

Risk Assessment

Selenium

General information

Chemistry

Selenium is a metallic group VI element that is abundant and which can exist in 4 oxidation states (-2, +1, +2 and +6). Within this risk assessment, the word selenium refers to ionic selenium, except when specific selenium compounds are mentioned.

Natural occurrence

Selenium is found in soils and rocks and consequently may then accumulate in plants.

Occurrence in foods, food supplements and medicines

Selenium is present in foods particularly 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 derivatives selenomethionine and selenocysteine. Selenium is present in several licensed medicines both alone and in combination with other substances, and is present in a number of food supplements at doses up to 0.3 mg/daily dose.

Recommended amounts

COMA set RNIs of 0.075 and 0.060 mg selenium/day for males and females respectively, and 0.075 mg selenium/day for lactating women (COMA, 1991). The lower limit of the WHO safe range of the population mean intake to meet requirements is 0.040 mg selenium/day.

Analysis of tissue levels and selenium status

Selenium can be measured directly in plasma, serum, red cells, nails and hair. It can also be determined indirectly by measuring tissue glutathione peroxidase activity, although a plateau in activity may occur with higher levels of selenium intake not producing a corresponding increase in activity.

Brief overview of non-nutritional beneficial effects

Selenium has been claimed to reduce the incidence of a range of cancers, although the COMA report on Nutritional aspects of the Development of Cancer (1998) considered there to be insufficient evidence for such a link. Beneficial effects of selenium intake on AIDS symptoms, male fertility, skin disorders, anxiety and asthma have also been claimed.

Function

The biologically active form of selenium is selenocysteine. Selenocysteine is incorporated into selenoproteins, of which over thirty have been identified to date. The selenoproteins include the glutathione peroxidases, which protect against oxidative damage, the iodothyronine deiodinases (involved in the production of the hormone triiodothyronine from thyroxine), selenoprotein P (which is involved in antioxidant and transport functions) and the thioredoxin reductases (maintenance of the intracellular redox state).

Deficiency

In humans, selenium deficiency is associated with Keshan disease, an endemic cardiomyopathy which particularly affects children and women of child-bearing age, and possibly also Kashin-Beck disease, a musculoskeletal disorder.

Interactions

Since selenium is an essential component of the enzyme tetraiodothyronine 5'-deiodinase 1 (which is involved in iodine metabolism) there is a complex interaction between selenium and iodine. Severe selenium deficiency may increase the hypothyroid stress caused by iodine deficiency. However, supplementation with selenium alone may aggravate iodine deficiency by accelerating iodine loss. This interaction is likely to be significant only in cases of severe deficiency.

Selenium interacts with other metals and ascorbic acid. Selenium status affects the metabolism and thus the toxicities of some xenobiotics.

Absorption and bioavailability

Selenium compounds are readily absorbed from the small intestine. The extent of absorption depends on the nature of the compound, with soluble selenate and selenomethionine being most readily absorbed.

Distribution and metabolism

Selenium is widely distributed throughout the body and can be detected in breast milk. Selenium has also been reported to cross the placenta in animals. Selenium levels are slightly higher in the liver and kidneys than in other tissues. Selenium can be incorporated into selenoproteins, bind to selenium binding proteins or be incorporated into volatile methylated metabolites, which are subsequently excreted.

Excretion

Selenium is largely excreted in the urine, with some volatile metabolites being excreted in the breath. Some faecal excretion occurs, particularly after chronic administration.

Toxicity

The toxicity of selenium depends on the nature of the selenium compound, particularly its solubility. Thus, insoluble selenium sulphide is much less toxic than selenite, selenate and selenomethionine. Selenium toxicity is cumulative.

Human data

Acute selenium toxicity in humans is characterised by hypersalivation, emesis and a garlic aroma on the breath due to the excretion of volatile selenium metabolites. These effects may be accompanied by gastrointestinal effects (severe vomiting and diarrhoea), hair loss, neurological disturbance (restlessness, spasms, tachycardia) and fatigue.

Chronic selenium poisoning, or selenosis, is associated with changes to the hair and nails, skin lesions and clinical neurological effects such as peripheral hypoaesthesia, acroparasthaesiae, pain and hyperreflexia; numbness, convulsions and paralysis may then develop. Studies undertaken in subjects living in seleniferous areas of the USA and China indicate that selenosis is associated with intakes greater than 0.91 mg/day (0.015 mg/kg bw for a 60 kg adult).

Supplementation trials

Supplementation of human volunteers with 0.2 mg/day for 10 years did not result in selenosis (Clark *et al.*, 1992). Other data from supplementation trials indicate that doses of up to 0.388 mg selenium/day for shorter periods are without apparent ill effect, although a formal clinical examination for symptoms and/or signs of selenosis was not always made.

Animal data

Selenium has moderate to high acute oral toxicity. Acute toxicity results in effects on the nervous system, liver and lungs. Chronic exposure results in reduced growth rates and weight gain. High levels of selenium exposure have adverse effects on some reproductive parameters, such as the oestrous cycle in females and sperm concentration and quality in males. Multi-generation studies suggest that selenium reduces post-natal survival and weight of the offspring. Specific teratogenic effects have been observed in birds, fish, sheep and pigs and in hamsters at maternally toxic doses. Selenium is not teratogenic in the macaque monkey. Some studies have indicated that pre-weanling animals are more sensitive to selenium toxicity.

Carcinogenicity and genotoxicity

Selenium sulphide is carcinogenic in rats and mice. Other selenium compounds are not carcinogenic. The results of *in vitro* mutagenicity tests are inconsistent. Selenium compounds are largely negative in the available *in vivo* mutagenicity tests. An increase in chromosomal aberrations in hamster bone marrow has been reported, but this occurred at lethal doses of sodium selenite only.

Mechanism of toxicity

No specific mechanisms have been identified. However, redox cycling of auto-oxidisable metabolites, glutathione depletion, inhibition of protein synthesis, depletion of S-adenosyl-methionine and the replacement of sulphur by selenium in critical sulphhydryl groups have been suggested.

Dose-response characterisation

The epidemiological studies of Yang and colleagues demonstrated a dose response relationship for selenium toxicity. In adult humans the estimated intake associated with the onset of selenosis (clinical selenium poisoning, which includes the occurrence of nail, hair and skin lesions) is 0.910 mg/day (0.015 mg/kg bw/day). Acute selenium poisoning is harder to assess but appears to occur at doses of 0.5 mg/kg bw and above.

In animals, doses of soluble selenium compounds of approximately 0.5 mg/kg bw/day are not associated with any adverse effects.

Vulnerable groups

In subjects suffering from iodine as well as selenium deficiency, supplementation with selenium alone may aggravate the iodine deficiency. However, this is likely to be significant only in cases of severe deficiency and would not be applicable to the UK.

Genetic variations

No relevant genetic variations have been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

Studies in seleniferous areas

Yang et al., 1983

The intake of selenium was investigated in areas of China where selenium intakes were classified as high (with or without endemic selenosis), adequate or deficient. The average daily intake of selenium was 0.75 mg/day (range 0.24-1.51) in areas where selenium intake was high but where there was no selenosis. In areas of chronic selenosis, selenium intake was 3.2-6.99 mg/day. Intake was estimated from information on dietary habits and by measuring the selenium content of typical cereal and vegetable staples.

Yang et al., 1989a

Individual selenium intake was calculated for the inhabitants of areas with low, moderate or high selenium levels (selenosis cases occurred in high selenium areas only). Selenium intake was then correlated with selenium levels in a range of tissues from the same individuals. At physiological levels of selenium intake, whole blood selenium levels were the best reflection of intake, whereas at higher intake levels, hair, finger and toenails were more sensitive markers. Selenium intake was calculated from a three day dietary survey, collecting and weighing samples of raw and cooked food.

Yang et al., 1989b

Individual selenium intake was calculated for the inhabitants of areas with low, moderate or high selenium levels (1989a study described above). Selenium intake was then correlated with a range of biochemical parameters. Morphological changes in the fingernails were used as the main diagnostic criterion of selenosis and this occurred largely in adults. There was no correlation between blood selenium levels and clinical signs attributed to day to day variations in selenium intake causing variations in blood selenium levels. However, long term selenosis was apparent in 5 patients with blood selenium concentrations in excess of 1.054 to 1.854 mg/L. This concentration was estimated to represent a selenium intake of 0.91 mg/day and was considered by the authors to be the level indicating marginal selenium toxicity. Prothrombin time increased significantly from 12.2 seconds to 13.4-13.5 at selenium intake levels greater than 0.85 mg/day; it is unclear whether this is outside the normal range for this population. White cell count also increased with selenium intake. Whole blood reduced glutathione levels were lower in the high selenium intake areas compared to the low ones. No evidence of liver toxicity was apparent but the authors suggested that the population may have adapted to high selenium intakes. No specific neurological symptoms were found. There was no evidence of birth defects in humans (although it was noted that malformed chickens were hatched from locally produced eggs). The authors suggested that the maximum safe level of selenium intake was 0.4 mg/day (using a safety factor of 2).

Longnecker et al., 1991

Over a 2 year period, 142 subjects were recruited from ranches in the USA where a high selenium intake was suspected. Subjects underwent physical examinations, completed health questionnaires, and provided tissue samples. Duplicate-plate collections were used to estimate selenium intake. Specific questions were asked about neurological symptoms, and changes to hair and nails. A range of clinical chemistry tests were also conducted. Approximately half of the subjects had selenium intakes > 0.2 mg/day (average 0.239 mg/day, range 0.068 to 0.724 mg/day). No physical characteristics of selenium toxicity, or any other significant effects were apparent. Increasing selenium intake was associated with increasing serum alanine aminotransferase (ALT) levels but the differences, even at the extremes of intake, were considered to be clinically insignificant. The increase in prothrombin time found by Yang was not apparent in this study.

Yang and Zhou, 1994

In a follow-up study of the 5 selenosis patients described in Yang *et al.*, (1989b) a decrease in average blood selenium levels from 1.346 to 0.968 mg/L was reported which was attributed to dietary changes. The decrease in blood selenium levels was associated with a loss of clinical signs of selenosis. The corresponding safe selenium intake was equivalent to approximately 0.8 mg/day, which was suggested by the authors to represent the mean NOAEL. The lower limit of the 95% confidence interval for the correlation equivalent to an intake of 0.6 mg/day, was taken to approximate the maximum individual

safe selenium intake. Based on these data, Yang and Zhou confirmed the previous recommendation that 0.4 mg/day as the maximum safe daily dietary intake for selenium.

The reporting of the work of Yang and colleagues is confusing since Yang *et al.* (1989b) reported that there was no correlation between blood selenium and selenium intake due to daily variation in food supply. However, a regression equation was then used to estimate selenium intakes in subjects with selenosis from their blood levels. This appears to be based on work in Yang *et al.* (1989a) which used plots of average blood selenium levels and average selenium intakes to derive a regression equation. Generally, blood selenium is considered to be a reliable indicator of selenium intake where the composition of the diet is not very varied.

Studies in non-seleniferous areas

Clark et al., 1996

In a double blind, randomised placebo controlled trial, 1312 patients (with a history of basal cell or squamous cell carcinoma) were given a 0.2 mg selenium supplement, or placebo, for up to 10.3 years (mean 4.5 years) in an attempt to establish whether selenium had a protective effect on skin cancer. Patients were evaluated for signs of selenosis (pathological nail changes, brittle hair and garlic breath) every 6 months. The dietary selenium intake of the participants was unknown but mean baseline serum selenium levels were comparable between the groups. No dermatological signs of selenium toxicity were found. A total of 14 and 21 patients from the control and selenium supplementation groups, respectively, withdrew from the trial as result of adverse effects (mainly gastrointestinal symptoms). Within each group the patients reporting adverse effects did not have significantly different plasma selenium concentrations from those not reporting such effects.

Exposure assessment

Total exposure/intake:

Food	Mean: 0.039 mg/day 97.5 percentile: 0.1 mg/day (1994 TDS)
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Supplements	up to 0.3 mg/day (Annex 4)
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Estimated maximum intake: $0.1 + 0.3 = 0.4$ mg/day

No potential high intake groups have been identified

Risk assessment

Selenium has a variety of toxic endpoints in both animals and humans. In man, the first signs of chronic toxicity appear to be pathological changes to the hair and nails, followed by adverse effects on the nervous system. Changes in biochemical parameters have also been reported. The available studies indicate the development of selenosis is associated with selenium intakes in excess of 0.85 mg/day (0.014 mg/kg bw for a 60 kg adult).

Supplementation studies in humans indicate that up to 0.3 mg/day additional selenium is not associated with overt adverse effects over a short period of time, although specific symptoms have not always been investigated. However, the study by Clark, which specifically considered symptoms of selenosis, indicated that 0.2 mg/day additional selenium for up to 10 years did not result in symptoms of selenosis.

In addition to reduced growth rates, similar symptoms to those in humans are found in animals treated with selenium.

Selenium sulphide is carcinogenic but other selenium compounds are not. Selenium compounds are not mutagenic *in vivo*. Adverse effects have been reported on the reproductive system of various animals, though not primates as determined by Tarantal *et al.* (1991). Reproductive toxicity is not an issue that has been examined in detail in the available human epidemiological studies.

ESTABLISHMENT OF SAFE UPPER LEVEL

Key Studies:	Yang <i>et al.</i> (1989 a and b)
LOAEL:	0.91 mg selenium/day
Uncertainty Factor:	2 (LOAEL to NOAEL extrapolation)
Safe Upper Level: for daily consumption over a lifetime	$0.91/2 = 0.45$ mg total selenium/day

The most sensitive indicators of selenium toxicity are changes in the nails and hair. In a study by Yang *et al.* (1989a and b) conducted in an area of China where dietary selenium exposure is high, selenium intakes were correlated with blood levels to determine the intakes at which marginal selenium toxicity occur. This was at a total intake of 0.91 mg/day selenium.

There are some discrepancies in the NOAELs described by Yang and colleagues in that the range of intakes in high selenium areas that was not associated with selenosis were given as 0.24-1.51 mg/day whereas a LOAEL of 0.91 mg selenium/day was determined in a later study. This may have resulted from the way in which the dietary intakes were calculated but it has also been argued that subjects may have become sensitised to selenium as a result of earlier outbreaks of selenosis. A follow up study (Yang and Zhou, 1994) indicated that the symptoms of selenosis could be reversed if selenium intake was reduced.

The intake of 0.91 mg selenium/day produced slight effects and was close to a NOAEL. Because of this an uncertainty factor of 2 was applied for LOAEL to NOAEL extrapolation. Because this is based on a population study, an uncertainty factor for inter-individual variation is not required. A Safe Upper Level for total selenium intake of 0.45 mg/day can therefore be derived (equivalent to 0.005 mg/kg bw/day in a 60 kg adult). This Safe Upper Level is consistent with the findings of other groups who have reported that intakes of 0.2 mg/day supplemental selenium and 0.24 mg/day total selenium are not associated with any adverse effects (Clark *et al.*, 1996; Longnecker *et al.*, 1991). Assuming a maximum intake of 0.1 mg/day from food, a margin of 0.35 mg/day selenium is available for supplementation or other additional intake. No vulnerable groups have been identified.

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