European Food Safety Authority

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SCIENTIFIC OPINION

Se-methyl-L-selenocysteine added as a source of selenium for nutritional purposes to food supplements [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(Question No: EFSA-Q-2005-170, EFSA-Q-2006-306, EFSA-Q-2006-308)

Adopted on 28 April 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety of Se-methyl-L-selenocysteine (Se-methylselenocysteine) added for nutritional purposes as a source of selenium in food supplements and on the bioavailability of selenium from this source.

The present opinion deals only with the safety of Se-methylselenocysteine as a source of selenium and the bioavailability of selenium from this source. The safety of selenium itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

Se-methylselenocysteine is a naturally occurring monomethylated selenoamino acid in which selenium replaces the sulphur of the S-methylcysteine molecule. Se-methylselenocysteine is found in plants of the *Allium* and the *Brassica* families and also in yeast. As much as 80% of the total selenium found in vegetables such as broccoli, radish, Brussels sprouts, cabbage, garlic, onion, leek, ramps, and milk vetch (*Astragalus* spp, *Fabaceae*) is present as Se-methylselenocysteine.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on Se-Methyl-L-Selenocysteine as a source of selenium added for nutritional purposes to food supplements following a request from the European Commission. *The EFSA Journal* (2009) 1067, 1-23.

Se-methylselenocysteine is readily absorbed from the gastrointestinal tract and has been shown to be bioavailable in studies in animals. It is converted via the action of β-lyase, found in many tissues, to methylselenol and then to hydrogen selenide, which is also the key metabolite derived from the inorganic forms of selenium, selenite or selenate. Hydrogen selenide is then used for the production of specific selenoproteins such as glutathione peroxidase. Excess hydrogen selenide is sequentially methylated to mono-, di-, and trimethylated metabolites that are ultimately excreted in human urine and/or breath, or converted into selenosugars and excreted. It is also oxidised to selenium dioxide, a pathway associated with toxicity.

Four-week toxicity studies with Se-methylselenocysteine in rats and dogs, together with shorter-term studies in mice, indicate that the toxicity is comparable to or possibly higher than that of other selenium compounds. No specific studies are available on the genotoxicity, carcinogenicity or developmental and reproductive toxicity of Se-methylselenocysteine. While positive results have been reported for a number of selenium compounds in *in vitro* genotoxicity assays, results from genotoxicity studies *in vivo* in rodents are mainly negative.

Intakes of selenium in the range of 3200-6990 µg/day by humans are associated with chronic selenosis, with no selenosis being observed for the intake range of 240-1510 µg/day (mean 750 µg/day). The Scientific Committee on Food (SCF) has previously given an opinion on the Tolerable Upper Intake Level (UL) of selenium, defining proportionately lower intake levels for children, based on body weight differences compared to adults. On the basis of the findings in humans, the SCF noted that an intake of about 850 µg/day could be taken as a No-Observed-Adverse-Effect-Level (NOAEL) for clinical selenosis. Using an uncertainty factor of 3 to allow for the remaining uncertainties of the studies, the SCF derived a UL for selenium of 300 µg/day.

The use level of Se-methylselenocysteine in food supplements proposed by the petitioners, of 200 µg selenium/day, will be below the UL of 300 µg selenium/day in adults and that of 250 µg selenium/day for children aged 15-17, established by the SCF in 2000. The Panel notes however that the proposed use level is equal to the UL for children between 11 and 14 years old, and is above the ULs of 60, 90, and 130 µg selenium/day for children in the age ranges of 1-3, 4-6 and 7-10 years respectively as defined by the SCF. The Panel also notes that when dietary intake is taken into consideration in addition to supplementation with Se-methylselenocysteine at the proposed use level of 200 µg selenium/day, the ULs of 250 µg selenium/day as defined by the SCF for children between 15 and 17 years old and the UL of 300 µg selenium/day for adults will be exceeded at the high percentile intake level.

However, the Panel considers that given the absence of human studies on Se-methylselenocysteine, the relatively sparse database on the bioavailability of selenium from this source, and the limited data on its safety compared with other selenium compounds used in food supplements, the ULs for selenium defined by the SCF for adults and children cannot be used for judging its safety. The Panel has therefore used the 28-day toxicity studies carried out with Se-methylselenocysteine in the dog and the rat for the purpose of risk assessment.

The Panel concludes that an additional uncertainty factor of 5 should be applied to the lowest-observed-adverse-effect-levels (LOAELs) determined in these studies in dogs and rats, which also allows for additional deficiencies in the database. The Panel considers that the margins of safety derived, of 4 to 12 at the supplementation dose of 200 µg/day in humans (equivalent to approximately 3.3 µg/day for a 60 kg person) proposed by the petitioners, is inadequate, and concludes that there is concern regarding the safety of this source of supplemental selenium at the proposed use level.

The Panel considers that given the sparsity of the experimental database on this substance, the concerns expressed by the SCF in 1999 about the way in which the body handles organic selenium compared with inorganic forms, are still applicable to Se-methylselenocysteine.

Key words:

Se-methyl-L-selenocysteine, Se-methylselenocysteine, selenium, CAS N^{o} 26046-90-2, food supplements.

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BACKGROUND AS PROVIDED BY THE COMMISSION

The European Community legislation lists substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of Se-methyl-L-selenocysteine added as a source of selenium for nutritional purposes in food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements[2].

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion on the safety and bioavailability of Se-methyl-L-selenocysteine as a source of selenium added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group A on Food Additives and Nutrient Sources of the ANS Panel for the preparation of this opinion: F. Aguilar, N. Bemrah, P. Galtier, J. Gilbert, S. Grilli, R. Guertler, G.E.N. Kass, C. Lambré, J.C. Larsen, J-C. Leblanc, A. Mortensen, I. Pratt, I. Stankovic.

[2] OJ L 183, 12.7.2002, p.51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of Se-methyl-L-selenocysteine (hereafter referred to Se-methylselenocysteine) added for nutritional purposes as a source of selenium in food supplements and with the bioavailability of selenium from this source. The safety of selenium itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Se-methylselenocysteine is a white to off-white moderately water-soluble crystalline solid**.**

Chemical Name: Se-methyl-L-selenocysteine

Synonyms

Alanine, 3-(methylselenyl)-, L-

2-Amino-3-(methylselenyl)propionic acid

3-(Methylseleno)-L-alanine

Methylseleno-L-cysteine;

Methylselenocysteine;

Se-Methylselenocysteine

SeMC

CAS Registry Number: 26046-90-2

Molecular weight: 182.08 g/mol

Molecular and structural formula: $C_4H_9NO_2Se$

Figure 1 shows the structure of Se-methylselenocysteine

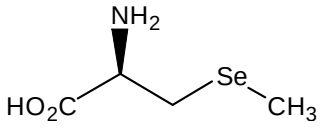

Figure 1. Structure of Se-methylselenocysteine

2.2. Specifications

Information provided by the petitioners provides the following specifications for Se-methylselenocysteine:

Loss on drying:	Not more than 1.0%	
Specific optical rotation	+6.5° - +8. 5° (1% in 1N HCl at room temperature)	
Melting Range	178 °C - 182 °C	
Heavy Metals:	Lead	≤1 mg/kg
	Arsenic	≤ 0.5 mg/kg
	Mercury	≤0.5 mg/kg
	Cadmium	≤0.5 mg/kg
	Selenium	41.0 - 44.0%
Assay by HPLC	≥ 98.0% (≥97% L-isomer, ≤ 3% D-isomer)	

The Panel notes that according to Commission Regulation (EC) No 629/2008 (EC, 2008) the maximum level of mercury in food supplements as sold should be 0.1 mg/kg.

2.3. Manufacturing process

The petitioners indicate that Se-methylselenocysteine is produced by chemical synthesis. An adequate description of the manufacturing process has been made available to the Panel.

2.4. Methods of analysis in food

According to the petitioners, Se-methylselenocysteine can be determined in food by ion exchange High Performance Liquid Chromatography (HPLC) with mass spectrometric detection, or by Gas Chromatography with Atomic Emission Detection (GC-AED).

2.5. Reaction and fate in foods to which the source is added

Se-methylselenocysteine is reported by the petitioners to be stable. No information on reaction and fate in foods was provided.

2.6. Case of need and proposed uses

According to the information provided by the petitioners, Se-methylselenocysteine is intended to be used by adults as a source of selenium in food supplements, e.g. in capsules, tablets, ampoules or powders, to provide 200 µg selenium/day.

2.7. Information on existing authorisations and evaluations

According to one petitioner, Se-methylselenocysteine is approved by the US Food and Drug Administration (FDA) for food supplement use for adult supplementation at 200 µg selenium/day.

A Population Reference Intake (PRI) of 55 µg selenium per day for adults was established by the SCF in 1993 (SCF, 1993). The SCF has also established a UL for selenium of 300 µg/day for adults (SCF, 2000), while the UK Expert Group on Vitamins and Minerals (EVM) derived a safe upper level (SUL) of 450 µg/day for total selenium (EVM, 2003). The US Food and Nutrition Board (FNB) estimated a UL of 400 µg /day for adults (FNB, 2000). Both the SCF UL and that of the FNB also apply to pregnant and lactating women, and while the SCF commented that there were no specific data to support a derivation of a UL for children, they noted that there are no reports indicating that children are more susceptible than adults to adverse effects from selenium. Hence, they concluded that it was appropriate to extrapolate the UL for selenium from adults to children on a body weight basis (SCF, 2000). This provided ULs ranging from 60 µg/day for children aged 1-3 years, 90 µg/day for children aged 4-6 years, 130 µg/day for children aged 7-10 years, 200 µg/day for children aged 11-14 years and 250 µg/day for ages 15-17 years. Specific legislative provisions on nutrient sources apply to foods manufactured for infants and young children.

2.8. Exposure

Selenium is a natural component of the diet, and is present in fish (0.32 mg/kg), offal (0.42 mg/kg), brazil nuts (0.25 mg/kg), eggs (0.16 mg/kg) and cereals (0.02 mg/kg). In foods, selenium is generally present as the amino acid derivates selenomethionine, Se-methylselenocysteine and selenocysteine (EVM, 2003), with lesser amounts of inorganic forms such as selenite (SeO_3^{2-}) and selenate (SeO_4^{2-}). Plants initially absorb selenium from the soil and convert it to selenium-containing amino acids such as Se-methylselenocysteine and selenomethionine. Se-methylselenocysteine is a naturally occurring L-form selenoamino acid found in plants of the *Allium* and the *Brassica* families and also in yeast. As much as 80% of the total selenium found in vegetables such as broccoli, radish, brussels sprouts, cabbage, garlic, onion, leek, ramps, and milk vetch (*Astragalus* spp, *Fabaceae*) is present as Se-methylselenocysteine (Cai *et al.,* 1995; Medina *et al.,* 2001; Whanger, 2002). The amount of selenium available in the soil for plant growth and corresponding variations in the intake of selenium by humans varies considerably among regions and countries (SCF, 2000).

Table 1 summarises information on selenium intake from food in various European countries, anticipated exposure to selenium by using Se-methylselenocysteine in food supplements as proposed by the petitioners, and ULs. According to the petitioners, Se-methylselenocysteine is intended to be used in food supplements to provide an intake of 200 µg selenium/day. The latter intake is equivalent to 461 µg Se-methylselenocysteine/day.

Assuming a mean dietary selenium intake for an adult in Europe in the range of 24–89 µg/day and a high percentile intake of 108 µg/day, the Panel estimated that consumption of an additional food supplement containing 200 µg selenium/day (proposed use level) would result in a total anticipated dietary exposure between 224 and 289 µg selenium /day at the average level of dietary exposure, and a high total anticipated exposure of 308 µg selenium/day.

Table 1: **Summary information on selenium intake and anticipated exposure to selenium from Se-methylselenocysteine**

Nutrient: Selenium	**Intake (µg/day)**		**References**
Recommended Intake (range) for adults (all ages)	55 (8 - 70)		SCF, 1993
Tolerable Upper Intake Level for adults	300		SCF, 2000
Tolerable Upper Intake Level for children (1-3 y/15-17y)	60 - 250		SCF, 2000
Nutrient: Selenium	**Average intake (µg/day)**	**High intake (95th or 97.5th, µg/day)**	**References**
Intake range from food in Europe for adults	24 - 89	108	SCF, 2000; Paturi *et al.*, 2008
Intake range from food in Europe for children (2-17 y)	23 - 42	32 - 77	Lyhne *et al.*, 2005; Ocké *et al.*, 2008; Enghardt Barbieri *et al.*, 2006; AFSSA, 2009
Amount of selenium added to supplements by Se-methylselenocysteine as indicated by the petitioners	200		Technical dossiers
Total anticipated exposure to selenium from supplement and food intake[1] for adults	224 - 289	308	Calculation by Panel
Total anticipated exposure to selenium from supplement and food intake[2] for children (2-17 y)	223 - 242	232 - 277	Calculation by Panel

[1]calculation based on proposed use level of 200 µg/day plus average dietary intake of 24-89 µg/day and high dietary intake of 108 µg/day for adults

[2]calculation based on proposed adult use level of 200 µg/day plus average dietary intake of 23-42 µg/day and high dietary intake of 32–77 µg/day for children

Assuming a mean dietary selenium intake for European children aged between 2 and 17 years in the range of 23-42 µg/day and a high percentile intake range of 32-77 µg/day, the Panel estimated that daily consumption of an additional food supplement containing 200 µg selenium (proposed adult use level) would result in a total anticipated exposure between 223 and 242 µg/day at the average level of dietary exposure and an anticipated high exposure between 232 and 277 µg selenium/day.

The Panel noted that these estimates include higher intake figures from selenium-rich foods, or where selenium is coming from addition of selenium to fertilisers e.g. Finland (Rayman, 2004; SCF, 2000) or to animal feed (EFSA, 2006a, b).

3. Biological and toxicological data

3.1. Bioavailability

No information was provided by the petitioners on the bioavailability of selenium from Se-methylselenocysteine.

A recent study compared the bioavailability of selenium from Se-methylselenocysteine with that of nanoparticulate elemental selenium (Nano-Se) in selenium-deficient male Kunming mice (Zhang *et al.*, 2008). Mice (n=6 per group) were orally administered saline (as control), Se-methylselenocysteine and Nano-Se at single bolus doses of 35, 70, and 1000 µg

selenium/kg bw once daily for seven consecutive days and were killed 24 h after the last dose. Bioavailability of selenium from the two sources was assessed by measurement of plasma and red blood cell selenium, activity of glutathione peroxidase (GPx) and thioredoxin reductase (TrxR). The study showed that both Se-methylselenocysteine and Nano-Se caused a significant increase of selenium in whole blood, liver and kidney tissue compared with control, in a dose-dependent manner. At 35 and 70 µg selenium/kg bw/day there was no significant difference in selenium accumulation between the two forms; however, selenium accumulation in Se-methylselenocysteine-treated mice was higher than that in Nano-Se–treated mice at 1000 µg selenium/kg bw/day. Both forms of selenium possessed equal efficacy in increasing the activities of GPx in a dose-related manner at all three dose levels. The authors concluded that selenium was bioavailable from both sources, as assessed by the activity of the selenoenzymes GPx and TrxR and tissue selenium levels (Zhang *et al.,* 2008).

It has been reported that humans readily absorb selenium from broccoli (Finley, 1999); in which the predominant form of selenium has been shown to be Se-methylselenocysteine (Cai *et al.,* 1995). In a study in which 27 healthy young male subjects were placed on a low selenium (32.6 µg/day) or high selenium (226.5 µg/day) diet for 85 days, and then fed a test meal that contained selenium-74 [^{74}Se] in the form of selenite or selenate, or selenium-82 [^{82}Se] incorporated into hydroponically-raised broccoli, isotope absorption was similar for selenate and for selenium from broccoli, while the results obtained for selenite were highly variable (Finley, 1999).

Maximal plasma concentration of selenium occurred within a few hours after ingestion. Urinary isotope excretion was greater when selenate was fed than when broccoli was fed, and consequently more selenium from broccoli, as compared to selenate, was retained (59.2 ± 2.4 and 36.4 ± 4.6% for selenium in broccoli and selenate, respectively). However, despite the higher retention, the maximal plasma concentration of isotope and area under curve (AUC) were significantly lower when the isotope source was broccoli than when it was selenate. The author concluded that humans retain and distribute selenium from broccoli in a different manner than selenium from inorganic salts (Finley, 1999). The study also showed that significantly more isotope was absorbed by subjects previously fed the high selenium diet than by those fed the low selenium diet. The Panel noted that interpretation of the results of this study is complicated by possible interactions between dietary sulphur (e.g. in the form of sulphate) and selenium.

3.2. Metabolic fate and biological distribution

Se-methylselenocysteine is a monomethylated selenoamino acid in which selenium replaces the sulphur of the S-methylcysteine molecule. As shown in Figure 2, dietary Se-methylselenocysteine (CH_3SeCys) is converted via the action of β-lyase, found in many tissues, to methylselenol (CH_3SeH) and then to hydrogen selenide (H_2Se), which is also the key metabolite derived from the inorganic forms of selenium, selenite or selenate. In addition to conversion to selenophosphate ($HSePO_3$) followed by incorporation into essential selenoproteins (Berry *et al.,* 1991, 1993), hydrogen selenide may be sequentially methylated to mono-, di-, and trimethylated metabolites that are ultimately excreted in human urine and/or breath, or converted into selenosugars and excreted. Hydrogen selenide is also oxidised to selenium dioxide, a pathway associated with toxicity, due to the production of superoxide and other reactive oxygen species (ROS) (Rayman *et al.,* 2008). The Panel noted that the metabolism of Se-methylselenocysteine shares common pathways with other organic and inorganic forms of selenium.

It has been suggested that Se-methylselenocysteine is converted to metabolites that are more rapidly excreted than those from other selenium compounds, resulting in lower tissue retention of selenium (Rayman *et al.,* 2008). Also, unlike selenomethionine Se-methylselenocysteine is not incorporated non-specifically into proteins (Whanger, 2002; Keck and Finley, 2004). However, as shown in Figure 2, metabolism to hydrogen selenide contributes to the general selenide pool which is used for the production of specific selenoproteins such as GPx.

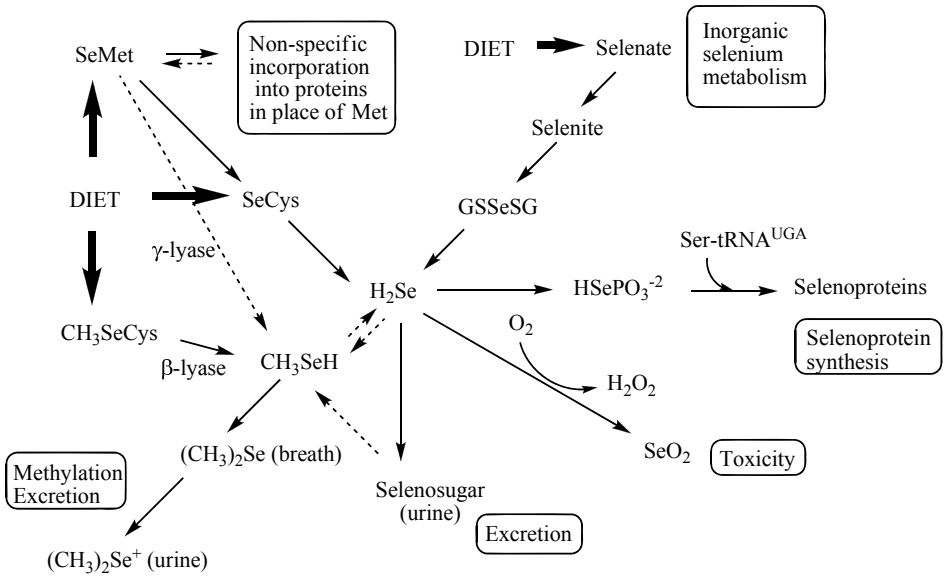

Figure 2. **Metabolic fate of dietary selenium compounds (adapted from Rayman (2004) and Combs (2001))**

The tissue distribution of radiolabelled Se-methylselenocysteine, methylseleninic acid and selenite were compared following a single oral dose of 10 µg selenium/kg bw to selenium-depleted rats (Suzuki *et al.,* 2008). Se-methylselenocysteine was taken up more efficiently by most organs, especially by the pancreas and duodenum, than methylseleninic acid and selenite except in the kidney, liver, and spleen, where radiolabel from the three compounds was detected at comparable concentrations. Speciation analysis suggested that Se-methylselenocysteine was delivered in its intact form to the liver and other organs, where it was then transformed into methylselenol. The authors suggested that Se-methylselenocysteine is metabolised to methylselenol much more efficiently than selenomethionine, and that it is the most efficient methylselenol source in most organs/tissues (Suzuki *et al.,* 2008).

3.3. Toxicological data

Limited information on the toxicity of Se-methylselenocysteine was provided by the petitioners. It has been reported that Se-methylselenocysteine is less toxic to cells in culture than inorganic selenium compounds as it does not readily generate superoxide in the presence of reduced glutathione *in vitro,* although like other selenium compounds it is converted to methylselenol both *in vitro* or *in vivo* (Spalholz, 2004). It has been suggested that Se-methylselenocysteine is less toxic than selenite (Rayman *et al.,* 2008), and it has also been reported that methylated forms of selenium are generally less toxic than non-methylated compounds (Hasegawa *et al.,* 1996).

A number of expert bodies (e.g. EVM, 2003; FNB, 2000; SCF, 2000) have reviewed the toxicity of selenium.

3.3.1. Acute toxicity

No information was provided by the petitioners on the acute toxicity of Se-methylselenocysteine. A recent study compared the toxicity of Se-methylselenocysteine with nanoparticulate elemental selenium (Nano-Se) in male Kunming mice (Zhang *et al.,* 2008). Se-methylselenocysteine caused 100% mortality at a dose of 27.5 mg selenium/kg bw, while Nano-Se caused 10% mortality at a dose of 36 mg selenium/kg bw and 70% mortality at a dose as high as 150 mg selenium/kg bw. The LD_{50} of Se-methylselenocysteine was 14.6 mg Se/kg bw (with 95% confidence limits of 13.1–16.2) while that of Nano-Se was 92.1 mg Se/kg bw (with 95% confidence limits of 71.1–131.1), respectively.

3.3.2. Subacute, subchronic and chronic toxicity studies in animals

In a 28-day oral toxicity study in rats, groups of 20 male and 20 female CD rats received 0, 0.5, 1.0, or 2.0 mg Se-methylselenocysteine/kg bw (equivalent to 0, 200, 400 or 800 µg selenium/kg bw) daily by gavage (Johnson *et al.,* 2008). Dose-related hepatomegaly was seen in both sexes; mild anaemia, thrombocytopenia, and elevated liver enzymes were observed in high dose females only. Microscopic pathology included hepatocellular degeneration in high dose males and at all dose levels in females; arrested spermatogenesis (high dose males); and atrophy of corpora lutea (middle and high dose females). Since treatment-related histopathological changes were seen in female rats in all dose groups, the authors report that a NOAEL was not established for Se-methylselenocysteine in this study (a LOAEL of 500 µg Se-methylselenocysteine/kg bw/day was established, equivalent to 200 µg selenium/kg bw/day) (Johnson *et al.,* 2008). The dose levels used in this study were reported by the authors to provide 20 to 200 times the presumed human doses resulting from consumption of commercially available capsules containing 100 to 250 µg of Se-methylselenocysteine.

The same publication also reports the results of a 28-day study in Beagle dogs, in which the animals received daily gavage doses of 0, 0.15, 0.3, or 0.6 mg/kg bw (equivalent to 0, 60, 120 or 240 µg selenium/kg bw/day) (Johnson *et al.,* 2008). Se-methylselenocysteine induced mild anaemia in middle and high dose males and in high dose females. Toxicologically significant microscopic lesions in dogs were seen only in the liver (peliosis and vacuolar degeneration in high dose males, midzonal necrosis in males in all dose groups). As in the parallel study in rats, given the alterations in liver morphology in male dogs in all dose groups, the authors report that no NOAEL was established for Se-methylselenocysteine in this study (a LOAEL of 150 µg Se-methylselenocysteine/kg bw/day was established, equivalent to 60 µg selenium /kg bw/day) (Johnson *et al.,* 2008).

In a 13-week oral gavage toxicity study, rats received 0, 0.4, 0.8, or 2.0 mg Se-methylselenocysteine/kg bw (equivalent to 0, 160, 320 or 640 µg selenium/kg bw) (Chen *et al.,* 2006). The authors reported that the NOAEL of Se-methylselenocysteine in this study was 0.4 mg/kg bw/day (equivalent to 160 µg selenium/kg bw/day). The Panel was unable to confirm this NOAEL, as the study was published only as an abstract rather than as a peer-reviewed publication.

In a study designed to compare the toxicity of Se-methylselenocysteine Nano-Se in selenium-deficient male Kunming mice, animals (n=10 per group) were orally administered Se-

methylselenocysteine or Nano-Se at single bolus doses of 5000 or 10 000 µg selenium/kg bw once daily for seven consecutive days (Zhang *et al.,* 2008). At 10 000 µg selenium/kg bw there was 80% mortality in the animals receiving Se-methylselenocysteine by day 7, compared with 10% in the animals receiving Nano-Se. At 5000 µg selenium/kg bw Se-methylselenocysteine significantly affected body weight gain compared with control from day 3 onwards, while Nano-Se had a similar effect from day 5 onwards. Liver damage was assessed in the animals receiving 5000 µg selenium/kg bw by measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) and histopathological examination. Greater increases in serum ALT and LDH were seen in Se-methylselenocysteine-treated mice than in Nano-Se–treated mice, although the increase in AST was similar for both forms. Liver histopathology showed that Se-methylselenocysteine produced severe liver damage, as evidenced by necrosis and nuclear pyknosis whereas Nano-Se caused mild hydropic hepatocellular degeneration. Lipid peroxidation due to ROS was also assessed by measurement of liver malondialdehyde (MDA). Both compounds caused an increase in MDA, but the effect was more marked and of longer duration for Se-methylselenocysteine than for Nano-Se. The authors reported that doses of 500, 1000, and 1500 µg selenium/kg bw in either form for seven days did not produce liver damage as evidenced by increases in AST, ALT or LDH, but did increase glutathione transferase (GST). The Panel considered that this study provided little information regarding the toxicity of Se-methylselenocysteine relative to other organic or inorganic forms of selenium, given the very high doses used by the authors. The Panel also considered that the differences might be due to factors other than particle size since the chemical structures of the compounds are different; Se-methylselenocysteine being an organic selenium compound while the Nano-Se is an inorganic compound.

In a study investigating the hypoglycemic properties of Se-methylselenocysteine in control and alloxan-diabetic rabbits given 1000 µg selenium/kg bw daily for 3 weeks via intraperitoneal injection, there was a 50% mortality rate in the control (non-diabetic) animals (Kiersztan *et al.,* 2009). Marked decreases in plasma glucose concentration and decreased reduced glutathione(GSH)/oxidised glutathione (GSSG) ratios in blood, liver and kidney cortex were accompanied by increased GPx and glutathione reductase activities and a diminished renal γ-glutamylcysteine synthetase activity. Plasma urea and creatinine levels were increased and necrotic changes occurred in the kidney cortex, accompanied by albuminuria. Similar effects were not seen in the Se-methylselenocysteine-treated alloxan-diabetic rabbits (Kiersztan *et al.,* 2009).

Overall, the Panel considered that the LOAELs of 150 µg Se-methylselenocysteine/kg bw/day in the dog and 500 µg/kg bw/day in the rat (Johnson *et al.,* 2008) represent the most robust estimates of oral toxicity of Se-methylselenocysteine over a 28-day period, to be taken forward for the purposes of risk assessment.

3.3.3. Reproductive and developmental toxicity studies in animals

No specific information was provided on the reproductive and developmental toxicity of Se-methylselenocysteine. The effects seen on testis (arrested spermatogenesis) in male rats receiving 2.0 mg Se-methylselenocysteine/kg bw daily by gavage in a 28-day toxicity study, and atrophy of corpora lutea in female rats at the same dose level, may suggest a potential effect on fertility at high doses (Johnson *et al.,* 2008). Selenium compounds have been reported to have effects on fertility and development of offspring in rodents and other species, usually associated with maternal toxicity (SCF, 2000).

3.3.4. Genotoxicity

No specific information was provided on the genotoxicity of Se-methylselenocysteine. Studies with selenium compounds (selenite, selenate, selenide, selenocysteine and selenosulphide) have given positive results in several *in vitro* systems (SCF, 2000). Mainly negative results were obtained in micronucleus and chromosomal aberration studies *in vivo* in rodents (Norppa *et al.,* 1980; Moore *et al.,* 1996) and primates (Choy *et al.,* 1989; 1993). The mutagenic effects of selenium salts *in vitro* are considered to be associated with the production of reactive oxygen radicals (Kramer and Ames, 1988). Auto-oxidisable selenium metabolites, such as hydrogen selenide, are known to undergo redox cycling producing reactive oxygen radicals and cause DNA strand breaks (Anundi *et al.,* 1984; Garberg *et al.,* 1988).

3.3.5. Carcinogenicity

No specific carcinogenicity studies have been carried out on Se-methylselenocysteine.

3.3.6. Human studies

One petitioner stated that Se-methylselenocysteine has been on the market as a human food supplement (200 µg) for over five years in Belgium and the Netherlands and no adverse effects indicative of selenosis (such as cracked fingernails, extensive hair loss, garlic breath) or allergenicity/intolerance have been reported. However, data from human studies involving Se-methylselenocysteine were not provided.

Investigations into the health effects of high dietary intakes of selenium in populations living in the seleniferous areas of South Dakota, Venezuela and China have indicated that the highest long-term daily dose that can be taken without the development of toxicity in most individuals is approximately 800 µg while prolonged intakes (e.g. lifetime exposure) of daily selenium doses of 1000 µg or greater may cause adverse reactions. (Yang *et al.,* 1983, 1989a,b; SCF, 2000). The available literature suggests that intakes of selenium in the range of 3200-6990 µg/day (mean 4990 µg/day) by humans are associated with chronic selenosis, with no selenosis observed in the intake range of 240-1510 µg/day (mean 750 µg/day) (Yang *et al.,* 1983, 1989a,b). Signs of selenosis are hair loss, brittle, thickened and stratified nails, garlic breath and skin lesions (Whanger *et al.,* 1996).

The SCF report (2000) on the UL of selenium provides information on the lack of toxicity in humans, of selenium-containing supplements or dietary selenium taken over a prolonged period (up to 6 months) (SCF, 2000). Clinical trials with selenium-enriched yeast have indicated that intakes of up to 343 µg selenium/day are not associated with toxicity, even after prolonged periods (years) of exposure (EFSA, 2008). The recent SELECT trial, in which L-selenomethionine was given as a supplement providing 200 µg selenium/day to a large male study population for a period of up to 7 years has provided evidence of a slight increase in the incidence of alopecia and dermatitis compared with placebo, but no other evidence of adverse effects apart from a non-statistically significant increase in diabetes mellitus associated with selenium supplementation, the clinical significance of which is as yet unknown (Lippman *et al.,* 2009).

4. Discussion

Se-methylselenocysteine is a monomethylated selenoamino acid in which selenium replaces the sulphur of the S-methylcysteine molecule. Based on data from bioavailability and toxicity studies in the rat, mouse and dog, the Panel considers that Se-methylselenocysteine is readily absorbed from the gastrointestinal tract and selenium is bioavailable from this source, although there is a lack of data on its bioavailability relative to that from other selenium compounds, either inorganic (e.g. selenite or selenate) or organic (e.g. selenomethionine).

In a 28-day oral toxicity study in the rat, a NOAEL was not established for Se-methylselenocysteine (a LOAEL of 500 µg/kg bw/day was established, equivalent to 200 µg selenium/kg bw/day) based on the microscopic liver pathology seen in female rats in all dose groups. In a 28-day oral toxicity study in dogs, a NOAEL was also not established for Se-methylselenocysteine (a LOAEL of 150 µg/kg bw/day was established, equivalent to 60 µg selenium/kg bw/day), given the alterations in liver morphology in male dogs in all dose groups. In short-term studies in selenium-deficient mice, Se-methylselenocysteine was appreciably more toxic than nanoparticulate selenium (Nano-Se). The Panel noted however that this latter study employed very high doses of selenium, approaching acutely toxic doses. Also, the differences might be due to factors other than particle size since the chemical structures of the compounds are different, Se-methylselenocysteine being an organic selenium compound while the Nano-Se is an inorganic selenium compound. No specific studies are available on the genotoxicity, carcinogenicity or reproductive and developmental toxicity of Se-methylselenocysteine. While positive results have been reported for a number of selenium compounds in *in vitro* genotoxicity assays, results from genotoxicity studies *in vivo* in rodents are mainly negative.

The results of the toxicological studies in animals did not enable the Panel to reach a definitive conclusion regarding the toxicity of Se-methylselenocysteine relative to other selenium compounds, with the exception of the finding of enhanced toxicity compared to Nano-Se discussed above. While it has been suggested that Se-methylselenocysteine is less toxic than selenite and that methylated forms of selenium are generally less toxic than non-methylated compounds, *in vivo* studies in the open literature do not provide convincing evidence of this. The available studies have mainly been carried out with Se-methylselenocysteine alone, with no other reference selenium compound, either organic or inorganic, reported to have been included. Se-methylselenocysteine has however been demonstrated to have lower toxicity than some other forms of selenium in *in vitro* studies.

The Panel considers that the toxicity of Se-methylselenocysteine is broadly similar to or possibly higher than that seen for other forms of selenium. For example a 90-day study carried out by the NCI with L-selenomethionine in rats provided a NOAEL of 400 µg selenium/kg bw/day, which is higher than the LOAEL of 200 µg selenium/kg bw/day reported for Se-methylselenocysteine in the 28-day study of Johnson *et al.*. The EVM have reported that the NOAEL of selenium from either selenate or selenite in 90-day studies in rats is also approximately 400 µg /kg bw/day. A 90-day study with L-selenomethionine in Beagle dogs provide a NOAEL of 120 µg selenium/kg bw/day, while a 28-day study with Se-methylselenocysteine in Beagle dogs provided a LOAEL of 60 µg selenium/kg bw/day. The Panel noted the apparent greater sensitivity of dogs, compared with rats, to the toxicological effects of either L-selenomethionine or Se-methylselenocysteine in these studies.

Intakes of selenium in the range of 3200-6990 µg/day (mean 4990 µg/day) by humans are associated with chronic selenosis, with no selenosis being observed for the intake range of 240-1510 µg/day (mean 750 µg/day). On the basis of the findings of the studies carried out by Yang *et al.* in Chinese subjects living in seleniferous areas, the SCF noted that an intake of about 850 µg/day "could be taken as a NOAEL for clinical selenosis". The various expert bodies,

including the SCF, that have derived ULs or other standards for selenium have all agreed that the human data provided by the Yang *et al.* and other epidemiological studies are an appropriate basis for standard-setting, and that the NOAEL of approximately 850 µg/day could be used as a departure point. The SCF decided to use an uncertainty factor of 3 to allow for the remaining uncertainties of the studies in arriving at a UL of 300 µg/day for selenium.

The use level of Se-methylselenocysteine in food supplements proposed by the petitioners, of 200 µg selenium/day, will be below the UL of 300 µg selenium/day in adults and that of 250 µg selenium/day for children aged 15-17, established by the SCF in 2000. The Panel notes however that the proposed use level is equal to the UL for children aged between 11 and 14 years old, and is above the UL of 60, 90, and 130 µg selenium/day as defined by the SCF for children in the age ranges of 1-3, 4-6 and 7-10 years respectively. The Panel also notes that when dietary intake is taken into consideration in addition to supplementation with Se-methylselenocysteine at the proposed use level of 200 µg selenium/day, the ULs of 250 µg selenium/day as defined by the SCF for children between 15 and 17 years old and the UL of 300 µg selenium/day for adults will be exceeded at the high percentile intake level.

However, the Panel considers that, given the absence of human studies on Se-methylselenocysteine and the relatively sparse database on the bioavailability of selenium from this source and on the safety of the source, the ULs for selenium defined by the SCF for adults and children cannot be used for judging the safety of Se-methylselenocysteine. The Panel has therefore used the 28-day toxicity studies of Johnson *et al.*, carried out with Se-methylselenocysteine in the dog and the rat, for the purpose of risk assessment.

These studies with Se-methylselenocysteine provided LOAELs of 60 µg selenium/kg bw/day in the dog and 200 µg selenium/kg bw/day in the rat (equivalent to 150 and 500 µg Se-methylselenocysteine/kg bw/day respectively). This is approximately 18 to 60 times higher than the level of supplementation of 200 µg selenium/day in humans (equivalent to 3.3 µg/kg bw/day, assuming a body weight of 60 kg) proposed for supplementation with Se-methylselenocysteine by the petitioners. The Panel considers that an uncertainty factor should be applied for the extrapolation of a LOAEL to a NOAEL. The Panel additionally notes that these LOAELs were derived from short-term (28-day) repeat-dose toxicity studies in rats and dogs, and that there was a lack of longer-term studies, and other deficiencies in the database. The Panel therefore considers that an uncertainty factor should also be applied to account for these deficiencies. The Panel concludes that an overall uncertainty factor of 5 would be sufficient to encompass the use of a LOAEL and the deficiencies in the database.

Applying this uncertainty factor of 5 would provide estimated NOAELs of 12-40 µg selenium/kg bw/day dependent on the species (equivalent to 28–92 µg Se-methylselenocysteine/kg bw/day), which would be approximately 4-12 times higher than the anticipated level of supplementation, expressed on a kg/bw/day basis. The Panel considers that the margins of safety of approximately 4-12 at the supplementation dose of 200 µg/day in humans (equivalent to approximately 3.3 µg/kg bw/day) proposed by the petitioners are not adequate, and concludes that there is concern regarding the safety of this source of supplemental selenium at the proposed use level.

The Panel considers that the concerns expressed by the SCF in 1999 (SCF, 1999), about the way in which the body handles organic selenium compared with inorganic forms, are still applicable to Se-methylselenocysteine, given the sparsity of the experimental database on this substance.

CONCLUSIONS

The present opinion deals only with the safety of Se-methylselenocysteine added for nutritional purposes as a source of selenium in food supplements and with the bioavailability of selenium from this source.

Se-methylselenocysteine is a monomethylated selenoamino acid in which selenium replaces the sulphur of the S-methylcysteine molecule. Selenium is bioavailable from Se-methylselenocysteine, and the Panel concludes that the bioavailability is likely to be similar to that from other organic selenium compounds.

The Panel concludes that, given the absence of human studies on Se-methylselenocysteine, the relatively sparse database on the bioavailability of selenium from this source and the limited data on the safety of this source compared with other selenium compounds used in food supplements, the UL defined by the SCF for selenium cannot be used for judging its safety. The Panel has therefore used the 28-day toxicity studies of Johnson *et al.* carried out with Se-methylselenocysteine in the dog and the rat for the purposes of risk assessment.

The Panel concludes that an additional uncertainty factor of 5 should be applied to the LOAELs determined in these studies in dogs and rats, which also allows for additional deficiencies in the database. The Panel considers that the margins of safety derived, of 4 to 12 based on the supplementation dose of 200 µg/day in humans as proposed by the petitioners, are inadequate and concludes that there is concern regarding the safety of this source of supplemental selenium at the proposed use level.

DOCUMENTATION PROVIDED TO EFSA

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2. Dossier on Se-Methyl-L-Selenocysteine. June 2006. Submitted by Sabinsa Corporation. USA.

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GLOSSARY / ABBREVIATIONS

ALT	Alanine aminotransferase
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources added to Food
AST	Aspartate aminotransferase
CAS	Chemical Abstract Service
EC	European Commission
EFSA	European Food Safety Authority
EVM	UK Expert Group on Vitamins and Minerals
FNB	Food and Nutrition Board
HPLC	High Performance Liquid Chromatography
GPx	Glutathione Peroxidase
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect-level
NOAEL	No-observed-adverse effect level
PRI	Population Reference Intake
SCF	Scientific Committee on Food
SUL	Safe upper level
UL	Tolerable Upper Intake Level
TrxR	Thioredoxin reductase