium Supplementation in Women at Elevated Risk for Breast Cancer: Lessons for Re-Emergent Interest in Selenium and Cancer', *Biomedicines,* 11(1).

Thompson, P. A., Ashbeck, E. L., Roe, D. J., Fales, L., Buckmeier, J., Wang, F., Bhattacharyya, A., Hsu, C. H., Chow, H. H., Ahnen, D. J., Boland, C. R., Heigh, R. I., Fay, D. E., Hamilton, S. R., Jacobs, E. T., Martinez, M. E., Alberts, D. S. and Lance, P. (2016) 'Selenium Supplementation for Prevention of Colorectal Adenomas and Risk of Associated Type 2 Diabetes', *J Natl Cancer Inst,* 108(12).

Uden, P. C., Boakye, H. T., Kahakachchi, C., Hafezi, R., Nolibos, P., Block, E., Johnson, S. and Tyson, J. F. (2003) 'Element selective characterization of stability and reactivity of selenium species in selenized yeast', *Journal of Analytical Atomic Spectrometry,* 19(1), pp. 65-73.

Vanek, V. W. (2015) 'Review of Trace Mineral Requirements for Preterm Infants: What Are the Current Recommendations for Clinical Practice?', *Nutr Clin Pract,* 30(5), pp. 720-1.

Vinceti, M., Filippini, T., Cilloni, S., Bargellini, A., Vergoni, A. V., Tsatsakis, A. and Ferrante, M. (2017) 'Health risk assessment of environmental selenium: Emerging evidence and challenges (Review)', *Mol Med Rep,* 15(5), pp. 3323-3335.

Vinceti, M., Filippini, T., Del Giovane, C., Dennert, G., Zwahlen, M., Brinkman, M., Zeegers, M. P., Horneber, M., D'Amico, R. and Crespi, C. M. (2018) 'Selenium for preventing cancer', *Cochrane Database Syst Rev,* 1, pp. CD005195.

Wang, X.-l., Yang, T.-b., Wei, J., Lei, G.-h. and Zeng, C. (2015) 'Association between serum selenium level and type 2 diabetes mellitus: a non-linear dose–response meta-analysis of observational studies', *Nutrition Journal,* 15(1), pp. 48.

Wang, X., Yang, Y., Zhang, H. and Liu, J. (2017) 'Safety Assessment and Comparison of Sodium Selenite and Bioselenium Obtained from Yeast in Mice', *Biomed Res Int,* 2017, pp. 3980972.

Wichman, J., Winther, K. H., Bonnema, S. J. and Hegedus, L. (2016) 'Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis', *Thyroid,* 26(12), pp. 1681-1692.

Winther, K. H., Bonnema, S. J., Cold, F., Debrabant, B., Nybo, M., Cold, S. and Hegedus, L. (2015) 'Does selenium supplementation affect thyroid function? Results from a randomized, controlled, double-blinded trial in a Danish population', *Eur J Endocrinol,* 172(6), pp. 657-67.

Xia, Y., Hill, K. E., Li, P., Xu, J., Zhou, D., Motley, A. K., Wang, L., Byrne, D. W. and Burk, R. F. (2010) 'Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects', *Am J Clin Nutr,* 92(3), pp. 525-31.

Xie, D., Liao, Y., Yue, J., Zhang, C., Wang, Y., Deng, C. and Chen, L. (2018) 'Effects of five types of selenium supplementation for treatment of Kashin-Beck disease in children: a systematic review and network meta-analysis', *BMJ Open,* 8(3), pp. e017883.

Yoon, I. and McMillan, E. (2006) 'Comparative effects of organic and inorganic selenium on selenium transfer from sows to nursing pigs', *J Anim Sci,* 84(7), pp. 1729-33.

Zachara, B. A., Gromadzinska, J., Palus, J., Zbrog, Z., Swiech, R., Twardowska, E. and Wasowicz, W. (2011) 'The effect of selenium supplementation in the prevention of DNA damage in white blood cells of hemodialyzed patients: a pilot study', *Biol Trace Elem Res,* 142(3), pp. 274-83.

Zhan, X., Qie, Y., Wang, M., Li, X. and Zhao, R. (2011) 'Selenomethionine: an effective selenium source for sow to improve Se distribution, antioxidant status, and growth performance of pig offspring', *Biol Trace Elem Res,* 142(3), pp. 481-91.

Zheng, H., Wei, J., Wang, L., Wang, Q., Zhao, J., Chen, S. and Wei, F. (2018) 'Effects of Selenium Supplementation on Graves' Disease: A Systematic Review and Meta-Analysis', *Evid Based Complement Alternat Med,* 2018, pp. 3763565.

Zhou, H., Wang, T., Li, Q. and Li, D. (2018) 'Prevention of Keshan Disease by Selenium Supplementation: a Systematic Review and Meta-analysis', *Biol Trace Elem Res,* 186(1), pp. 98-105.

Zuo, Y., Li, Y., Gu, X. and Lei, Z. (2021) 'The correlation between selenium levels and autoimmune thyroid disease: a systematic review and meta-analysis', *Ann Palliat Med,* 10(4), pp. 4398-4408.

Uncategorized References

SOP	Standard Operating Procedures

B. Appendices

Appendix 1 Quality Assurance/Quality Control (QA/QC) Program in Summary

Production Protocol
SelenoExcell® High Selenium Yeast 1200

- A pure, selected culture of a pure *Saccharomyces cerevisiae* strain is maintained as the starting material.
- The pure culture grows in consecutive stages to reach the inoculation volume of the commercial fermentation.
- After inoculation of the commercial fermenter, nutrients (e.g., carbon source, nitrogen, and phosphorous) are added in precisely controlled rates that optimize yeast growth.
- During this aerobic fermentation, sodium selenite (Na_2SeO_3) is added at the specific time intervals that maximize the selenium binding to the protein structure of the yeast–which typically ranges from 50% to 55%.
- Key monitoring factors throughout the process are nutrient feed rate, pH, temperature, and alcohol concentration.
- Once target selenium potency is achieved –after about 18 hours of fermentation–, clean water is added, and the selenium yeast is separated by centrifugation. This process guarantees the removal of the growth media and the absence of free, inorganic selenium.
- Following the wash cycle and complete separation of the yeast, the yeast cream is held in cold storage in preparation for downstream processing.
- Prior to spray drying, the yeast cream is inactivated through a high-temperature system. This step ensures the microbiological quality of the finished product, which exceeds USDA standards for human consumption.
- The spray drying turns the product into a uniform powder that can be effortlessly added to food and dietary supplements (within guidelines for selenium dose).
- All the operations are performed under cGMP procedures.

QA/QC Program
SelenoExcell® High Selenium Yeast 1200

The quality of Cypress Systems' products is supported by an experienced and qualified team that works under a continuous improvement program, focused on customer attention and superior quality.

The process is based on Good Manufacturing Practices, considering all applicable regulations. Batch Records specify the quantity and identity of raw materials, equipment utilized, and the critical process parameters, which provide traceability throughout the supply chain. Every operation is performed as established by Standard Operating Procedures (SOP).

In the first stage of the QA / QC program, raw materials are strictly evaluated to keep the quality and standardization of all products.

Composite samples are taken during the spray drying phase, which are analyzed by outside, independent laboratories for nutrient and microbial composition to assure the finished product exceeds USDA human food requirements. Third-party testing lends confidence to Cypress and provides validation for our customers.

Routine testing of SelenoExcell® certifies the absence of "free," inorganic selenium.

A batch is approved only if it complies with the specifications outlined in Part 3 of this dossier (Table 2). Test methods are included in the same section.

After confirmation of compliance from the independent laboratories, the product is released for sale with a supporting Certificate of Analysis.

Appendix 2 Yeast Specification and Culture Media Food Grade Statement

Raw Material Specification

Name: ***Saccharomyces cerevisiae*** (strain) **CODE:** RMS.YEAST.PD22-0 **Date:** October 2022		
1.Description and Production Method		
Saccharomyces cerevisiae is a unicellular fungus. It is a type of yeast which is used industrially in the manufacture of bread, beer and wine. *Saccharomyces cerevisiae* yeast strain is propagated in flasks with Agar as medium. They are closed and stored at a 4°C until use.		
2. **Preparation Method/Treatment before use or process**: Not applicable		
3. **Composition (Including additives and processing aids):** Not applicable		
4. ***Source****: Biological*		
5. **Applicable legal requirements***: None*		
6. **Allergens:** *None*		
7. **GMO status***: Non-GMO*		
8. **Other status***: Kosher and Halal status*		
9. **Country of origin***: Australia*		
10. **Specifications and Food Safety Characteristics:**		
PHYSICAL CHARACTERISTICS		
PARAMETER	**Specification**	**Test Method**
Extraneous Material	Negative. Absence of harmful material including animals, insects, wood, plastic, glass, etc.	HACCP
BIOLOGICAL CHARACTERISTICS		
PARAMETER	**Specification**	**Test Method**
Microbiological contamination	Absence of any microbiological contamination	YTM 3.9.2 General Infection Whey Test.
11. **Material and packaging material:** Sterile and closed bottles with cap and intact seal		
12. **Storage conditions:** This product must be stored below at 4°C, in a clean and dry place free of foreign material and according to Good Storage Practice.		
13**. Shelf life:** 6 months under storage conditions specified above		
14. **Shipping conditions, transportation (methods of distribution):** The following requirements must be met: Clean closed transport with climate, strains should not be transported at temperatures higher than 20°C		
15. **Mandatory:**		
This is information to be used as reference. AB Mauri (our manufacturing supplier) oversees it since it is a relevant step in production process. AB Mauri's supplier is responsible for keeping up to date with reference to applicable laws and regulations that imply a change of specification and/or label of the product.		

Adriana Pescador
QA/QC and Food Safety-PCQI

Culture Media Statement
SelenoExcell®

Our SelenoExcell® is manufactured at AB Mauri, represented in Mexico by AB Calsa S.A de C.V., Veracruz plant. The facility works under a FSSC 22000 certification, which is recognized by the GFSI (Global Food Safety Initiative). The standards include pre-requisite programs and a HACCP Plan to ensure the critical limits for all CCPs are maintained under control. AB Mauri is committed to establishing, maintaining, and continuously improving its Integrated Management System based on compliance with the legal and regulatory requirements established by national and international standards.

SelenoExcell® is grown under aseptic and aerobic conditions. The fermentation medium used throughout the process allows the yeast to grow and replicate at the different stages, and all its components/ingredients are treated before addition to ensure meet the standards needed by the process and all finished product specifications.

The medium is considered safe from a food grade perspective. It is separated by centrifugation, repeatedly washed and no trace of culture media would be found in the final product.

Ingredients

Component	*Function*	*Origin*	*Country of Origin*
Sugar cane molasses	Carbon source	a by-product of the sugar extraction and refining process that is used to feed the yeast throughout the fermentation process	Mexico
Anhydrous ammonia and Urea	Nitrogen source, supplied to aid protein formation	Industrial ammonia synthesis	Mexico
Phosphoric acid	Phosphate source which plays a vital role in cell division.	Industrial chemical synthesis	Mexico
Vitamins/Minerals	Growth/conditioning factor	Fermentation and/or industrial production from inorganic compounds	Various (Mexico, China)

Processing aids

Component	*Function*	*Origin*	*Country of Origin*
Food Grade Antifoam	Antifoam agent during fermentation	Industrial Production	Various (UK, Austria)
Sulfuric Acid	pH control	Industrial Production	Mexico

None of these ingredients are classified as allergens or are derived from animal sources. In addition, all raw materials, processing aids, and food contact substances used in the manufacture of SelenoExcell are in accordance with existing U.S. regulations. They are submitted to strict QA/QC procedures including risk assessment, HACCP review, and supplier approval, before inclusion in the manufacturing process.

[redacted]
Adriana Pescador
QA/QC and Food Safety-PCQI
September 2022

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Appendix 3 Product Data Sheet and Certificates of Analysis for Multiple Lots

SELENOEXCELL®

HIGH SELENIUM YEAST 1200

Yeast Strain: *Saccharomyces cerevisiae*

	Typical Analysis	
Item	**Expected**	**Range**
Total Selenium	1,200 µg/g	1,200 - 1,380 µg/g
Organically Bound Se	100%	100%
Moisture	6.00%	2.5 - 7.5%
Color	Tan to light brown	Tan to light brown
Extraneous Material	Negative	Negative
Microbiological Assay		
Salmonella spp.	Negative/60g	Negative/60g
E. coli	Negative/10g	Negative/10g
S. aureus	Negative/10g	Negative/10g
*Cronobacter sakazakii**	Negative/10g	Negative/10g
*Listeria monocytogenes**	Negative/25g	Negative/25g
Total Coliforms	< 3 MPN/g	< 3 MPN/g
Total Plate Count	< 10 CFU/g	< 150 CFU/g
Yeast/Mold	< 10 CFU/g	< 50 CFU/g
Heavy Metals		
Arsenic (As)	< 0.5 µg/g	< 1 µg/g
Cadmium (Cd)	< 0.25 µg/g	< 1 µg/g
Mercury (Hg)	< 0.05 µg/g	< 0.1 µg/g
Lead (Pb)	< 0.1 µg/g	< 1 µg/g
Particle Size		
Through 60 mesh:	99% min	98% min
Through 100 mesh:	95% min	95% min
Bulk Density:	0.7 g/mL	0.6 to 0.9 g/mL

*These parameters are guaranteed each lot, but not routinely tested.

Shelf Life: 3 - 5 years when properly stored in original container and kept dry.
Packaging: Product is packaged in 25 kg boxes lined with 6 mil polyethylene bags.

PDS.IF.SE1200.PD22-0

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Manufacturer's Certificate of Analysis

SelenoExcell® High Selenium Yeast 1200

Company: **PO #:**
Customer Item #:
Date of Manufacture: March 7, 2021
Date of Expiration: March 7, 2024 **Shelf Life:** 3 years
Country of Origin: Mexico **Storage:** Cool, dry, reclose bag
Lot Number: SE-127

Nutrient Analysis	Standard Limits	Analytical Method	Results
Total Selenium:	1200 – 1380 µg/g	ICP MS	1360 µg/g
Organically Bound Selenium:	100%	MBRT Method	100%
Moisture:	2.5% – 7.5%	AOAC 927.05	5.05 %
Color:	Tan to light brown	Visual	Tan
Extraneous Material:	Negative	HACCP	Negative
Microbiological Assay			
Salmonella spp.:	Negative/60g	AOAC 2004.03	Negative/60g
E. coli:	Negative/10g	Current USP/NF<62>	Negative/10g
S. aureus	Negative/10g	Current USP/NF<62>	Negative/10g
*Cronobacter sakazakii**	Negative/10g*	ISO22964	Negative/10g
*Listeria monocytogenes**	Negative/25g*	FDA-BAM 7th Ed.	Negative/25g
Total Coliforms:	< 3 MPN/g	AOAC 966.24	< 0.3 MPN/g
Total Plate Count:	< 150 CFU/g	AOAC 966.23	20 CFU/g
Yeast:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Mold:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Heavy Metals			
Arsenic (As):	< 1 µg/g	ICP MS	< 0.50 µg/g
Cadmium (Cd):	< 1 µg/g	ICP MS	< 0.25 µg/g
Mercury (Hg):	< 0.1 µg/g	ICP MS	< 0.050 µg/g
Lead (Pb):	< 1 µg/g	ICP MS	< 0.10 µg/g
Particle Size			
Through 60 mesh:		ASTA 10.0 (Ro-Tap Sieve)	100%
Through 100 mesh:		ASTA 10.0 (Ro-Tap Sieve)	98%
Bulk Density:		Internal method (ASTA 25.0)	0.72 g / mL

*These parameters are guaranteed each lot, but not routinely tested.

These results are reported by:

Mark E. Whitacre, Ph.D.
Chief Science Officer
May 5 , 2021

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Manufacturer's Certificate of Analysis

SelenoExcell® High Selenium Yeast 1200

Company: **PO #:**
Customer Item #:
Date of Manufacture: June 15, 2021
Date of Expiration: June 15, 2024 **Shelf Life:** 3 years
Country of Origin: Mexico **Storage:** Cool, dry, reclose bag
Lot Number: SE-128

Nutrient Analysis	Standard Limits	Analytical Method	Results
Total Selenium:	1200 – 1380 µg/g	ICP MS	1220 µg/g
Organically Bound Selenium:	100%	MBRT Method	100%
Moisture:	2.5% – 7.5%	AOAC 927.05	5.09 %
Color:	Tan to light brown	Visual	Tan
Extraneous Material:	Negative	HACCP	Negative
Microbiological Assay			
Salmonella spp.:	Negative/60g	AOAC 2004.03	Negative/60g
E. coli:	Negative/10g	Current USP/NF<62>	Negative/10g
S. aureus	Negative/10g	Current USP/NF<62>	Negative/10g
*Cronobacter sakazakii**	Negative/10g*	ISO22964	Negative/10g
*Listeria monocytogenes**	Negative/25g*	FDA-BAM 7th Ed.	Negative/25g
Total Coliforms:	< 3 MPN/g	AOAC 966.24	< 0.3 MPN/g
Total Plate Count:	< 150 CFU/g	AOAC 966.23	< 10 CFU/g
Yeast:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Mold:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Heavy Metals			
Arsenic (As):	< 1 µg/g	ICP MS	< 0.50 µg/g
Cadmium (Cd):	< 1 µg/g	ICP MS	< 0.25 µg/g
Mercury (Hg):	< 0.1 µg/g	ICP MS	< 0.10 µg/g
Lead (Pb):	< 1 µg/g	ICP MS	< 0.10 µg/g
Particle Size			
Through 60 mesh:		ASTA 10.0 (Ro-Tap Sieve)	100%
Through 100 mesh:		ASTA 10.0 (Ro-Tap Sieve)	99%
Bulk Density:		Internal method (ASTA 25.0)	0.73 g / mL

*These parameters are guaranteed each lot, but not routinely tested.

These results are reported by:

[redacted]

Adriana Pescador
QA/QC and Food Safety
Jul 8, 2021

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Manufacturer's Certificate of Analysis

SelenoExcell® High Selenium Yeast 1200

Company: **PO #:**
Customer Item #:
Date of Manufacture: September 12, 2021
Date of Expiration: September 12, 2024 **Shelf Life:** 3 years
Country of Origin: Mexico **Storage:** Cool, dry, reclose bag
Lot Number: SE-130

Nutrient Analysis	Standard Limits	Analytical Method	Results
Total Selenium:	1200 – 1380 µg/g	ICP MS	1238 µg/g
Organically Bound Selenium:	100%	MBRT Method	100%
Moisture:	2.5% – 7.5%	AOAC 927.05	5.04 %
Color:	Tan to light brown	Visual	Tan
Extraneous Material:	Negative	HACCP	Negative
Microbiological Assay			
Salmonella spp.:	Negative/60g	AOAC 2004.03	Negative/60g
E. coli:	Negative/10g	Current USP/NF<62>	Negative/10g
S. aureus	Negative/10g	Current USP/NF<62>	Negative/10g
*Cronobacter sakazakii**	Negative/10g*	ISO22964	Negative/10g
*Listeria monocytogenes**	Negative/25g*	FDA-BAM 7th Ed.	Negative/25g
Total Coliforms:	< 3 MPN/g	AOAC 966.24	< 0.3 MPN/g
Total Plate Count:	< 150 CFU/g	AOAC 966.23	< 10 CFU/g
Yeast:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Mold:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Heavy Metals			
Arsenic (As):	< 1 µg/g	ICP MS	< 0.50 µg/g
Cadmium (Cd):	< 1 µg/g	ICP MS	< 0.25 µg/g
Mercury (Hg):	< 0.1 µg/g	ICP MS	< 0.10 µg/g
Lead (Pb):	< 1 µg/g	ICP MS	< 0.10 µg/g
Particle Size			
Through 60 mesh:		ASTA 10.0 (Ro-Tap Sieve)	100%
Through 100 mesh:		ASTA 10.0 (Ro-Tap Sieve)	98%
Bulk Density:		Internal method (ASTA 25.0)	0.69 g / mL

*These parameters are guaranteed each lot, but not routinely tested.

These results are reported by:

Adriana Pescador
QA/QC and Food Safety-PCQI/October 26, 2021

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Manufacturer's Certificate of Analysis

SelenoExcell® High Selenium Yeast 1200

Company: **PO #:**
Customer Item #:
Date of Manufacture: May 16, 2022
Date of Expiration: May 16, 2025 **Shelf Life:** 3 years
Country of Origin: Mexico **Storage:** Cool, dry, reclose bag
Lot Number: SE-131

Nutrient Analysis	Standard Limits	Analytical Method	Results
Total Selenium:	1200 – 1380 µg/g	ICP MS	1222 µg/g
Organically Bound Selenium:	100%	MBRT Method	100%
Moisture:	2.5% – 7.5%	AOAC 927.05	4.53 %
Color:	Tan to light brown	Visual	Tan
Extraneous Material:	Negative	HACCP	Negative
Microbiological Assay			
Salmonella spp.:	Negative/60g	AOAC 2004.03	Negative/60g
E. coli:	Negative/10g	Current USP/NF<62>	Negative/10g
S. aureus	Negative/10g	Current USP/NF<62>	Negative/10g
*Cronobacter sakazakii**	Negative/10g*	ISO22964	Negative/10g
*Listeria monocytogenes**	Negative/25g*	FDA-BAM 7th Ed.	Negative/25g
Total Coliforms:	< 3 MPN/g	AOAC 966.24	< 0.3 MPN/g
Total Plate Count:	< 150 CFU/g	AOAC 966.23	< 10 CFU/g
Yeast:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Mold:	< 50 CFU/g	FDA-BAM 7th Ed.	< 10 CFU/g
Heavy Metals			
Arsenic (As):	< 1 µg/g	ICP MS	< 0.50 µg/g
Cadmium (Cd):	< 1 µg/g	ICP MS	< 0.25 µg/g
Mercury (Hg):	< 0.1 µg/g	ICP MS	< 0.10 µg/g
Lead (Pb):	< 1 µg/g	ICP MS	< 0.10 µg/g
Particle Size			
Through 60 mesh:		ASTA 10.0 (Ro-Tap Sieve)	100%
Through 100 mesh:		ASTA 10.0 (Ro-Tap Sieve)	98%
Bulk Density:		Internal method (ASTA 25.0)	0.69 g / mL

*these parameters are guaranteed each lot, but not routinely tested.

These results are reported by:

[redacted]

Adriana Pescador /QA/QC and Food Safety-PCQI/October 26, 2021

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Appendix 4 Stability Report

High Selenium Yeast
Stability/Shelf Life Statement

Stability studies include testing of those attributes that are susceptible to change during storage and are likely to influence quality. For Cypress Systems' High Selenium Yeast, mineral content has been evaluated through time in order to demonstrate its consistency.

The table below shows test results reported by PAR Laboratories, Inc. in different samples of SelenoExcell® High Selenium Yeast 1200.

The data in the original manufacturing period is compared to the values obtained on August 3, 2010 and October 30, 2014. PAR Laboratories, Inc. is a certified third-party laboratory, independent from Cypress Systems, with facilities in Charlotte, NC, USA. The product was drawn from retained samples ranging in age from 1998 to 2010. The established test method is based on ICP-OES detection and allows for a +/-5% variance:

		Selenium potency (ppm)				
Batch number	Production	Original result	2010	Variation	2014	Variation
SE-21	03/1998	1,250	1,234	1.3%	1,233	1.4%
SE-37	09/1999	1,230	1,236	0.5%	1,224	0.5%
SE-48	03/2001	1,245	1,259	1.1%	1,232	1.0%
SE-59	11/2002	1,243	1,256	1.0%	1,229	1.1%
SE-63	12/2003	1,258	1,250	0.6%	1,214	3.5%
SE-73	07/2005	1,253	1,240	1.0%	1,245	0.6%
SE-85	01/2009	1,240	1,252	1.0%	1,223	1.4%
SE-87	09/2009	1,230	-	-	1,226	0.3%
SE-88	06/2010	1,220	-	-	1,232	1.0%
				0.9%		1.4%

Average variation

This minimal variation confirms the stability that Cypress Systems' High Selenium Yeast products offer, even after the guaranteed shelf life period, provided it is stored under our recommended conditions that are based on the general powder storage guidelines and the Good Storage Practices set by the U.S Pharmacopeia.

Cypress Systems, Inc. CORPORATE SEAL August 17, 1995 CALIFORNIA

[redacted]

Adriana Pescador
QA/QC and Food Safety PCQI
February 2022

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Appendix 5 GMO Statement

Non-GMO Statement

Cypress Systems certifies that the yeast cultures used for the manufacturing of SelenoExcell® are propagated from a pure *Saccharomyces cerevisiae* strain, which is sub-cultured annually and tested for purity and genetic drift. All culture work is undertaken under strict aseptic conditions using work instructions and media to ensure Kosher and non-GMO status is maintained. The yeast strain has not been genetically modified (GM), and no GM materials are introduced at any stage of the process.

Genetic modification comprises the controlled and precise modification of an organism's genome using recombinant DNA and other molecular techniques to alter a trait of interest.

The Organic Materials Review Institute (OMRI) in the USA defines *Genetically Engineered* (GE) as "a product made with techniques that alter the molecular or cell biology of an organism by means that are not possible under natural conditions or processes. Genetic engineering includes recombinant DNA, cell fusion, micro- and macro-encapsulation, and the following results when achieved by recombinant techniques: gene deletion and doubling, introduction of a foreign gene, and changing the positions of genes. It does not include traditional breeding, conjugation, fermentation, hybridization, in-vitro fertilization, or tissue culture."

This definition agrees with the description made by the Non-GMO Project, the National Organic Project (NOP), and the 2001 joint World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) Expert Consultation Report.

In addition, according to the definitions of current European legislation—Directive 2001/18/EC and Regulation 2003/1829/EC—SelenoExcell® is considered a non-GMO product.

Appendix 6 Allergen Statement

ALLERGEN/SENSITIVE MATERIALS STATEMENT

Product: SelenoExcell® High Selenium Yeast 1200 **Country of Origin**: Mexico
Supplier Name: Cypress Systems, Inc.

Material	Yes	No	Details (concentration, if it is used in the same site)	Material	Yes	No	Details (concentration, if it is used in the same site)
Alcohol and/or derivatives		X		MSG (monosodium glutamate)		X	
Animal Derivatives (specify)		X		Mushrooms (specify)		X	
Artificial Color (specify if tartrazine, or caramel color)		X		Peanut and/or derivatives		X	
Artificial Flavor (e.g., vanillin, smoke flavor)		X		Pectin (specify source)		X	
Artificial Sweetener (e.g., aspartame)		X		Potato and/or derivatives		X	
Canola and/or derivatives		X		Preservatives (e.g., BHA, BHT, nitrates, nitrites, propionates)		X	
Celery and/or derivatives		X		Rice and/or derivatives		X	
Corn and/or derivatives		X		Other seeds (e.g., safflower, sesame, sunflower, lupin, mustard, etc.) or derivatives		X	
Egg and/or derivative		X		Sodium (specify source)		X	
Excipients / Carriers (specify)		X		Soybean and/or derivative		X	
Fish / Crustacean / Mollusks (specify)		X		Starch (specify source)		X	
Fluoridated Water		X		Sugar (specify source)		X	
Fruits (e.g., berries, apple, tomato)		X		Sulfur dioxide and sulfites		X	
Gluten containing materials (wheat, barley, rye, oats)		X		Tree Nut / Tree Nut Oil		X	
HVP (hydrolyzed vegetable or plant protein. Specify)		X		Yeast and/or derivatives	X		Pure baker's yeast strain
Milk and/or derivatives (including lactose)		X		Others (specify)		X	
Sesame (spice or flavor)		X					

Product Status:

Category	Yes	No	Comments
Meets vegetarian/vegan standards	X		No animal-derived ingredients are included
Risk of BSE/TSE contamination		X	No contact with animal products at any stage
Use of pesticides		X	The product does not contain pesticides
Use of solvents		X	Solvents are not used at any stage of the process
Use of Irradiation/Ethylene Oxide		X	None of these sterilization methods is applied
Use of petrochemical substrate/sulfite waste liquor		X	These substrates are not used in the process
Use of sewage sludge		X	Use not suitable or permitted in food products
Containing or involving GMOs		X	Non-GMO, pure culture of *S. cerevisiae* yeast

Name/Title/Signature: Adriana Pescador /QA/QC and Food Safety PCQI Date Signed: Feb 2022

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Appendix 7 GRAS Associates Expert Panel Report

The Generally Recognized as Safe (GRAS) Status of the Proposed Use of High Selenium Yeast in Infant Formula

June 15, 2023

Foreword

An independent panel of experts ("Expert Panel") was convened by GRAS Associates, LLC on behalf of their client, Cypress, to evaluate the safety and Generally Recognized as Safe (GRAS) status of Cypress's proposed use of SelenoExcell® (high selenium yeast) in non-exempt infant formula for term infants. The members of this Expert Panel† are qualified to serve in this capacity by qualification of scientific training and experience in the safety of food and food ingredients.

GRAS Associates and Cypress ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety, toxicology, and nutrition. The Expert Panel was selected and convened in accordance with the Food and Drug Administration (FDA)'s guidance for industry on "Best Practices for Convening a GRAS Panel"[8]. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel and no such conflicts of interest or "appearance issues" were identified. The Expert Panel members received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel members were not contingent upon the outcome of their deliberations.

Discussion

The manufacturing process utilizes *Saccharomyces cerevisiae* as the yeast into which inorganic selenium, as Na_2SeO_3, is incorporated. A food-grade, pure culture of a *Saccharomyces cerevisiae* strain is the starting material for fermentation and all materials used in the manufacturing process (fermentation media, processing aids and food contact substances) are food grade and comply with any applicable regulations per Title 21 of the Code of Federal Regulations (CFR). The strain is maintained at the American Type Culture Collection (ATCC) and has not been genetically modified (GM) and no GM materials are introduced during any stage of the process. Allergenic substances are not included at any step of the manufacturing process of SelenoExcell® or in the fermentation medium (except for yeast). The potential for an allergenic response to SelenoExcell® has been reviewed in detail in GRN 260 (Cypress Systems Inc, 2008). A comprehensive review of the published literature did not identify reports of allergenicity associated with ingestion of either *Saccharomyces cerevisiae* or high-selenium yeast and authoritative bodies have stated that "food

† Dr. Dolan, Chair of the Expert Panel, is a board-certified toxicologist (DABT) with over 25 years of experience in regulatory submissions and safety assessments. She is a Fellow of the American College of Nutrition (FACN) and past president of the Food Safety Specialty Section of the Society of Toxicology (SOT). Dr. Dolan previously served as a Senior Toxicologist in the Contaminant Assessment Branch at FDA's Center for Food Safety and Nutrition and is currently Senior Staff Toxicologist for GRAS Associates. Dr. Lönnerdal is a Distinguished Professor Emeritus, Department of Internal Medicine, at UC Davis. Dr. Lönnerdal's research program is focused on two main areas: infant/pediatric nutrition and trace element metabolism. Dr. Kraska holds a PhD in Pharmacology and has over 35 years of experience related to assessing safety of food additives, GRAS ingredients and food contact materials. Dr. Kraska worked on GRAS and food additive safety issues within FDA's Division of Food and Color Additives earlier in his career, and subsequently continued working within this area in the private sector. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety and in participating in deliberations of GRAS Expert Panels.

[8] Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm583856.htm

uses of the selenium-enriched yeast were unlikely to present an allergenic risk to consumers" (EFSA, 2008).

SelenoExcell® contains 1200-1380 µg/g total organically bound selenium and no residual non-organic selenium. The specifications are appropriate for the intended use and analyses of five representative lots show compliance with specifications. SelenoExcell® has been successfully notified as GRAS (GRN 260) for other food uses (Cypress Systems Inc, 2008) and the specifications for the substance have not been changed with the exception that a specification for absence of *Cronobacter sakazakii spp.* has been added and heavy metal limits lowered, which is appropriate for use of a substance in infant formula.

FDA recognizes that selenium is essential for optimal health and development of infants and has issued a Final Rule for use of 2.0 µg selenium per 100 kilocalories (/100 kcal) as the minimum level of selenium in infant formulas and 7.0 µg/100 kcal as the maximum level of selenium in infant formulas (FDA, 2013; FDA, 2015). The form of selenium is not specified in the rule. Australia and New Zealand permit the use of selenomethionine in infant formula (He et al., 2018). EFSA has opined that selenomethionine is readily bioavailable and that organic selenium species tend to be 1.5 – 2 times more bioavailable than the inorganic forms of selenium, but the increased bioavailability of selenium from organic sources of selenium as with the high-selenium yeasts does not translate to increased toxicity for the organic selenium species (EFSA, 2008). Results of studies in mice and swine (growers and sows) which concurrently examined the toxicity of inorganic and organic forms of selenium support EFSA's conclusion (Wang et al., 2017; Mahan and Peters, 2004; Yoon and McMillan, 2006; Zhan et al., 2011; Kim et al., 2022).

In order to comply with the FDA rule (and regulation 21 CFR § 107.100) and avoid exceeding the upper limits (UL) of 45 µg for infants 0-6 months (IOM, 2000) and the most conservative UL of 55 µg for infants 7-12 months (EFSA NDA Panel et al., 2023), the proposed use of SelenoExcell® in non-exempt term infant formula is as follows:

- Addition of 1.8 mg SelenoExcell®, providing approximately 2.5 µg selenium, per 100 kcal formula intended for 0-6 month-old infants; and
- Addition of 2.5 mg of SelenoExcell® providing approximately 3.5 µg selenium per 100 kcal formula intended for 7-12 month-old infants.

The maximum estimated daily intake of selenium from the proposed use in non-exempt term infant formula for 0-6 month-old infants is approximately 31 µg/day, well below the tolerable upper limit (UL) of 45 µg established by the Institute of Medicine (IOM) for infants 0-6 months of age (IOM, 2000). A use level of 2.5 mg of SelenoExcell® per 100 kcal of infant formula provides approximately 3.5 µg selenium and the daily selenium intake from addition of SelenoExcell® to infant formula is estimated at 35.7 µg. Utilizing the IOM calculation of average selenium from complementary foods for 7 to 12-month-old infants at 11 µg/day, the maximum estimated daily intake of selenium would be approximately 47 µg per day, well below the ULs established by the IOM (60 µg) and EFSA (55 µg) for this age group (EFSA NDA Panel et al., 2023; IOM, 2000).A significant amount of safety information is generally available for organic forms of yeast, which was discussed in GRN 260 and updated for this GRAS Determination. These studies included clinical studies in adults and infants. Overall, the data support that up to 100 µg/day selenium from SelenoExcell® is safe (consistent with GRN 260) for adults. Two clinical trials in infants indicate that use of 5 µg/day selenium from 4.8 mg of "yeast-selenium" is safe for use in very low birth weight preterm infants. While this intake level of

selenium is lower than the estimated selenium intake from use of SelenoExcell® in infant formula, there is no reason to suspect that SelenoExcell® would be more toxic than other forms of selenium.

In summary, sufficient qualitative and quantitative scientific evidence in the composite is available to support the safety-in-use of Cypress's SelenoExcell® preparation provided that the ingredient continues to meet the designated specifications and is produced in accordance with Current Good Manufacturing Practices (cGMP), as stated in Appendix 1.

Conclusion

The Expert Panel critically reviewed the data provided by Cypress for their SelenoExcell® preparation, as well as publicly available published information obtained from peer-reviewed journals and other safety assessments prepared by other Expert Panels and well-respected international regulatory bodies.

The ingestion of Cypress's SelenoExcell® from the intended uses results in selenium intakes that are safe within the limits of established historical use and published safety studies and the FDA regulation for the use of selenium in infant formula.

The Expert Panel unanimously concluded that the proposed uses of Cypress's SelenoExcell® preparation, manufactured as described in Part 2.B. of their dossier and declared within the subject notification meets the FDA definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and Cypress's SelenoExcell® preparation is generally recognized as safe (GRAS).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that High Selenium Yeast, when used as described in this dossier, is GRAS based on scientific procedures.

Laurie C. Dolan, PhD, DABT, FACN
Chair

Bo Lönnerdal, PhD

Richard Kraska, PhD

References

Cypress Systems Inc (2008) *GRAS Assessment of high-selenium yeast, GRN 000260*: U.S. Food and Drug Administration (FDA). Available at: https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264257.pdf

EFSA (2008) 'Selenium-enriched yeast as source for selenium added for nutritional purposes in foods for particular nutritional uses and foods (including food supplements) for the general population', EFSA Journal, 766, pp. 1-42.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K. I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Peláez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aggett, P., Crous Bou, M., Cubadda, F., Ciccolallo, L., de Sesmaisons Lecarré, A., Fabiani, L., Titz, A. and Naska, A. (2023) 'Scientific opinion on the tolerable upper intake level for selenium', EFSA Journal, 21(1), pp. e07704.

FDA (2013) 'Proposed Rule. Infant formula: The addition of minimum and maximum levels of selenium to infant formula and related labeling requirements', *Federal Register,* 78 FR 22442, pp. 22442-22451.

FDA (2015) 'Final Rule. Infant formula: The addition of minimum and maximum levels of selenium to infant formula and related labeling requirements', *Federal Register,* 80 FR 35834, pp. 35834-35841.

He, M. J., Zhang, S. Q., Mu, W. and Huang, Z. W. (2018) 'Selenium in infant formula milk', *Asia Pac J Clin Nutr,* 27(2), pp. 284-292.

IOM (2000) 'Selenium. Food and Nutrition Board Institute of Medicine (IOM)', Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. Washington, D.C.: The National Academies Press, pp. 284-324.Jin, X. H., Kim, C. S., Gim, M. J. and Kim, Y. Y. (2022) 'Effects of selenium source and level on the physiological response, reproductive performance, serum Se level and milk composition in gestating sows', Anim Biosci, 35(12), pp. 1948-1956.

Kim, C. S., Jin, X. H. and Kim, Y. Y. (2022) 'Effects of mixed selenium sources on the physiological responses and blood profiles of lactating sows and tissue concentration of their progeny', Anim Biosci, 35(11), pp. 1725-1732.

Mahan, D. C. and Peters, J. C. (2004) 'Long-term effects of dietary organic and inorganic selenium sources and levels on reproducing sows and their progeny', J Anim Sci, 82(5), pp. 1343-58.

Wang, X., Yang, Y., Zhang, H. and Liu, J. (2017) 'Safety Assessment and Comparison of Sodium Selenite and Bioselenium Obtained from Yeast in Mice', Biomed Res Int, 2017, pp. 3980972.

Yoon, I. and McMillan, E. (2006) 'Comparative effects of organic and inorganic selenium on selenium transfer from sows to nursing pigs', J Anim Sci, 84(7), pp. 1729-33.

Zhan, X., Qie, Y., Wang, M., Li, X. and Zhao, R. (2011) 'Selenomethionine: an effective selenium source for sow to improve Se distribution, antioxidant status, and growth performance of pig offspring', Biol Trace Elem Res, 142(3), pp. 481-91.

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