WHO/SDE/WSH/03.04/13
English only

Selenium in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Originally published in **Guidelines for drinking-water quality**, 2nd ed. Vol. 2. *Health criteria and other supporting information.* World Health Organization, Geneva, 1996.

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

The work of the following coordinators was crucial in the development of this background document for development of WHO *Guidelines for drinking-water quality*:

J.K. Fawell, Water Research Centre, United Kingdom
(inorganic constituents)
U. Lund, Water Quality Institute, Denmark
(organic constituents and pesticides)
B. Mintz, Environmental Protection Agency, USA
(disinfectants and disinfectant by-products)

The WHO coordinators were as follows:

Headquarters:
H. Galal-Gorchev, International Programme on Chemical Safety
R. Helmer, Division of Environmental Health

Regional Office for Europe:
X. Bonnefoy, Environment and Health
O. Espinoza, Environment and Health

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom of Great Britain and Northern Ireland and United States of America.

GENERAL DESCRIPTION

Identity

Selenium is present in the earth's crust, often in association with sulfur-containing minerals. It can assume four oxidation states (-2, 0, +4, +6) and occurs in many forms, including elemental selenium, selenites and selenates (*1*).

Physicochemical properties (1)

Property	*Value*
Physical state	Grey metallic/red amorphous powder or vitreous form
Boiling point	685 °C
Water solubility	Insoluble

Organoleptic properties

Many selenium compounds are odoriferous, some having an odour of garlic (*1*).

Environmental fate

Acid and reducing conditions reduce inorganic selenites to elemental selenium, whereas alkaline and oxidizing conditions favour the formation of selenates. Selenites and selenates are usually soluble in water. Elemental selenium is insoluble in water and not rapidly reduced or oxidized in nature. In alkaline soils, selenium is present as water-soluble selenate and is available to plants; in acid soils, it is usually found as selenite bound to iron and aluminium oxides in compounds of very low solubility (*2*).

ANALYTICAL METHODS

Atomic absorption spectrometry with hydride generation is the most convenient method of determining selenium in drinking-water. If 10-ml samples are used for routine analysis, the detection limit is about 0.5 µg/litre. Lower levels can be determined if larger sample volumes are used (*3*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

The level of selenium (mostly bound to particles) in most urban air ranges from 0.1 to 10 ng/m^3, but higher levels may be found in certain areas, e.g. in the vicinity of copper smelters (*4*).

Water

The levels of selenium in groundwater and surface water range from 0.06 to about 400 µg/litre (*5–7*); in some areas, levels in groundwater may approach 6000 µg/litre (*8*). Concentrations increase at high and low pH as a result of conversion into compounds of greater solubility in water. Levels of selenium in tapwater samples from public water supplies around the world are usually much less than 10 µg/litre (*9,10*). Drinking-water from a high-selenium area in China was reported to contain 50–160 µg/litre (*1*).

Food

Vegetables and fruits are mostly low in selenium content (<0.01 mg/kg). Levels of selenium in meat and seafood are about 0.3–0.5 mg/kg. Grain and cereal products usually contain <0.01–0.67 mg/kg. Great variations in selenium content have been reported in China, where those of corn, rice, and soya beans in high- and low-selenium areas were 4–12 and 0.005–0.01 mg/kg, respectively (*1,2*).

Estimated total exposure and relative contribution of drinking-water

Foodstuffs constitute the main source of selenium for the general population. Daily dietary intake varies considerably according to geographical area, food supply, and dietary habits. Recommended daily intakes have been set at 1.7 µg/kg of body weight in infants and 0.9 µg/kg of body weight in adults (*11*).

Most drinking-water contains much less than 10 µg/litre, except in certain seleniferous areas. A level of 1 µg/litre corresponds to an intake of 2 µg of selenium per day. Thus, given an intake from food of about 60 µg/day, the relative contribution from drinking-water is small. Even in high-selenium areas, the relative contribution of selenium from drinking-water may be small in comparison with that from locally produced food (*1*).

The intake of selenium by the general population from air and smoking appears to be insignificant and has been estimated to be less than 1–2 µg/day (*12*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Most water-soluble selenium compounds and selenium from food are effectively absorbed in the gastrointestinal tract (*13*). Elemental selenium (*14*) and selenium sulfide (*15*) are poorly absorbed. After absorption, water-soluble selenium compounds appear to be rapidly distributed to most organs, the highest concentrations being in kidney, liver, spleen, and testes (*16,17*).

Selenium compounds are biotransformed into excretable metabolites, including unknown as well as methylated selenides and trimethylselenonium ion at higher doses (*1,12,13,18*). Selenides may react with metals in the body to form metal selenides (*12*). Most (49–70%) selenium is excreted in urine (*19*). In humans, selenite is eliminated in three phases, with half-lives of 1, 8–20, and 100 days, respectively (*13*).

Selenium is an essential trace element for many species, including humans (*2,11,20*). It is incorporated into proteins via a specific selenocysteine tRNA with co-translational synthesis of selenocysteine from phosphoserine tRNA and inorganic selenium (*20,21*). Selenium is found as selenocysteine in glutathione peroxidase (*2,20*) and is incorporated into other proteins, such as tetraiodothyronine deiodinase and selenoprotein P (*20,22,23*). (-)-Selenomethionine from food is apparently nonspecifically incorporated in proteins in competition with (-)-methionine.

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Selenite, selenate, selenocysteine, and selenomethionine are highly toxic and kill laboratory animals in single doses of 1.5–6 mg/kg of body weight (*1,12*).

Long-term exposure

Signs of selenium deficiency in many farm and laboratory animals include degenerative changes of several organs, growth retardation, and failure to reproduce (*2,24*).

In rats, 5 mg of selenium per kg of diet may result in growth reduction (*25,26*). At a dietary level of 6.4 mg of selenium per kg (given as selenite), liver changes and splenomegaly occurred. At 8 mg of selenium per kg, anaemia, pancreatic enlargement, and increased mortality were observed (*25*). Based on growth retardation, apparently caused by reduced secretion of growth hormone from the anterior pituitary gland as a result of local selenium accumulation (*27*), a NOAEL of about 0.4 mg of selenium per kg of body weight per day was suggested. Hepatotoxic effects have also been described following dietary administration of selenium (*28,29*). Based on both growth retardation and organ toxicity, a LOAEL of 0.03 mg/kg of body weight per day has been suggested.

The syndromes "blind staggers" and "alkali disease" have been described in livestock and are associated with the consumption of selenium in accumulator plants (*30*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Selenate, selenite, and the amino acids selenocysteine and selenomethionine are teratogenic in avian species (*31*) and fish (*32*). Teratogenicity has also been observed in sheep (*33*) and pigs (*34*). In recent studies on monkeys (*Macaca fascicularis*) fed selenomethionine (25, 150 or 300 µg/kg of body weight per day) during organogenesis, no signs of teratogenicity were observed (*35*).

Adverse effects of selenate (3 mg/litre in drinking-water) on reproduction in mice and rats have been reported (*36*), but there are also two negative reports on the effects of selenite in hamsters and mice (*37*). Only at doses associated with overt maternal poisoning and nutritional deprivation was evidence of selenomethionine-induced embryonic or fetal toxicity observed in rabbits and hamsters (*38,39*).

Mutagenicity and related end-points

A weak base-pair substitution mutagenic activity has been demonstrated for both selenite and selenate in *Salmonella typhimurium* strain TA100 (*40,41*). Selenite, selenate, and selenide induced unscheduled DNA synthesis, sister chromatid exchange, and chromosomal aberrations in cell cultures *in vitro*, often in the presence of glutathione (*42–44*). In one *in vivo* study, chromosomal aberrations and increased sister chromatid exchange were seen in hamster bone marrow cells after selenite treatment, but only at toxic doses (*45*).

Carcinogenicity

Early studies in which tumours were seen in test animals (*46,47*) have been seriously questioned because of study limitations (*48*), and several evaluators have found the data to be inconclusive. In two studies on mice, there was either no increase or a decrease in the incidence of tumours after the administration of selenite or selenate (3 mg of selenium per litre of drinking-water) (*49*) or selenium oxide (2 mg of selenium per litre of drinking-water) (*50*). Further data indicate an anticarcinogenic effect of selected selenium compounds. Viewed collectively, these data seem to show that the compounds studied will not act as carcinogens at low or moderate doses (*12*).

Selenium sulfide given by gavage resulted in hepatocellular carcinomas in rats and mice (*51*) but caused no increased incidence in tumours when applied to the skin of mice (*52*).

EFFECTS ON HUMANS

In humans, few reports of clinical signs of selenium deficiency are available. It has been suggested that it may be a factor in endemic cardiomyopathia (Keshan disease) and possibly also in the joint and muscle disease (Kaschin-Beck disease) in the Keshan region of China (*1,12*).

Acute oral doses of selenite and other selenium compounds cause symptoms such as nausea, diarrhoea, abdominal pain, chills, tremor, numbness in limbs, irregular menstrual bleeding, and marked hair loss (*12,53*).

High dietary intakes of selenium have been investigated in selenium-rich areas of South Dakota, USA (54). Symptoms in people with high urinary selenium levels included gastrointestinal disturbances, discoloration of the skin, and decayed teeth (*54*).

Children living in a seleniferous area in Venezuela exhibited more pathological nail changes, loss of hair, and dermatitis than those living in Caracas (*55*). Based on Chinese data on blood level–intake relationships (*56*), their estimated daily intake was about 0.66 mg of selenium. However, the groups concerned differed nutritionally in several ways.

In China, endemic selenium intoxication has been studied by Yang and colleagues (*57*). Morbidity was 49% among 248 inhabitants of five villages where the daily intake was about 5 mg of selenium. The main symptoms were brittle hair with intact follicles, lack of pigment in new hair, thickened and brittle nails, and skin lesions. Symptoms of neurological disturbances were observed in 18 of the 22 inhabitants of one heavily affected village only. Those affected recovered once diets were changed following evacuation from the areas concerned.

In a follow-up study, Yang et al. studied a population of about 400 individuals with average daily intakes ranging from 62 to 1438 µg (*56,58*). Clinical signs of selenosis (hair or nail loss, nail abnormalities, mottled teeth, skin lesions, and changes in peripheral nerves) were observed in 5 of 439 adults having a mean blood selenium of 1346 µg/litre, corresponding to a daily intake of 1260 µg of selenium. A decrease in prothrombin time and in the concentration of glutathione in blood were seen at dietary intakes exceeding 750–850 µg.

In a recent study, 142 subjects from geographical areas where the average selenium intake was 239 µg/day (68–724 µg/day) were examined over 2 years (*59*). An association between selenium intake and alanine aminotransferase (ALAT) levels in serum was observed but considered to be clinically insignificant. None of the effects, including nail abnormalities, were related to selenium intake.

One case of selenium toxicity directly attributable to a water source has been reported. A family was exposed for about 3 months to well-water containing 9 mg of selenium per litre. They suffered from loss of hair, weakened nails, and mental symptoms, but recovered when they stopped using the water from the well concerned (*33*).

Two individuals received about 350 and 600 µg of selenium per day via diet and selenium-containing yeast for 18 months. Marginal haematological changes and a borderline increase in ALAT levels were seen (*60*). In a small group of patients with rheumatoid arthritis receiving daily supplements of 250 µg of selenium in selenium-enriched yeast in addition to selenium from food for 6 months, levels of selenium in serum and erythrocytes were increased considerably in comparison with those in a group receiving placebo (*61*).

GUIDELINE VALUE

Except for selenium sulfide, which does not occur in drinking-water, selenium does not appear to be carcinogenic. IARC has placed selenium and selenium compounds in Group 3 (*62*). Selenium compounds have been shown to be genotoxic in *in vitro* systems with metabolic activation. There was no evidence of teratogenic effects in monkeys. Long-term exposure in rats may result in growth retardation and liver pathology.

In humans, the toxic effects of long-term selenium exposure are manifested in nails, hair, and liver. Data from Chinese indicate that clinical and biochemical (decreased liver prothrombin synthesis) signs occur at a daily intake above 0.8 mg. Daily intakes by Venezuelan children with clinical signs were estimated at about 0.66 mg on the basis of their blood levels and the Chinese data on the relationships between blood level and intake. Effects on the synthesis of a liver protein were also seen in a small group of patients with rheumatoid arthritis given selenium at a rate of 0.25 mg/day (total daily intake from all sources about 0.35 mg). No clinical or biochemical signs of selenium toxicity were reported in a group of 142 persons with a mean daily intake of 0.24 mg (maximum 0.72 mg) from food. However, the liver enzyme ALAT was positively correlated within reference values with selenium intake.

On the basis of these data, the NOAEL in humans was estimated to be about 4 µg/kg of body weight per day, on the assumption that soluble selenium salts in drinking-water may be more toxic than organic-bound selenium in food. The recommended daily intake of selenium is 0.9 µg/kg of body weight for adults. An allocation of 10% of the NOAEL in humans to drinking-water gives a health-based guideline value of 0.01 mg/litre (rounded figure).

REFERENCES

1. *Selenium.* Geneva, World Health Organization, 1987 (Environmental Health Criteria, No. 58).
2. National Research Council. *Selenium in nutrition.* Washington, DC, National Academy Press, 1983.
3. Verlinden M, Deelstra H, Adriaenssens E. The determination of selenium by atomic absorption spectrometry: a review. *Talanta*, 1981, 28:637.
4. Zoller WH, Reamer DC. Selenium in the atmosphere. In: *Proceedings of the Symposium on Selenium-Tellurium in the Environment*. Pittsburgh, PA, Industrial Health Foundation, 1976:54-66.
5. Lindberg P. Selenium determination in plant and animal material, and in water. *Acta veterinaria Scandinavica*, 1968, Suppl. 23.
6. Smith MJ, Westfall BB. Further field studies on the selenium problem in relation to public health. *US public health report*, 1937, 52:1375-1384.
7. Scott RC, Voegeli PT Jr. *Radiochemical analysis of ground and surface water in Colorado.* Colorado Water Conservation Board, 1961 (Basic Data Report 7).
8. Cannon HG. *Geochemistry of rocks and related soils and vegetation in the Yellow Cat area, Grand County, Utah*. Washington, DC, US Geological Survey, 1964 (Bulletin No. 1176).
9. National Academy of Sciences. *Selenium.* Washington, DC, 1976.
10. National Academy of Sciences. *Drinking water and health.* Washington, DC, 1977.
11. National Research Council. *Recommended dietary allowances*, 10th ed. Washington, DC, National Academy Press, 1989.
12. Högberg J, Alexander J. Selenium. In: Friberg L, Nordberg GF, Vouk VB, eds. *Handbook on the toxicology of metals*, Vol. 2, 2nd ed. Amsterdam, Elsevier, 1986:482-520.
13. Bopp BA, Sonders RC, Kesterson JW. Metabolic fate of selected selenium compounds in laboratory animals and man. *Drug metabolism reviews*, 1982, 13:271-318.

14. Medinsky MA. A simulation model describing the metabolism of inhaled and ingested selenium compounds. *Toxicology and applied pharmacology*, 1981, 59:54-63.
15. Cummins LM, Kimura ET. Safety evaluation of selenium sulfide antidandruff shampoos. *Toxicology and applied pharmacology*, 1971, 20:89-96.
16. Brown DG, Burk RF. Selenium retention in tissues and sperm of rats fed a torula yeast diet. *Journal of nutrition*, 1973, 103:102-108.
17. Thomassen Y, Aaseth J. Selenium in human tissues. In: Ihnat M, ed. *Occurrence and distribution of selenium*. Boca Raton, FL, CRC Press, 1986.
18. Palmer IS, Olson OE. Relative toxicities of selenite and selenate in the drinking-water of rats. *Journal of nutrition*, 1974, 104:306-314.
19. Levander OA. Selenium in foods. In: *Proceedings of the Symposium on Selenium and Tellurium in the Environment.* Pittsburgh, PA, Industrial Health Foundation, 1976:26-53.
20. Böck A et al. Selenoprotein synthesis: an expansion of the genetic code. *Trends in biochemical science*, 1991, 16:463-467.
21. Mullenbach GT et al. Selenocysteine's mechanism of incorporation and evolution revealed in cDNAs of three glutathione peroxidases. *Protein engineering*, 1988, 2:239-246.
22. Yang JG, Hill KE, Burk RF. Dietary selenium intake controls rat plasma selenoprotein P concentration. *Journal of nutrition*, 1989, 119:1010-1012.
23. Deagen JT, Beilstein MA, Whanger PD. Chemical forms of selenium in selenium containing proteins from human plasma. *Journal of inorganic biochemistry*, 1991, 41:261-268.
24. Diplock AT. Metabolic aspects of selenium action and toxicity. *CRC critical reviews in toxicology*, 1976, 4(3):271-329.
25. Halverson AW, Palmer IS, Guss PL. Toxicity of selenium to post-weanling rats. *Toxicology and applied pharmacology*, 1966, 9:477-484.
26. Ip C. Prophylaxis of mammary neoplasia by selenium supplementation in the initiation and promotion phases of chemical carcinogenesis. *Cancer research*, 1981, 41:4386-4390.
27. Thorlacius-Ussing O. Selenium-induced growth retardation. *Danish medical bulletin*, 1990, 37:347-358.
28. Harr JR, Muth OH. Selenium poisoning in domestic animals and its relationship to man. *Clinical toxicology*, 1972, 5:175-186.
29. Harr JR et al. Selenium toxicity in rats. II. Histopathology. In: Muth OH et al., ed. *Selenium in biomedicine*. Westport, CT, AVI Publishing Co., 1967:153-178.
30. Shamberger RJ. *Biochemistry of selenium*. New York, NY, Plenum Press, 1983.
31. Hoffman DJ, Ohlendorf HM, Aldrich TW. Selenium teratogenesis in natural populations of aquatic birds in central California. *Archives of environmental contamination and toxicology*, 1988, 17:519-525.
32. Birge WJ et al. Fish and amphibian embryos—a model system for evaluating teratogenicity. *Fundamental and applied toxicology*, 1983, 3:237-242.
33. Rosenfeld I, Beath OA. Selenium, geobotany, biochemistry, toxicity and nutrition. New York, NY, Academic Press, 1964.
34. Wahlström RC, Olson OG. The effect of selenium on reproduction in swine. *Journal of animal science*, 1959, 18:141-145.
35. Tarantal AF et al. Developmental toxicity of L-selenomethionine in *Macaca fascicularis*. *Fundamental and applied toxicology*, 1991, 16:147-160.
36. Schroeder HA, Mitchener M. Selenium and tellurium in rats: effect on growth, survival and tumors. *Journal of nutrition*, 1971, 101:1531-1540.
37. Nobunaga T, Satoh H, Suzuki T. Effects of sodium selenite on methyl mercury embryotoxicity and teratogenicity in mice. *Toxicology and applied pharmacology*, 1979, 47:79-88.
38. Berschneider F et al. [Fetal and maternal damage to rabbits following application of sodium selenite, injectable Ursoselevit, and Ursoselevit premix.] *Monatshefte für Veterinärmedizin*, 1977, 8:299-304 (in German).
39. Ferm VH et al. Embryotoxicity and dose-response relationships of selenium in hamsters. *Reproductive toxicology*, 1990, 4:183-190.

40. Löfroth G, Ames BN. Mutagenicity of inorganic compounds in *Salmonella typhimurium*: arsenic, chromium, and selenium. *Mutation research*, 1978, 53:65-66.
41. Noda M, Takano T, Sakurai H. Mutagenic activity of selenium compounds. *Mutation research*, 1979, 66:175-179.
42. Khalil AM. The induction of chromosome aberrations in human purified peripheral blood lymphocytes following *in vitro* exposure to selenium. *Mutation research*, 1989, 224:503-506.
43. Ray JH, Altenburg LC. Sister-chromatid exchange induction by sodium selenite: dependence on the presence of red blood cells or red blood cell lysate. *Mutation research*, 1978, 54:343-354.
44. Whiting R, Wei L, Stich HF. Unscheduled DNA synthesis and chromosome aberrations induced by inorganic and organic selenium compounds in the presence of glutathione. *Mutation research*, 1980, 78:159-169.
45. Norppa H, Westermark T, Knuutila S. Chromosomal effects of sodium selenite *in vivo*. *Hereditas*, 1980, 93:101-105.
46. Inne JR et al. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *Journal of the National Cancer Institute*, 1969, 42:1101-1114.
47. Volgarev MN, Tscherkes LA. Further studies in tissue changes associated with sodium selenate. In: Muth OH et al., ed. *Selenium in biomedicine*. Westport, CT, AVI Publishing, 1967:179-184.
48. International Agency for Research on Cancer. *Some aziridines, N-, S- and O-mustards and selenium*. Lyon, 1975:245-259 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 9).
49. Schroeder HA, Mitchener M. Selenium and tellurium in mice. Effects on growth, survival, and tumours. *Archives of environmental health*, 1972, 24:66-71.
50. Schrauzer GN, Ishmael D. Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C_3H mice. *Annals of clinical laboratory science*, 1974, 4:441-447.
51. *Bioassay of selenium sulfide for possible carcinogenicity (gavage study)*. Bethesda, MD, US Department of Health and Human Services, National Cancer Institute, 1980 (Technical Report Series 194).
52. *Bioassay of selenium sulfide for possible carcinogenicity (dermal study)*. Bethesda, MD, US Department of Health and Human Services, National Cancer Institute, 1980 (Technical Report Series 197).
53. Sioris LJ, Cuthrie K, Pentel PR. Acute selenium poisoning. *Veterinary and human toxicology*, 1980, 22:364.
54. Smith MJ, Westfall BB. Further field studies on the selenium problem in relation to public health. *US public health report*, 1937, 52:1375-1384.
55. Jaffe WG. Effect of selenium intake in humans and in rats. In: *Proceedings of the Symposium on Selenium and Tellurium in the Environment.* Pittsburgh, PA, Industrial Health Foundation, 1976:188-193.
56. Yang G et al. Studies of safe maximal daily selenium intake in a seleniferous area in China. Part I. *Journal of trace elements and electrolytes in health and disease*, 1989, 3:77-87.
57. Yang GQ et al. Endemic selenium intoxication of humans in China. *American journal of clinical nutrition*, 1983, 37:872-881.
58. Yang G et al. Studies of safe maximal daily selenium intake in a seleniferous area in China. Part II. *Journal of trace elements and electrolytes in health and disease*, 1989, 3:123-130.
59. Longnecker MP et al. Selenium in diet, blood and toenails in relation to human health in a seleniferous area. *American journal of clinical nutrition*, 1991, 53:1288-1294.
60. Schrauzer GN, White DA. Selenium in human nutrition: dietary intakes and effects of supplementation. *Bioinorganic chemistry*, 1978, 8:303-318.
61. Tarp U et al. Selenium treatment in rheumatoid arthritis. *Scandinavian journal of rheumatology*, 1985, 14(4):364-368.

62. International Agency for Research on Cancer. *Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1-42*. Lyon, 1987:71 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7).