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Hazard Assessment of Germanium Supplements

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Germanium-containing dietary supplements became popular in the 1970s in Japan and later in other countries, as elixirs for certain diseases (e.g., cancer and AIDS). Germanium is not an essential element. Its acute toxicity is low. However, at least 31 reported human cases linked prolonged intake of germanium products with renal failure and even death. Signs of kidney dysfunction, kidney tubular degeneration, and germanium accumulation were observed. Other adverse effects were anemia, muscle weakness, and peripheral neuropathy. Recovery of renal function is slow and incomplete even long after germanium intake was stopped. The total dose of ingested germanium (as dioxide, carboxyethyl germanium sesquioxide, germanium–lactate–citrate, or unspecified forms) varied from 15 to over 300 g; the exposure duration varied from 2 to 36 months. In laboratory animals, elevated germanium in tissues and impaired kidney and liver function were observed in a life-time drinking water (5 ppm germanium) study. Other toxicities associated with ingested germanium products in human cases were also demonstrated in animal studies with germanium dioxide and sometimes other germanium compounds. Based on the evidence of persistent renal toxicity associated with germanium dioxide, the lack of conclusive findings of differential nephrotoxicity of organic germanium compounds, and the possibility of contamination of the organic germanium products with inorganic germanium, it is clear that germanium products present a potential human health hazard.

INTRODUCTION

Dietary supplements have become increasingly popular in recent years as new products introduced into the market on a daily basis. In 1994, Congress passed the Dietary Supplements Health and Education Act (DSHEA), which allows certain information or claims on product labels and also allows marketing of a supplement without undergoing a premarket demonstration of safety.

Germanium (Ge) is a naturally occurring trace element that is widely used in the electronics industry. World production is estimated at 30–80 tons per year (Scansetti, 1992). However, there is no evidence of any essential function in living organisms, including humans, and no germanium deficiency syndromes have been documented. The use of germanium and its compounds in elixirs or dietary supplements to "promote health" and "cure diseases" became popular in the 1970s in Japan and then in the mid-1980s in Great Britain and elsewhere. Beginning in the early 1980s, human case reports from Japan appeared in the literature which documented marked and prolonged renal toxicity associated with the chronic consumption of germanium preparations (Nagata *et al.,* 1985). Recently, similar cases from Europe have also been reported (Van der Spoel *et al.,* 1990; Hess *et al.,* 1993). Up to the present, there are at least 31 reported cases associated with oral intakes of germanium containing products of which 9 were fatal. Our assessment evaluates the potential hazard of germanium dietary supplements and compares the human case reports with the animal data. This analysis focuses mainly on germanium dioxide (GeO_2) and carboxyethyl germanium sesquioxide ($(GeCH_2CH_2COOH)_2O_3$, Ge-132, also known as propagermanium or SK-818) because of their presence in germanium elixir supplements and the availability of animal data for comparison.

Occurrence, Sources, and Intake of Germanium

Germanium was discovered in 1886, has an atomic number of 32 and atomic weight of 72.6, with both nonmetallic and metallic properties in between silicon and tin. Germanium represents only about 7 ppm of the earth crust (Geber, 1988). Some soil and freshwater in the United States were found to contain 0.6–1.3 mg Ge/kg and 0.004 to 0.6 mg Ge/L, respectively (Vouk, 1986). Some medicinal plants such as ginseng, aloes, and garlic were incorrectly reported earlier to contain high concentrations of germanium at ppm levels (see Kidd, 1987). They were later found to contain concentrations in ppb levels by more sensitive analytical techniques (see Kong, 1993; Mino *et al.,* 1980).

For the general population the major source of ger-

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manium is through food. Germanium is present in practically all food but only in minute amounts. Of 125 foods and beverages analyzed by Schroeder and Balassa (1967a,b) 4 had Ge levels greater than 2 ppm; 15 had levels between 1 and 2 ppm. A daily intake of 367 μg Ge was reported in the diet consumed by adults of the United Kingdom, whereas 1.5 mg Ge/day was calculated by Schroeder and Balassa (1967a) to be ingested by adults in United States.

Absorption, Excretion, and Tissue Distribution

In rats, intestinal absorption of inorganic germanium (10 mg of neutralized GeO_2 by gavage) is rapid and complete (over 95% in 8 hr) (Rosenfeld, 1954). Most of the absorbed germanium is rapidly excreted in the urine. In studies of four individuals, Schroeder and Balassa (1967b) found a total of 1.4 mg germanium of the calculated average daily dietary intake of 1.5 mg in urinary excretion. This suggests that dietary germanium is well absorbed from the intestinal tract and excreted largely through the kidneys. Chen *et al.* (1993) studied 11 healthy college students (10 males and 1 female, age 20 $\pm$ 1). After a single oral dose of 100 mg Ge-132, the urinary excretion rate of germanium peaked at around 3 hr. After 24 hr, the concentration returned to the level before dosing. Pharmacokinetics studies with an oral dose of 100 mg/kg of C^{14}-labeled Ge-132 in rats indicated a 30% intestinal absorption rate; blood germanium concentration peaked at 3 hr after administration, and the absorbed compound was completely excreted intact in urine within 72 hr (Miyao *et al.*, 1980). Similar to the rat, human patients treated with 25 to 75 mg/kg of Ge-132 also had an absorption rate of 30% and very rapid urinary excretion (Miyao *et al.*, 1980).

The biological half-life of germanium is relatively short, on the order of 1–2 days in the liver and whole body and 4.5 days in the kidneys of rats (Rosenfeld, 1954). A very short biological half-life of germanium, 2–2.5 hr, in mouse lung, liver, and kidneys has also been reported (Shinogi *et al.*, 1989; Shinogi *et al.*, 1990).

Tissue concentration and distribution depends upon dose and frequency of exposure. It has been reported from undetectable (by single low dose), evenly distributed in all tissues (by low dose, multiple exposure), to preferentially accumulated in the kidney and other tissues, such as intestine and spleen (by high repeated dose) (Shinogi *et al.*, 1990; Schroeder and Balassa, 1967b; Schroeder *et al.*, 1968).

Limited data reported that "normal" human tissues contain germanium in the range of 0.0009 (lymph node) to 9.0 ppm (kidney) (Vouk, 1986). Mean urinary levels of germanium were reported to range from 0.078 to 1.26 mg/L (Chen *et al.*, 1993; Schroeder and Balassa, 1967b). Blood germanium levels were reported in the range of 0.29 mg/L in serum (Schroeder and Balassa, 1967b) and 0.154 $\pm$ 0.020 mg/L in plasma (Kong, 1992).

Pharmacological and Therapeutic Effects

Many pharmacological activities of some organic germanium compounds including Ge-132 have been investigated. These include antitumor (Suzuki *et al.*, 1985; Brutkiewicz and Suzuki, 1987), anticancer (Jao *et al.*, 1990), antiviral (Aso, 1989), antimicrobial (Kaars Sijpesteijn *et al.*, 1964), analgesic (Suzuki and Taguchi, 1983), and immunomodulating effects (Nakada *et al.*, 1993; Ikemoto, 1996). Although animal studies showed promising results, clinical trials in humans with spirogermanium had little positive effects in advanced cancer patients and were not without adverse effects (Ajani *et al.*, 1986). Ge-132 was reported to have some beneficial effects in patients with advanced lung cancer, but the study was not performed with a well-controlled double-blind design. Detailed review and discussion are available (Goodman, 1988; Furst, 1987; Kong, 1993). Further studies are certainly warranted.

HUMAN CASE REPORTS

Clinical and Pathological Findings

At least 31 human cases of germanium users appeared in the literature (Omata *et al.*, 1986; Obara *et al.*, 1991; Okada *et al.*, 1989; Nagata *et al.*, 1985; Matsusaka *et al.*, 1988; Sanai *et al.*, 1990a; Iijima *et al.*, 1990; Higuchi *et al.*, 1989; Kamijo *et al.*, 1991; Okuda *et al.*, 1987; Van der Spoel *et al.*, 1990; Krapf *et al.*, 1992; Hess *et al.*, 1993; Fujimoto *et al.*, 1992; Rinno *et al.*, 1985; Kanda *et al.*, 1989; Takeuchi *et al.*, 1992), some of which have been reviewed by Schauss (1991a,b) and Takeuchi *et al.* (1992). The majority of these cases occurred in Japan and were originally reported only in Japanese literature. In 1985, a case report first appeared in the English literature (Nagata *et al.*, 1985). Recently, cases of germanium associated toxicity were reported from countries other than Japan (Van der Spoel *et al.*, 1990; Hess *et al.*, 1993).

The most common signs or symptoms seen in patients from these case reports were weight loss, fatigue, gastrointestinal disturbances (nausea, vomiting, and anorexia), anemia, muscle weakness, and renal failure. All cases had similar symptoms of renal failure: characteristic vacuolar tubuloepithelial degeneration and swollen mitochondria with electron-dense inclusions. Urine analysis was normal (absence of proteinuria and hematuria). Other organs affected were muscle (both skeletal and cardiac), nerve (both peripheral and central), bone marrow, and liver. These include myopathy characterized with abnormal mitochondria (swollen and with electron dense deposits), neuropathy (severe axonal degeneration, sensory impairment, truncal ataxia, and cerebellar ataxia), hypoplastic bone marrow, and a few with hepatosteatosis. One case had persisted paresthesia and frequent vomiting even 2 months after germanium use was stopped. In these

adverse effects, few or no indications of involvement of any immunological mechanism (few or absence of immunoglobulins or their complements) were found. This suggests a cytotoxicity effect or mitochondrial function disorder. Most of the patients had gastrointestinal symptoms such as nausea, vomiting, loss of appetite, and weight loss, anemia, and muscle weakness. Although no abnormalities were observed by routine gastrointestinal examination, a delay in intestinal transit time was noted in one case who vomited frequently, which indicates an impairment of gastrointestinal motor activity.

The four reported cases (Van der Spoel *et al.*, 1990; Krapf *et al.*, 1992; Hess *et al.*, 1993) that occurred in European countries were associated with the ingestion of germanium–lactate–citrate (Ge-lac-cit) with a total intake of 25 to 47 g of germanium over a period of 2 to 30 months. Two patients were diagnosed with breast cancer and two were HIV-positive. All four cases revealed renal dysfunction and renal biopsy disclosed tubulointerstitial nephropathy with distal tubular vacuolar degeneration in three cases. Liver biopsy was performed on three patients, and all showed moderate to severe hepatic steatosis. While liver function tests returned to normal within 2 months, renal failure persisted for 2 years after cessation of germanium intake. One breast cancer patient died of severe lactic acidosis. Tissue germanium levels were elevated in all three cases that were determined. The germanium product, Ge-lac-cit, was marketed as "organic germanium" but was actually an inorganic germanium (Krapf *et al.*, 1992). All the symptoms and clinical findings associated with oral Ge-lac-cit, another form of germanium products, were similar to the characteristics of those observed in patients associated with germanium toxicity induced by inorganic GeO_2.

Several studies indicate that the medical records of many patients confirmed a normal renal function before taking germanium supplements (Okada *et al.*, 1989; Matsusaka *et al.*, 1988; Sanai *et al.*, 1990a; Okuda *et al.*, 1987; Van der Spoel *et al.*, 1990; Krapf *et al.*, 1992). Renal dysfunction persisted and progressed rapidly in these cases; most patients (83%) were admitted in the hospital within 2 years, 40% in the first year, and 27% within the first 6 months after taking germanium-containing products. However, the recovery was very slow and incomplete. In some patients, renal function was still abnormal even after discontinuation of germanium products for 10 to 31 months (Matsusaka *et al.*, 1988; Sanai *et al.*, 1990a; Okuda *et al.*, 1987; Hess *et al.*, 1993).

Tissue Germanium Concentrations

While germanium is considered not to accumulate in the human or animal body if ingested as food that is normally low in germanium contents, high concentrations of germanium were found in many tissues, such as hair, nail, spleen, kidney, liver, lung, brain, muscle, pancreas, etc., of those patients who took supplements. Accumulated germanium levels can be as high as 10, 70 to 140, or 180 times the control levels (Hess *et al.*, 1993; Nagata *et al.*, 1985). The germanium in some tissues, such as nails, hair, and kidneys, was still high even after the patients had stopped taking germanium products more than 10 months (Obara *et al.*, 1991). It was still measurable in some cases even after germanium intake was stopped for 19–20 months (Obara *et al.*, 1991; Hess *et al.*, 1993), whereas it was not present in normal tissues. Urinary excretion of germanium was still high even 5, 6, and 12 months after use of germanium preparations was stopped (Okuda *et al.*, 1987). This indicates that germanium can be stored in the body for a long time if ingested in large quantities (over 50-fold) above the normal daily dietary intake range (1.5 mg/day).

Germanium Form and Levels

Although not all the germanium preparations taken by these patients were known for their chemical identity or content, some were actually verified by laboratory analysis for their germanium form, content, or both (Okada *et al.*, 1989; Matsusaka *et al.*, 1988; Sanai *et al.*, 1990a; Krapf *et al.*, 1992). In one case, the germanium preparation was found to contain 62.4% Ge by atomic absorption analysis. The major component, GeO_2, was identified by X-ray diffraction analysis; additionally, an organic germanium form very similar to Ge-132 was deduced from the C^{13} NMR spectrum (Nagata *et al.*, 1985). In another case, the germanium capsules of Ge-lac-cit were analyzed and the germanium content was verified by gas chromatography with mass spectrometry after hydride generation (Krapf *et al.*, 1992). The preparation taken by several other individuals was determined by inductively coupled plasma atomic emission spectrometry to contain 1500 μg/ml of germanium and was confirmed to be mainly the inorganic form because a carbon peak was not observed by C^{13} NMR spectrum analysis (Okada *et al.*, 1987). Sanai *et al.* (1990a) analyzed some germanium compounds with the X-ray diffraction method, and the amount of GeO_2 was found and confirmed by thin-layer chromatography, infrared absorption spectroanalysis, and atomic absorption spectrometry. GeO_2 was identified in some preparations that claimed to be the organic Ge-132 of unknown purity. Because GeO_2 is a starting material for Ge-132, it is possible that residual GeO_2 will be found in the final product, depending on the thoroughness of good manufacturing practice.

ANIMAL STUDIES

Acute Toxicity

Acute oral toxicity of germanium is low. The LD_{50}s for GeO_2 were 3.7 and 6.3 g/kg for rats and male mice,

respectively (Vouk, 1986); the corresponding values for Ge-132 were 11.7 for male and 11.0 g/kg for female rats, and 6.3 to 12.5 for male and 11.4 g/kg for female mice (Asai, 1984).

Although lethality studies indicate that germanium has low toxicity by ingestion, chronic oral toxicity has been shown in the laboratory animals even at low doses.

Subchronic and Chronic Toxicity

In a 13-week feeding study with young rats, Rosenfeld and Wallace (1953) reported that neutralized GeO_2 inhibited growth and caused a 50% mortality at 1000 ppm in diet or 100 ppm in drinking water. All deaths occurred during the first 4 weeks. Survivors recovered, even with continued exposure to the same daily dose, which indicated a possible adaptation phenomenon. No hematological effects or any signs of gross anatomical and morphological changes at autopsy were observed. Renal and hepatic function were not examined in this study. A fivefold difference of daily dose in rats receiving the GeO_2 in food to that in water (89.8 vs 17 mg/kg body wt/day) resulted in the same mortality. This may be due to the higher solubility of the GeO_2 in water. While a 50% mortality was observed in young rats receiving a daily dose of 17 mg/kg body wt of GeO_2 in water or a total dose of 119 mg/kg/wk, no systemic toxicity was observed in either young rats that received 13 weekly subcutaneous doses of 50 mg/kg or in adult rats that received 8 weekly intraperitoneal doses of 100 mg/kg. Whether germanium compounds are more toxic by mouth than parenterally or more toxic by chronic repeated exposure is not clear and needs to be further studied.

The characteristic renal dysfunction and nephropathy similar to those observed in humans who took germanium-containing preparations were produced in rats by feeding GeO_2 in diets or water. Sanai *et al.* (1990b) demonstrated that rats fed 150 mg/kg body wt/day of GeO_2 in the diet for 13 weeks had reduced body weight, increased blood urea nitrogen and serum creatinine, and decreased creatinine clearance. Renal distal tubules were markedly degenerated with electron-dense inclusion in the swollen mitochondria; however, glomeruli were normal and no immunoglobulin deposition was found. Liver function enzymes were elevated and mild vacuolar changes were observed around the central veins in the liver. Waxy cytoplasm and vacuoles were observed in myocardial cells. Moreover, in rats treated with germanium for only the first 4 weeks, renal dysfunction and histological abnormalities were still present 9 weeks after germanium withdrawal, a typical phenomenon of rapid developing but long-lasting renal effects by germanium, similar to that seen in humans. In another study with half the dose level (75 mg/kg body wt/day) and double exposure duration (24 wk) Sanai *et al.* (1991b) showed that, while liver dysfunction returned to normal, renal tubulointerstitial fibrosis was prominent, hematocrit was lower and tissue germanium levels were higher than the controls even at 14–16 weeks after discontinuation of germanium treatment.

In a 40-week pair-feeding study, Sanai *et al.* (1991a) demonstrated a dose-dependent effect of GeO_2 in rats. They also demonstrated that the higher the dose the shorter the exposure duration required to develop the adverse effects. A lowest observed adverse effect dose of 37.5 mg/kg body wt/day of GeO_2 or 26 mg/kg body wt/day of Ge was established for decreased growth, anemia, renal dysfunction, and renal tubular degeneration accompanied with elevated urinary and renal germanium. Both clinical changes and tissue pathological damages are identical to those observed in human cases described above. This is one of the very few studies that actually examined renal toxicity in a dose-related manner.

Germanium-induced myopathy was reproduced in young rats by feeding 0.15% GeO_2 in the diet for 23 weeks (Wu *et al.,* 1992). Skeletal muscles showed reduced weight, with numerous ragged red fibers and focal cytochrome c oxidase deficiency. Mitochondria were enlarged with proliferated cristae and some contained electron-dense granules. It was noted that no apparent neurologic abnormality was observed in this study. Higuchi *et al.* (1989) demonstrated similar myopathological changes in adult rats fed 0.2% GeO_2 in the diet, an average of 100–150 mg/kg body wt/day, for 4 months. They also demonstrated in another study in young rats the sequence of events in germanium-induced myopathy (Higuchi *et al.*, 1991). After 4 months on the germanium diet, skeletal muscle cytochrome c oxidase activity decreased and there was an accumulation of high electron-dense materials in abnormal mitochondria, but no obvious changes in muscle fibers histologically. Muscle fiber degeneration and phagocytosis became prominent with time. Finally, by 8 months, accumulation of lipid droplets was observed in some fibers.

Germanium-induced neuropathy was reproduced by feeding young rats a diet containing 0.15% GeO_2 for 8 months (Matsumuro *et al.,* 1993). Peripheral nerve lesions developed after long-term ingestion (6 mo) of germanium at a calculated dose of about 69 mg/kg body wt/day. The neuropathy was characterized by segmented demyelination and remyelination, nerve edema, and lack of fibers undergoing axonal degeneration. Electron microscopic examination demonstrated that the earliest pathological findings were in Schwann cells (increased cytoplasmic volume or disintegration of the cytoplasm). The exposure duration for the development of neuropathy was longer than that for the development of nephropathy and myopathy. According to the authors, these neuropathological changes are

different from those reported in humans in which axonal degeneration was the primary feature. Whether this is due to species difference or differences in exposure duration remains to be seen.

Nakano *et al.* (1987) and Nakano (1990) fed GeO_2 to rats in the drinking water at 0, 100, and 500 ppm for 9 and 10 months, respectively. Characteristic renal dysfunction and mitochondria abnormalities of the kidney and skeletal muscle were observed by 6 months in the 500 ppm treatment group. By 9 or 10 months, renal pathological changes including distal tubular degeneration with electron-dense deposits in the degenerated mitochondria were observed. Glomeruli appeared to have changed little. Skeletal and cardiac muscles showed focal changes with partial fiber atrophy and partial mitochondria swelling. Rats with unilateral nephrectomies were fed 1000 ppm GeO_2 in drinking water. Serum creatinine and serum urea nitrogen increased significantly at 6 weeks and markedly increased at 10 weeks. Pathological changes in the renal tubules were the same as those in rats fed 500 ppm GeO_2. Mortality was only 40% in the group receiving 1000 ppm GeO_2. Based on water consumption we calculate the average doses of GeO_2 to be 13 and 69 mg/kg body wt/day for rats fed 500 and 1000 ppm, respectively. The corresponding germanium doses are 9 and 48 mg/kg body wt/day, respectively. A life-time feeding study in rats also showed that in addition to an elevated tissue germanium levels, damage and impaired function were observed in the liver and kidneys of the treated rats that received a low level of sodium germanate, 5 ppm of Ge, in drinking water, although body weight was not affected (Schroeder *et al.*, 1968).

While nephrotoxicity similar to that reported in human cases was consistently induced by oral administration of GeO_2 in animals, results of animal studies with Ge-132 do not give a clear picture. Sanai *et al.* (1990b, 1991b) compared GeO_2 with Ge-132, at equal germanium doses, in subchronic rat studies and demonstrated that only GeO_2, the inorganic germanium, but not Ge-132, the organic germanium, causes the characteristic nephropathy and renal dysfunction. Oral doses of Ge-132 were administrated at 120 mg/kg body wt/day for 24 weeks or 240 mg/kg body wt/day for 10 weeks in the diet. Germanium was found in the kidney with Ge-132 but in a lesser concentration than that with GeO_2. Urinary germanium was elevated in both GeO_2 and Ge-132 groups. Similarly, Asano *et al.* (1994) recently reported that GeO_2 caused distal tubular nephrotoxicity, whereas SK-818 had no effects in both normal and glomeruli-injured rats. Germanium was given in drinking water as 2400 ppm of SK-818 or 1500 ppm of GeO_2 for 8 weeks. Intakes of Ge-132 and GeO_2 were calculated to correspond to 205 ± 10 and 138 ± 6 mg/kg body wt/day, respectively, by using average water consumption data. In this study, X-ray microanalysis did not reveal any evidence of renal germanium accumulation in the GeO_2-treated rats. The biochemical findings, which were published separately (Asano *et al.*, 1990), indicated that GeO_2 caused a decreased body weight and an increased blood urea nitrogen in both normal and adriamycin-treated rats, but SK-818 had no effects.

One chronic gavage study reported that SK-818 caused no biochemical or histopathological changes in rat kidneys even at a high dosage of 750 mg/kg body wt/day for 1 year (Nakagawa *et al.*, 1990). Another subchronic (3 months) gavage study reported that SK-818 caused 44–54% mortality in rats at a dose of 4000 mg/kg body wt/day. Decreased weight gain, soft stool, diarrhea, and increased water consumption occurred at doses $\geqslant$ 1600 mg/kg body wt/day and cecum was dilated and had rarefied wall at doses $\geqslant$ 640 mg/kg body wt/day. No effect on blood urea nitrogen was observed (Kanda *et al.*, 1990).

Contrary to the negative nephrotoxicity findings of Ge-132, a French research group (Anger *et al.*, 1992) reported a moderate renal dysfunction characterized by tubular abnormalities with the presence of cylinders, swelling of tubulus cells and flocculus deposits, in 60% of the male, but not the female, rats receiving Ge-132 orally in a subchronic (6 months) feeding study. The calculated dose from this study was 714 mg Ge-132/kg body wt/day. Elevated germanium levels were observed in several tissues including kidney, spleen, and liver, whereas germanium was not found in controls. Another study reported renal pathological changes with normal renal function in rats fed only 50 ppm germanium in the diet as Ge-132 or GeO_2 for 6 weeks (Taylor, 1991). Urinary germanium was higher in the Ge-132 group than in the GeO_2 group. Kidney germanium concentrations were all low.

Teratology, Reproduction, and Carcinogenesis

Germanium does not appear to be tumorigenic or carcinogenic. Life-time exposure to 5 mg Ge/L, a relatively low level, in drinking water as sodium germanate did not increase any incidence of spontaneous tumors (Kanisawa and Schroeder, 1967). No adverse effect of GeO_2 at doses of 19, 38, and 75 mg/kg (sc) to pregnant rats was observed on mother, embryos, or newborns (see Vouk, 1986). Teratogenicity tests with Ge-132 were negative in one intraperitoneal rat study and one intravenous rabbit study at doses up to 1000 and 500 mg/kg, respectively. Another rat study indicated that a "slightly significant difference was seen at 4000 mg/kg oral dose when compared with controls," but no mention was made of effects. All these studies with Ge-132 were from one report (Asai, 1984) in which results were presented as summary in tables.

DISCUSSION

A summary of these human data on germanium-associated toxicity is shown in Table 1: (1) Germanium

TABLE 1
Summary of Human Data on Germanium Toxicity

	Male	Female	Total
No. of cases:	16	15	31
Age ranges (years)	5–73	4–58	4–73
Total Ge intake[a] (g)	16–173	15–324	15–324
Cases with ⩽70 g	11/14 = 79%	11/13 = 85%	22/27 = 81%
Duration[b] (months)	3–24	2–36	2–36
Effects			
Death	4/16 = 25%	5/15 = 33%	9/31 = 29%
GI disturbances[c]			20/30 = 67%
Anemia			27/27 = 100%
Renal dysfunction/nephropathy			31/31 = 100%
Myopathy			13/21 = 62%
Neuropathy			13/22 = 59%
Liver dysfunction/necrosis			7/20 = 35%
Bone marrow (hypoplasia)			6/8 = 75%

[a] Four cases ingested unknown amounts of Ge.
[b] Duration of Ge was not known in one case.
[c] GI, nausea, vomiting, no appetite, and diarrhea.

intoxication in humans showed no sex nor age differences (about equal cases in male and female subjects and affected all ages, from 4 to 73 years old), all cases associated with subchronic to chronic exposure of germanium products (2–36 months), with a total dosage range of 15 to 324 g. (2) Reported human cases showed a high mortality rate (29%); 81% of the cases ingested only 70 g of germanium or less, with a daily dose as low as 30 to 50 mg. Among the five subjects known to take total doses higher than 100 g, three died. (3) 100% of the cases had nephrotoxicity, 67% had gastrointestinal disturbances (nausea, vomiting, and weight loss), 100% anemia, 62% myopathy, 59% neuropathy, and 35% liver dysfunction or hepatosteatosis.

Various forms of germanium (both organic and inorganic) were reported present in the germanium products which include GeO_2, Ge-132, Ge-lac-cit, a plant extract, a "mineral cheese" containing germanium, unspecified organic and inorganic germanium, and some were unknown.

Based on these human case reports, the lowest observed adverse effect levels (LOAEL) of 1–4 mg/kg body wt/day of germanium as inorganic Ge, GeO_2, Ge-132, or Ge-lac-cit were found in three-quarters of the cases (Table 2). Among the seven subjects who had a LOAEL greater than 4 mg/kg body wt/day, four died; each had 12–23, 10, 8, and 0.7–5.0 mg Ge/kg body wt/day as a preparation containing GeO_2, a preparation containing mainly GeO_2 with minor organic germanium, a preparation of Ge-lac-cit, and a GeO_2 capsule, respectively (Kamijo *et al.*, 1991; Nagata *et al.*, 1985; Krapf *et al.*, 1992; Matsusaka *et al.*, 1988).

All pathological conditions of germanium-induced nephropathy, myopathy, cardiomyopathy, neuropathy, as well as renal and liver dysfunction, weight loss, and anemia were reproduced in experimental animal studies with GeO_2. Renal toxicity appears to be the most sensitive end point. A LOAEL of 26 mg/kg body wt/day of germanium as GeO_2 in the diet (Sanai *et al.*, 1991a) or 9 mg/kg body wt/day in water (Nakano, 1990) has been derived. Compared with the LOAELs of 1–4 mg/

TABLE 2
Calculated Lowest Effect Levels of Germanium from Human Cases

Ge form in products	No. of cases[a]	Daily dose Ge (mg/day)	Total dose Ge (g)	LOAEL[b] (mg/kg/day)
Inorganic	8 (1)	60–333	16–70	0.9–6.7
GeO_2	9[c] (4)	30–961	21–324	0.7–23
Ge-132	2[d] (1)	128–257	15–31	1.7–5.6
Ge-lac-cit	4 (1)	51–405	25–47	0.8–8.0
Unknown	4 (0)	50–202	27–158	0.8–4.0

Note. Inorganic, as stated by the authors with no specified form; GeO_2, germanium dioxide; Ge-132, carboxyethylgermanium sesquioxide; Ge-lac-cit, germanium–lactate–citrate; Unknown, also including one from a plant extract and one as germanium "mineral cheese".

[a] Numbers with LOAEL greater than 4 are in parenthesis.
[b] LOAEL was calculated by dividing daily intake dose of germanium by body weight. When a body weight value was not available, 45–65, 50–75, and 20 kg were used for female and male adults and children, respectively. Ge dose was converted from GeO_2 and Ge-132 by factors of 0.694 and 0.428, respectively. Four subjects who had ingested unknown amounts of Ge were not included.
[c] Including one case who took a Ge product containing minor organic Ge component.
[d] These two cases were reported by Okuda *et al.* (1987) to have taken Ge-132, whereas Sanai *et al.* (1990) reported that GeO_2 was detected in the Ge products.

TABLE 3
Actions Taken against Germanium Products

June 28, 1988	Import alert issued by FDA to detain Ge products from Japan to be used as food or drug.
Oct. 6, 1989	Press notice released by the Department of Health in UK to advise the public not to take any preparations containing Ge.
March 26, 1990	Letter sent to the local food control authorities by Norwegian Food Control Authority that they regard germanium as a health hazard and to ban preparations containing germanium above the normal background level.
Sept. 14, 1993	Notice sent by National Nutritonal Food Association (NNFA) advising its members and suppliers to remove Ge or Ge-containing products from stores and to stop marketing.
Oct. 14, 1993	Letter sent by Center for Food Safety and Applied Nutrition of FDA to the dietary supplement industry via dietary supplement trade association to share the safety concerns regarding the marketing of Ge products.
Nov. 30, 1993	Ge recommendation issued by Council for Responsible Nutrition to its members to discontinue marketing of any Ge products with Ge levels greater than 1 mg/day.

kg body wt/day of those human cases, these values clearly indicate that humans appear to be more sensitive to germanium toxicity than the rodents by a factor of 2 to 26.

Although most of the reported cases ingested an inorganic form of germanium (GeO_2, Ge-lac-cit, or unknown inorganic) including some cases with a combination of inorganic and organic germanium form (Ge-132 or unknown organic), we cannot exclude the possibility that long-term ingestion or higher levels of organic Ge-132 will cause similar adverse effects as the GeO_2. This is supported by the animal data that higher doses of Ge-132 than GeO_2 did elicit similar tissue pathology and tissue Ge accumulation (Taylor, 1991; Anger *et al.*, 1992). Moreover, Ge-132 is a synthetic compound and some preparations may use GeO_2 as the starting material; thus, Ge-132 can be easily contaminated with GeO_2, the form that was proven to cause germanium intoxication in both humans and animals. The danger of adverse effects by other starting materials such as acrylates that are known carcinogens cannot be disregarded, especially because the purity of germanium preparations is usually not certified. Furthermore, adverse effects associated with ingestion of Ge-132 were reported in humans (Okuda *et al.*, 1987; Kong, 1993). In clinical trials with Ge-132, Chinese research groups reported adverse effects on gastrointestinal and cardiovascular systems (cited in Kong, 1993). One report showed abnormal EKGs in 62.9% of the elderly who took a daily oral dose of 10 mg Ge-132 for 12 weeks. Others reported 12 of the 73 peptic ulcer patients (16.4%) developed nausea, loss of appetite, and diarrhea with Ge-132 treatment. It is not known whether renal and/or other organ systems were affected because most of the studies did not examine renal functions or organ histopathology.

The mechanism of action of adverse effects of germanium on renal function and multiple organ pathology is not clear. Studies are also lacking in the areas of interactions of germanium with other trace elements or drugs. Germanium can affect tissue levels of some trace elements, e.g., decreasing chromium in the liver, lungs, kidneys, and spleen and increasing copper in the liver (See Gerber, 1988; Nielsen, 1986). This potentially puts children and elderly citizens, a vulnerable subpopulation, at risk. Case reports appearing in the literature and supporting evidence from animal studies have prompted several countries including United States to take action against germanium products (Table 3).

CONCLUSION

Germanium is not an essential element in animals or humans nor have any germanium deficiency syndromes been documented. In addition, prolonged intake of germanium-containing products was reported in at least 31 human cases to be associated with renal failure with characteristic renal dysfunction and tubular degeneration, anemia, myopathy, neuropathy, tissue germanium accumulation, and even death. In laboratory animals, GeO_2 has been shown to be nephrotoxic and to accumulate in kidneys, liver, spleen, hair, nail, and other tissues. Evidence of Ge-132 toxicity is inconclusive; nephrotoxicity was shown in some studies but not in others. However, Ge-132 has also been shown to accumulate, although to a lesser degree than the dioxide, in kidneys, liver, spleen, and other tissues. Based upon the evidence of persistent renal toxicity associated with GeO_2, the lack of conclusive findings that organic germanium compounds are nephrotoxic, and the possibility of contamination of the organic germanium products with inorganic germanium, it is clear that germanium products present a potential hazard to human health.

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