Risk Assessment — Germanium

General information

Chemistry

Germanium is a non-metallic element, which can exist in valence states of 2 and 4. Within this risk assessment, the word germanium refers to ionic germanium, except when specific compounds are mentioned.

Natural occurrence

Germanium is found in a range of minerals and ores. Both organic and inorganic germanium compounds occur.

Occurrence in food, food supplements and medicines

Germanium is present in foods including beans, tomato juice, oysters, tuna and garlic. Germanium is not currently present in any licensed medicines. Germanium food supplements were voluntarily withdrawn by industry in the UK due to toxicity but can be obtained by mail order over the internet and are available in other parts of the world (for example, supplements containing 100 mg Ge-132).

Other sources of exposure

No data were identified.

Recommended amounts

Germanium is not considered to be an essential trace element.

Analysis of tissue levels and germanium status

No data on the analysis of tissue levels and germanium status have been identified.

Brief overview of non-nutritional beneficial effects.

Germanium has been claimed to have beneficial effects on a number of conditions including cancer, AIDS, liver disease, hypertension, arthritis, food allergies and malaria. The results of trials using spirogermanium (an organic compound) as a cancer treatment are inconclusive.

Function

There is no known biological function for germanium. It has been suggested that germanium may be involved in carbohydrate metabolism.

Deficiency

No deficiency disease has been described. It has been suggested that germanium deficiency could be a contributory factor in Kashin-Beck disease (an osteo-arthritic condition affecting children in China and the former Soviet Union) but this is based on a reported association from a single study.

Interactions

It has been suggested that germanium can interact with silicon in bone metabolism. It can interfere with the action of loop diuretic drugs and inhibit the activity of a number of enzymes including lactate and alcohol dehydrogenase. Hexabarbital-induced sleeping times are increased in mice treated with germanium compounds suggesting that inhibition of cytochrome P450 activity may also occur. Organic germanium compounds have been reported to inhibit the detoxication enzyme glutathione-S-transferase.

Absorption and bioavailability

Germanium compounds are readily absorbed following oral exposure.

Distribution and metabolism

Germanium is distributed throughout the body tissues, particularly the kidney and thyroid. Organic germanium is thought not to accumulate to the same extent as inorganic germanium compounds but few data on germanium metabolism are available.

Excretion

Germanium is excreted largely in the urine. Some biliary and faecal excretion also occurs.

Toxicity

Inorganic forms of germanium compounds are more toxic than organic germanium compounds.

Human data

Germanium toxicity in humans has generally occurred following consumption of inorganic germanium as a food supplement. Initial symptoms include anorexia, weight loss, fatigue and muscle weakness. This is followed by renal dysfunction and failure, which can be fatal. Peripheral neuropathy has also been reported. Where patients have recovered, renal function has not returned to normal. Transient neurotoxic side effects have been reported from the use of spirogermanium in clinical trials.

No data on trials in healthy human volunteers have been identified.

Animal data

Germanium has low acute oral toxicity. Symptoms of acute toxicity from large doses include sedation, vasodilation, ptosis, cyanosis and tremors with death resulting from respiratory paralysis. Symptoms of chronic and sub-chronic effects of inorganic germanium include weight loss, changes in organ weights, progressive neuropathy (characterised by de- and re-myelination, nerve oedema and changes to Schwann cells) and renal damage. Organic compounds are less toxic but produce weight loss and decreased red blood cell counts. Few data are available on reproductive toxicity.

Carcinogenicity and genotoxicity

Sodium germanate was not carcinogenic in rats. Mutagenicity data are limited, but negative results were obtained with the germanium compounds tested.

Vulnerable groups

No vulnerable groups have been identified.

Genetic variations

No genetic variations resulting in increased susceptibility to germanium toxicity have been identified.

Mechanism of toxicity

The precise mechanism is uncertain but specific pathological effects on the mitochondria of the kidney and nervous system have been observed.

Dose-response characterisation

The toxicity of inorganic germanium compounds is clearly progressive. It is difficult to define a threshold since the available data consist of human case reports and animal studies where few dose levels have been used. Fatal renal failure in humans has occurred following cumulative doses of $>$ 20 g germanium. In animals no toxicity was reported for inorganic germanium when the animals were dosed with 5 mg germanium/kg bw/day for 4 weeks only. However, adverse effects were apparent at the same dose level over longer periods of exposure. Organic germanium compounds are less toxic but adverse effects have been reported.

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).

Human data

Schauss, 1991

18 case reports of germanium-induced renal toxicity were reviewed, two of which were fatal. The patients took supplements of germanium dioxide or Ge-132, an organic form. The cumulative doses consumed ranged from 16-328 g over a 4 to 36 month period. However it is considered possible that the Ge-132 may have been contaminated with inorganic germanium compounds.

Animal data

Kanisawa and Schroeder, 1967

A group of 135 Swiss CD mice were given drinking water containing 5 mg/L sodium germanate from weaning throughout their lifespan. The control group consisted of 198 mice. The authors estimated that germanium intake was 0.35 mg/kg bw/day with an additional 0.019 mg/kg germanium being supplied by the diet. The body weights of the treated males were lower throughout the study, becoming significantly so in the second year. The body weights of the treated females were lower than the controls in the second year of treatment, but this was only significant at 15 months. Few historical control data were provided, not all of the animals were autopsied, and only tissues considered to be abnormal were microscopically evaluated. Sodium germanate was not found to be carcinogenic.

Sanai et al., 1991

Groups of female Wistar rats were fed 75mg/kg bw germanium dioxide or 120mg/kg carboxyethylgermanium sesquoxide (GeO_2, Ge-132) for 24 weeks in the diet. The doses contained equivalent quantities of germanium. Treatment was then withdrawn for a further 16 week recovery period. By week 24, weight loss, anaemia, liver dysfunction, and increased blood urea nitrogen, sodium phosphate and creatinine were apparent in the GeO_2 group only. Vacuolar degeneration and granular deposition were observed in the degenerated renal tubules of this group. The scores for tubular degeneration were 95 $\pm$ 9%, 3 $\pm$ 1% and 1 $\pm$ 1 %, in the GeO_2, Ge-132 and control groups respectively. After discontinuation of the treatment, fibrosis became prominent in the GeO_2 treated group even at week 40, 16 weeks after treatment. No effects on renal histology were found in the control or Ge-132 groups. The only adverse effects observed in the Ge-132 group were elevated liver weights at week 16 and decreased liver weights compared to the controls following the recovery period.

Anger et al., 1992

Groups of 30 male and female Wistar rats were given an oral dose of 1000 mg/kg bw/day Ge-132 five days a week for 6 months (the route was unclear but appears to be stomach tube/gavage). Three deaths occurred in the treated group as a result of accidental damage to the animals made when administering the dose. A small decrease in body weight was observed in the treated animals. A significant decrease in erythropoiesis and leukocyte ratios was also found. The main toxic effect was a slight renal dysfunction, characterised by increased serum creatinine levels (significant in males only). Urinary germanium

excretion was constant and related to achieved dose. It is stated that no preferential accumulation of germanium occurred, but it is apparent that germanium levels in the kidney and liver were 3 times higher than those in tissues such as the heart or the lung. The study is limited, in that it is not well-reported and few details are provided on many aspects of the investigation. However it suggests that higher and/or more sustained doses of Ge-132 are associated with renal dysfunction in male rats.

Yim et al., 1999

Sprague Dawley rats were treated with doses of 5, 10, 20, 50, 100 or 150 mg/kg germanium dioxide dissolved in water and administered by orogastric tube for up to 24 weeks. The aim of the experiment was to determine the earliest onset of germanium-induced myopathy and the minimum dose of GeO_2 that would cause the effect. The earliest pathological changes in the muscle fibres observed by electron microscopy were abnormalities of mitochondrial shape and size and increased numbers of mitochondria. A number of rats died during the study. The minimal dose of GeO_2 causing myopathy was 10 mg/kg bw/day for 4 or more weeks.

Exposure assessment

Total exposure/intake

Food	mean: 0.004 mg/day 97.5th percentile: 0.007 mg/day (1994 TDS)
Estimated maximum intake:	0.007 mg/day

No potential high intake groups were identified.

Risk assessment

Germanium is not considered to be an essential element although it has been marketed as such and was available in the UK as a dietary supplement prior to its voluntary withdrawal.

Germanium causes specific toxic effects on the kidney, the muscle and the nervous system in both animals and man. A number of human case reports are available, many of these involving fatal renal failure. However, the incidence of renal toxicity as a fraction of all those taking germanium supplements is uncertain. The effects of germanium on the kidney are not completely reversible following the cessation of treatment. Comparable data are available from animal studies.

Germanium toxicity has been largely associated with consumption of inorganic germanium dioxide and it has been suggested that organic germanium compounds do not cause adverse effects. For example Sanai *et al.* (1991) showed that an organic germanium compound carboxyethylgermanium sesquoxide (Ge-132) did not cause tubular degeneration in rats compared to a comparable dose of germanium dioxide over the same 16 week period. However, Anger *et al*. (1992) demonstrated moderate tubular damage when a higher dose of Ge-132 was given over a longer time period. Sources claiming the lack of toxicity of

organic germanium are generally secondary and are not available in the peer-reviewed scientific literature. Although organic germanium compounds are less toxic than their inorganic equivalents, adverse effects are still apparent. The mechanisms of germanium-induced target organ toxicity are uncertain.

Naturally-occurring germanium present in food does not appear to be associated with any adverse effects.

EVM OPINION

Germanium is not considered to be an essential element. Germanium is a cumulative toxin causing serious, and potentially fatal, adverse effects on the kidneys. Naturally-occurring germanium present in food does not appear to be associated with any adverse effects, but there are insufficient data to define a NOAEL for chronic exposure in either animals or humans at levels in excess of this. Whilst organic forms of germanium appear to be less toxic than inorganic ones, at present there are also insufficient data to establish a NOAEL or to rule out cumulative toxicity of a similar type to that of inorganic germanium, albeit occurring at higher doses.

Dietary supplements containing germanium were voluntarily withdrawn in the UK but may be obtained by mail order over the Internet.

Given the cumulative nature of germanium toxicity there are insufficient data to set a Safe Upper Level for any amount of germanium in excess of that provided by the diet.

References

Anger, F., Anger, J.P, Guillou, L. and Papillon (1992). Subchronic oral toxicity (six months) of carboxyethylgermanium sesquoxide [$(HOOCCH_2CH_2Ge)_2O_3$]*n* in rats. *Applied Organometallic Chemistry* **6**, 267-272.

Kanisawa, M. and Schroeder, H. (1967). Life term studies on the effects of arsenic, germanium, tin and vanadium on spontaneous tumours in mice. *Cancer Research*. **27**, 1192-1195.

Sanai, T., Okuda, S., Onoyama, K., Oochi, N., Takaichi, S., Mizuhira, V. and Fujishima, M. (1991). Chronic tubulointerstitial changes induced by germanium dioxide in comparison with carboxyethylgermanium sesquoxide. *Kidney International* **40**, 882-890.

Schauss, A. G. (1991) Nephrotoxicity and neurotoxicity in humans from organogermanium compounds and germanium dioxide. *Biological Trace Element Research* **29**, 267-280.

Yim, S.Y, Lee, I.Y, and Kim, T.S (1999). Enzyme histochemical study of germanium dioxide-induced mitochondrial myopathy in rats. *Yonsei Medical Journal* **40**, 69-75.