

Provisional Peer-Reviewed Toxicity Values for

Selenourea
(CASRN 630-10-4)

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Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL _{ADJ}	LOAEL adjusted to continuous exposure duration
LOAEL _{HEC}	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL _{ADJ}	NOAEL adjusted to continuous exposure duration
NOAEL _{HEC}	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF _A	animal to human uncertainty factor
UF _C	composite uncertainty factor
UF _D	incomplete to complete database uncertainty factor
UF _H	interhuman uncertainty factor
UF _L	LOAEL to NOAEL uncertainty factor
UF _S	subchronic to chronic uncertainty factor

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

- 1) U.S. EPA's Integrated Risk Information System (IRIS).
- 2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
- 3) Other (peer-reviewed) toxicity values, including
 - ▶ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
 - ▶ California Environmental Protection Agency (CalEPA) values, and
 - ▶ EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore,

users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Selenourea is an organic selenium compound with a molecular weight of 123.02 g/mol. Figure 1 shows the chemical structure of selenourea. No reference dose (RfD) for selenourea is currently available on IRIS (U.S. EPA, 2009) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) reports both a subchronic and chronic RfD of 0.005 mg/kg-day for selenourea. This RfD is derived from a lowest-observed-adverse-effect level (LOAEL) of 3.2 mg/day based on selenosis, resulting from selenium intake, observed in an epidemiology study (Yang et al., 1983). In this study, a human population exposed to high levels of selenium in their diet exhibited signs of chronic selenosis including loss of hair and nails, and lesions of the skin and nervous system. To derive this RfD, the LOAEL of 3.2 mg/day for a 55-kg body weight man was converted to a daily dose of 0.06 mg/kg-day. An uncertainty factor (UF) of 10 was used to extrapolate from the LOAEL and a modifying factor of 1.5 was used to account for differences in the absorption of selenium from food and water. This assessment for selenourea, which had been on IRIS, was withdrawn in 1991, and is not currently referenced by any U.S. EPA document. This same RfD is currently found in HEAST and on IRIS for "selenium and compounds," but it is based on a more recent study by Yang et al. (1989) that identifies a LOAEL of 1.3 mg/day based on selenosis observed in a human population. In deriving this RfD, a UF of 3 and a modifying factor of 1 were employed. The fact that this same RfD has been used for both selenourea and selenium and compounds suggests that the toxicity of these compounds is simply a reflection of the selenium that they contain.

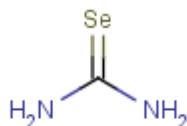


Figure 1. Chemical Structure of Selenourea

No inhalation reference concentration (RfC) or cancer assessment for selenourea is available on IRIS (U.S. EPA, 2009) or in the HEAST (U.S. EPA, 1997). The chemical assessments and related activities (CARA) lists (U.S. EPA, 1994, 1991) include no relevant documents for selenourea. CalEPA (2009a, b), ATSDR (2009), and the World Health Organization (WHO, 2009) have not evaluated the toxicity of selenourea. Occupational exposure limits for selenourea have not been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2009), or the Occupational Safety and Health Administration (OSHA, 2009). Neither the International Agency for Research on Cancer (IARC, 2009) or the National Toxicology Program (NTP, 2009, 2005) have evaluated the carcinogenicity of selenourea.

For this PPRTV, literature searches were conducted from the 1960s through July 2009 for studies relevant to provisional toxicity values for selenourea. The databases searched include RTECS, HSDB, TSCATS, MEDLINE, TOXLINE, DART, CCRIS, GENETOX, CHEMABS, BIOSIS, and Current Contents (last 6 months).

REVIEW OF PERTINENT DATA

Human Studies

There are no studies of the health effects of selenourea in humans exposed by any route in the available literature.

Animal Studies

Oral Exposure

Dhillon et al. (1990) conducted two experiments to determine whether chronic selenosis (via feeding of selenium-rich rice straw during the winter months) was the causative factor in a disease (called Degnala disease) observed in cattle and buffalo in India. In a short-term experiment, two buffalo calves (unspecified sex and breed) were administered selenourea (purity not specified) at 0.3 mg/kg-day (in water). There was no control group. Animals were examined daily for general condition, coat condition, leg coordination, appetite, rumen movements, and body temperature (every 4th day); body weight was not measured. Both calves treated with selenourea developed diarrhea by Day 5. One animal exhibited edema and redness on the tip of the tail and weakness; this animal died on Day 7. The remaining animal had skin cracks and edema in the fetlock region by Day 7 and died on Day 9. Gross postmortem evaluations revealed mild congestion of the gastrointestinal tract, but no other abnormalities.

In the second experiment conducted by Dhillon et al. (1990), five buffalo calves (sex and breed unspecified) were administered selenourea (purity not specified) at 0.15 mg/kg-day (in water) for 75 days (Dhillon et al., 1990). One animal was not treated and served as a control. Endpoints routinely evaluated throughout the study included general condition, coat condition, leg coordination, appetite, rumen movements, feces consistency, and temperature; body weight, however, was not measured. All calves survived for the duration of the experiment. At the conclusion of the study, two treated animals were sacrificed and received postmortem evaluation; the control animal was not examined. Histopathological examinations of the skin,

blood vessels, small intestine, heart, liver, and kidneys were performed on the sacrificed animals. The remaining animals were observed for up to 120 days; however, the study authors did not report the calves' ultimate disposition.

Clinical signs observed in treated animals include edema, hair loss, skin cracks, and wounds of the fetlock region; hoof cracks; tail edema and necrosis; ear tip necrosis; and hoof rings. Appetite and body temperature were not affected. Postmortem evaluation of two animals sacrificed at 75 days revealed mild congestion of the gastrointestinal tract and petechial hemorrhages on the epicardium. Histopathological analysis indicated necrosis of the epidermis; infiltration of the dermal epithelium with mononuclear cells, neutrophils, and eosinophils; and proliferation of fibrous tissue (location or nature of fibrous tissue was not specified). Thrombus formation in blood vessels was apparent. Degenerative changes were seen in hepatocytes, the walls of blood vessels, and the tubular epithelium of the kidney. In the liver, the central vein was observed to be dilated, and the portal triad had mild leukocytic infiltration. Dhillon et al. (1990) did not specify whether these effects occurred in one or both of the sacrificed animals, and there was no histopathologic evaluation in the control animal. The only selenourea dose tested in this study (0.15 mg/kg-day) may be considered a LOAEL based on clinical signs and possible effects on the blood vessels, kidney, and liver in buffalo calves. However, as there was no gross or microscopic postmortem evaluation of the control animal, the microscopic changes in the blood vessels, kidneys, and liver cannot be clearly attributed to selenourea treatment.

In a second subchronic study of buffalo calves, by Deore et al., 2002, selenourea was repeatedly administered to buffalo calves (3/dose of unspecified sex) in drinking water at 0 or 0.3 mg/kg-day for 75 days. Calves were evaluated daily for physical appearance, posture, gait, skin luster, temperature, and the appearance of toxic effects; body weight was not measured. Blood and hair samples were collected from the calves before the start of the experiment (Day 0) and at regular intervals for the duration of the experiment for analysis of selenium levels. The animals were not subjected to gross or microscopic examination at the end of the study. No animals died during the course of the experiment. Clinical signs in the form of redness of the eyes and lacrimation first appeared within 6–8 days in the treated animals. Other clinical signs observed as the study progressed included alopecia, skin cracks, ridges and rings on hooves, dried and curved ear tips, and hoof elongation. As shown in Table 1, the activity of erythrocytic glutathione peroxidase increased significantly over preexposure levels by Week 5, and it was increased more than 3-fold by the final week of the study. Hair selenium levels were significantly increased compared to the preexposure level after 4 weeks of selenourea administration, reaching a peak of 22.91 ppm by Week 11 (see Table 1). From Day 6 onward, blood selenium levels in treated animals were statistically significantly ($p < 0.05$) elevated compared to the preexposure level of 0.70 $\mu\text{g/mL}$; blood levels peaked at 3.12 $\mu\text{g/mL}$ on Day 75 (see Table 1). The study authors reported that clinical signs of chronic selenosis appeared when blood selenium reached a concentration of about 2.0 $\mu\text{g/mL}$, and that these signs became prominent at selenium concentrations ≥ 2.5 $\mu\text{g/mL}$. This study identifies a freestanding LOAEL of 0.3 mg/kg-day based on clinical signs of toxicity in buffalo calves.

Parameter	Control		0.3 mg/kg-day	
	Preexposure level (Day 0)	Terminal level (Day 75)	Preexposure level (Day 0)	Terminal level (Day 75)
Blood selenium ($\mu\text{g/mL}$) ^b	0.78 \pm 0.05	0.77 \pm 0.02	0.70 \pm 0.08	3.12 \pm 0.01 ^c
Hair selenium (ppm) ^b	2.94 \pm 0.55	3.04 \pm 0.47	2.42 \pm 0.60	22.91 \pm 2.6 ^c
Erythrocyte glutathione peroxidase activity (EU/mg Hb) ^b	6.21 \pm 1.4	6.24 \pm 1.39	5.35 \pm 0.94	18.81 \pm 0.46 ^c

^aDeore et al. (2002).

^bValues presented are means \pm standard error.

^cSignificantly different from preexposure control ($p < 0.01$).

Inhalation Exposure

No inhalation studies of selenourea were located.

Other Studies

Toxicokinetics

Deore et al., 2007 administered selenourea via gavage or intravenously at 0.75 mg/kg and followed for up to 48 hours after treatment to buffalo calves (three/group of unspecified sex). Selenium concentrations in blood and urine were measured spectrophotometrically in samples taken at intervals up to 48 hours after selenourea administration. Plots of blood concentrations of selenium over time following intravenous or oral dose of selenourea each showed two distinct peaks: Blood selenium levels averaged 3.59 $\mu\text{g/mL}$ 1 minute after intravenous injection, declined to 0.34 $\mu\text{g/mL}$ by 4 hours, and peaked again at 6 hours to 2.31 $\mu\text{g/mL}$. After oral dosing, an initial blood peak of 1.56 $\mu\text{g/mL}$ was observed at 2 hours, followed by a decline for the next 4 hours and a second peak of 1.05 $\mu\text{g/mL}$ at 8 hours. Oral administration of selenourea resulted in a lower area under the blood-time concentration curve (AUC) than intravenous administration (18.46 $\mu\text{g}/\text{hour}/\text{mL}$ after oral dosing vs. 23.97 $\mu\text{g}/\text{hour}/\text{mL}$ after intravenous dosing), but it had a longer mean residence time and elimination half-life and a larger steady-state volume of distribution. The oral bioavailability of selenium following selenourea treatment, calculated as the oral:intravenous ratio of AUCs, was estimated to be 77%. More selenium was excreted in the urine of calves treated intravenously than orally (22% total dose excreted by 24 hours after intravenous dosing vs. 5.9% after oral dosing).

In another toxicokinetic study, Cummins and Kimura (1971) administered oral doses of selenourea and several other selenium compounds (biphenyl selenium, sodium selenite, selenium sulfide, and elemental selenium, each at a dose equivalent to 2.0 mg selenium/kg body weight) to groups of two male mongrel dogs and collected blood samples at intervals up to 32 hours after dosing. Blood samples were analyzed for selenium content. Administration of selenourea resulted in a peak blood concentration of 0.6 μg selenium/mL blood (average for the two dogs, estimated from data presented graphically). The study authors reported that peak selenium blood concentration was positively correlated with toxicity (as measured by LD_{50} in rats) for all selenium compounds tested—except biphenyl selenium (which resulted in high selenium blood concentrations, but low toxicity); the more toxic sodium selenite resulted in a peak blood selenium concentration of approximately 1.0 $\mu\text{g/mL}$, while the less toxic selenium sulfide and elemental selenium resulted in slightly lower peak selenium blood levels of about 0.5 and 0.3 $\mu\text{g/mL}$, respectively.

Two studies examined the tissue distribution of radiolabeled selenourea (^{75}Se) administered via injection. Breccia et al. (1966) observed the highest radioactivity in the liver, kidney, and spleen of rats treated via intraperitoneal injection, while Carr and Walker (1964) reported the highest radioactivity in the liver, kidney, and lung of rabbits treated via intravenous injection.

In an acute lethality study, Cummins and Kimura (1971) treated Sprague-Dawley rats (six/dose of unspecified sex) with selenourea and several other selenium compounds via gavage at unspecified doses and followed for 7–10 days after treatment. The study authors reported an LD_{50} of 50 mg/kg (95% confidence interval, 35.7–70 mg/kg) for selenourea. Other selenium compounds exhibited a wide range of LD_{50} values in rats that ranged from 7 mg/kg (for sodium selenite) up to 6,700 mg/kg (for elemental selenium).

Other Routes of Exposure

Badiello et al. (1967) administered a single intraperitoneal injection of selenourea at 0, 0.4, 0.8, 1.6, or 3.0 mg (approximately 3, 5, 11, or 20 mg/kg body weight based on the reported average weight) to Wistar rats (eight males/dose, weighing an average of 150 g) and observed up to 3 months following treatment. Clinical signs were monitored throughout the study and hematological parameters (granulocyte and lymphocyte counts) were measured for the first 6 days. None of the rats administered 0.4 or 0.8 mg selenourea died, and the study authors noted no changes in physiological activity. Plots of lymphocyte and granulocyte counts over time showed an increase in granulocytes and a decrease in lymphocytes in rats given 0.8 mg selenourea 6–12 hours after treatment (data shown for this treatment group only); both cell counts were comparable to controls thereafter. Rats treated with 1.6 mg selenourea exhibited sluggishness and a diminished appetite. One rat in this group died; however, the study authors indicated that no macroscopic visceral changes were apparent. In the 3.0-mg treatment group, one rat died after 48 hours on study. Surviving rats in this dose group exhibited marked sluggishness, alopecia, total paralysis of the hind legs, and anorexia with a marked loss in body weight and accompanying cachexia (physical wasting).

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL ORAL RfD VALUES FOR SELENOUREA

Because of the lack of human oral data and the inadequacy of the animal oral data, provisional RfD values for selenourea cannot be derived. Oral data for selenourea are limited to two subchronic studies in which selenourea was administered to buffalo calves (Deore et al., 2002; Dhillon et al., 1990). Buffalo calves were tested because the studies were initially designed to determine whether chronic selenosis was the causative factor in a disease (called Degnala disease) observed in cattle and buffalo in India (Dhillon et al., 1990). Neither of these studies is useful for dose-response assessment because of the atypical animal model employed, as well as other study limitations, as follows: the sample sizes in both studies were very small (three to five animals/dose group). The study by Dhillon et al. (1990) includes only one control animal, and did not conduct any gross or microscopic postmortem examination of this animal. In the study by Deore et al. (2002), the toxicological evaluations were limited to clinical signs of toxicity and glutathione peroxidase activity. Finally, each study assessed the

toxicity of selenourea at only a single dose level—and neither study identified a no-observed-adverse-effect level (NOAEL).

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL INHALATION RfC VALUES FOR SELENOUREA

Because of the lack of human or animal inhalation data, provisional RfC values for selenourea cannot be derived

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR SELENOUREA

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is **“Inadequate Information to Assess the Carcinogenic Potential” of Selenourea**. There are no human or animal studies of the potential carcinogenicity of selenourea via any route, and selenourea has not been tested for genotoxicity.

Quantitative Estimates of Carcinogenic Risk

The lack of available data precludes derivation of quantitative estimates (i.e., p-OSF and p-IUR) of cancer risk for selenourea.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2008) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). (2009) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service. Online. <http://www.atsdr.cdc.gov/toxpro2.html>.

Badiello, R; Trenta, A; Mattii, M; et al. (1967) Toxicity of selenourea. *Ric Sci* 37:452–454.

Breccia, A; Trenta, A; Badiello, RR; et al. (1966) Rate of uptake of ⁷⁵Se, as selenourea-⁷⁵Se, in rats in vivo. *Experientia* 22(7):475.

CalEPA (California Environmental Protection Agency). (2009a) Chronic reference exposure levels adopted by OEHHA. Office of Environmental Health and Hazard Assessment. Online. http://www.oehha.ca.gov/air/chronic_rels/22more.html.

CalEPA (California Environmental Protection Agency). (2009b) Toxicity criteria database. Office of Environmental Health and Hazard Assessment. Online. <http://www.oehha.ca.gov/risk/ChemicalDB/index.asp?error=Unknown+Chemical&chemname=selenourea&casnum=>.

Carr, EA, Jr; Walker, BJ. (1964) The tissue distribution of Se-75-selenouracil and Se-75-selenourea. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 248:287–295.

Cummins, LM; Kimura, ET. (1971) Safety evaluation of selenium sulfite antidandruff shampoos. *Toxicol Appl Pharmacol* 20:89–96.

Deore, MD; Srivastava, AK; Sharma, SK. (2002) Blood selenium levels during different stages of selenosis in buffaloes and its evaluation as a diagnostic tool. *Vet Hum Toxicol* 44:260–263.

Deore, MD; Dumka, V; Sharma, S; et al. (2007) Selenium toxicokinetics after oral and intravenous administration in buffalo calves. *Environ Toxicol Pharmacol* 24:55–59.

Dhillon, KS; Dhillon, KS; Srivastava, AK; et al. (1990) Experimental chronic selenosis in buffalo calves. *Ind J of Anim Sci* 60:532–535.

IARC (International Agency for Research on Cancer). (2009) Complete list of all monographs and supplements. Online. <http://monographs.iarc.fr/ENG/Monographs/allmonos90.php>. Accessed March 19, 2009.

NIOSH (National Institute for Occupational Safety and Health). (2009) NIOSH pocket guide to chemical hazards. Online. <http://www.cdc.gov/niosh/npg/npgdcas.html>.

NTP (National Toxicology Program). (2005) 11th report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Online. <http://ntp-server.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932>.

NTP (National Toxicology Program). (2009) Management status report. Online. <http://ntp.niehs.nih.gov/index.cfm?objectid=78CC7E4C-F1F6-975E-72940974DE301C3F>.

OSHA (Occupational Safety and Health Administration). (2009) Table Z-1 Limits for air contaminants. OSHA Standard 1910.1000 Table Z-1. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

U.S. EPA (Environmental Protection Agency). (1991) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (Environmental Protection Agency). (1994) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA (Environmental Protection Agency). (1997) Health effects and assessment summary tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA (Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765–17817.

U.S. EPA (Environmental Protection Agency). (2006) Drinking water standards and health advisories. Office of Water, Washington, DC. EPA 822-R-06-013. Washington, DC. Online. <http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf>.

U.S. EPA (Environmental Protection Agency). (2009) Integrated Risk Information System (IRIS). Office of Research and Development, National center for Environmental Assessment, Washington, DC. Online. <http://www.epa.gov/iris/>.

WHO (World Health Organization). (2009) Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/index.html.

Yang, G; Wang, S; Zhou, R; et al. (1983) Endemic selenium intoxication of humans in China. *Am J Clin Nutr* 37:872–881.

Yang, G, Yin, S, Zhou, R, et al. (1989) Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine [published erratum appears in *J Trace Elem Electrolytes Health Dis* 1989 Dec 3(4):250]. *J Trace Elem Electrolytes Health Dis* 3(3):123–130.