

**Public Health Goal for
ANTIMONY
in Drinking Water**

Prepared by

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the

information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 20 ppb is developed for antimony and its compounds in drinking water. Humans who ingest large amounts of antimony have severe stomach upset resulting in vomiting. Antimony fumes and dusts inhaled by workers are associated with the development of benign tumors of the lungs, dermatitis and less commonly, effects on the heart and kidneys. Laboratory animals exposed to antimony by inhalation or ingestion exhibit effects similar to those noted in humans. At the present time there is insufficient evidence to suggest that antimony compounds cause malignant tumors by inhalation in humans or animals. By ingestion, there is no evidence that antimony compounds are associated with increased development of any tumors in animals. The PHG for antimony was calculated based on minor clinical signs and a slight decrease in longevity noted in a chronic oral study conducted in rats. Other information used to develop the PHG included estimates of human exposure to antimony derived from measurements taken of levels of antimony in air, food and water. Based on this information and other assumptions used in risk assessment, OEHHA calculated a PHG of 0.02 mg/L (20 ppb) for antimony in drinking water.

INTRODUCTION

Antimony is an element present in relatively insignificant amounts in the earth's crust. Rarely found in pure form in nature, compounds are found in several types of ore and in petroleum. Uses of antimony include being alloyed with a number of metals to improve their properties. By far the most significant production of antimony is for antimony trioxide for the purpose of flame retardation. Antimony is most environmentally available as dusts which, after becoming airborne, deposit on land or in water.

Antimony has been used since antiquity as a medicinal, to induce emesis and to treat other conditions; as well as in cosmetics. However, little was understood concerning antimony toxicity until major processing of ore began at around the turn of the century and specific toxic effects were noticed in workers processing antimony. These effects included "antimony spots" a form of dermatitis, and later respiratory, pulmonary and heart effects were noted and cancer was suspected.

CHEMICAL PROFILE

Antimony is a metalloid residing in the fourth row of group 5A in the periodic table between arsenic and bismuth. It has four oxidation states: Sb(-3), (0), (+3), (+5) and two stable isotopes: 121 (57.25%) and 123 (42.75%). Metallic antimony is inert and insoluble. Antimony compounds are soluble in very strong acid and basic solutions; under neutral conditions the predominant species is Sb(OH)₆ for pentavalent forms and Sb(OH)₃ for trivalent forms. Antimony is not readily oxidizable between its two ionic forms under neutral conditions (ATSDR, 1992). A summary of the chemical and physical properties of antimony is presented in Table 1.

Table 1. Chemical and Physical Properties of Antimony (ACGIH, 1991, ATSDR, 1992)

Antimony (Sb):

Atomic number:	51
Atomic weight:	121.75
Specific gravity:	6.68
Melting point:	630.5°C
Boiling point:	1,750°C
Solubility:	Insoluble in water and cold, dilute acids

Antimony trioxide: Sb₂O₃

Solubility:	Very slightly soluble in water, soluble in acetic and hydrochloric acids
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Historically, antimony in the form of the sulfide has been used as a cosmetic for over 5,000 years, and as a medicinal since at least the 16th century, as recorded by Paracelsus in *Opera omnia* published in 1556 (McCallum, 1989). These medicinals were principally tartar emetic (antimony potassium tartrate) and lead sibocaptate used in the treatment of schistosomiasis (McCallum, 1989). These uses have been largely superseded by better compounds. However, antimony in various cosmetic preparations appears to be still used in the third world (Alkofani, *et al.* 1989).

Stibine, SbH₃, the only form of antimony in the (-3) state, is a gaseous antimony compound formed by the action of acids on metal antimony alloys or during the electrolysis of acid/base solutions where antimony is present in the cathode. Release of stibine is reported with the overcharge of lead acid batteries. Other stibine-related, reduced and methylated antimony compounds may be produced by microorganisms in the aquatic environment (ATSDR, 1992).

Pure antimony (no charge) is a silvery white, strong but brittle metal that rarely occurs naturally. Because antimony metal is too brittle to be used alone, it is used in alloys with other metals to significantly to increase their hardness, mechanical strength, corrosion resistance and electrochemical stability or decrease their coefficient of friction. Most metallic antimony produced (55%) goes into grid metal in lead storage batteries. Other uses include solder, sheet and pipe metal, type metal, castings, ammunition and pewter (ATSDR, 1992).

Antimony trioxide (+3), a white powder, is the single most important economic form. It is a stable substance which is not volatile and dissolves in water slightly and is used for its fire retardation properties in plastics, textiles, rubber, adhesives, pigments and paper. About 75% of all antimony oxide production is for this use. Other uses include as an additive in glass, pigments, stabilizers in plastics, vulcanization, ammunition primers and fireworks. Antimony tartrates are even used in the treatment of bilharziasis (schistosomiasis) (ATSDR, 1992; U.S. EPA, 1995).

Metallic antimony and antimony trioxide are by far the most prevalent in the environment and more significant from the standpoint of human exposure (ATSDR 1992).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Releases to the environment of antimony and its compounds occur from natural discharges as windblown dust, volcanic eruption, sea spray, forest fires and other natural processes. Anthropogenic sources include mining and processing of ores and the production of antimony metal, alloys, antimony oxide, compounds containing antimony and recycling and incineration of antimony containing products. Toxic Release Inventory (TRI) data (1987 to 1993) indicate that approximately 12 million pounds of antimony are released to the land and 330,000 pounds to the water from anthropogenic sources (U.S. EPA, 1995).

Air

Little antimony ore is mined in the United States (U.S.). Therefore imports of antimony ore for processing and smelter operations have been steadily increasing. Recycling operations to recover antimony from lead acid batteries, type metal and bearings have become almost as significant of a source of antimony in the U.S. as smelting. Antimony volatilizes during combustion processes, but subsequently condenses on suspended particulate matter of less than 1 μm in size. These fine particles remain suspended for long periods of time (in days) and can be widely distributed. The range of airborne antimony concentrations measured in the U.S. in remote, rural and urban areas is 0.0045 to 1, 0.6 to 7 and 0.5 to 171 ng/m^3 , respectively (ATSDR, 1992).

U. S. EPA estimated that 4,000 workers are exposed to high concentrations of antimony in processing and production facilities. The highest exposure levels reported in workplace surveys was 6.2 mg/m^3 (ATSDR, 1992).

Soil

Antimony is not especially abundant in the earth's crust and soil concentrations range from less than 1 to 8.8 ppm, with a mean of 0.48 ppm (ATSDR, 1992).

Water

As with soil, low concentrations of antimony are found in ambient water. Antimony is transported into streams mostly from soil runoff. In a survey of dissolved antimony in surface waters, only 6% of over 100 measurements were above the detection limit of 5 ppb. Mean antimony concentrations of surface and ground water at various hazardous waste sites were 27 and 35 ppb, respectively. Antimony occurs predominantly in the pentavalent state in aerobic fresh water and sea water. The trivalent state is more common under anaerobic conditions. Some soluble forms of antimony are quite mobile in water (antimony potassium oxalate and antimony potassium tartrate) and do not precipitate out into the sediment (Callahan *et al.*, 1979). Furthermore, it has been demonstrated that anaerobic microorganisms in the sediment may release methylated antimony compounds which are volatile (ATSDR, 1992).

Food

The average intake of antimony from food and water has been roughly estimated at 4.6 $\mu\text{g}/\text{day}$ (Iyengar *et al.*, 1987). More precise monitoring using isotopes indicated that the contribution from the diet is approximately 4.5 $\mu\text{g}/\text{day}$ (Cunningham and Stroube, 1987). Even at highly contaminated smelter sites, studies indicate that uptake of antimony from soil in grass and

subsequent translocation in shoots is slight (ATSDR, 1992). Studies on fish and aquatic organisms indicate that bioconcentration is low (Callahan *et al.*, 1979). There is also little indication that antimony biomagnifies through the food chain (ATSDR, 1992).

METABOLISM AND PHARMACOKINETICS

Absorption

Antimony absorption from the gastrointestinal system is relatively low. About 15 to 20% of $^{124}\text{SbCl}_3$ was absorbed by cows (Van Bruwaene *et al.*, 1982), and 15% as potassium antimony tartrate in rats (Moskalev, 1959). Syrian hamsters ranged from 7 to 15% absorbed for both valence states of antimony tartrate (Felicetti *et al.*, 1974). In a repeated dosing protocol with SbCl_3 , BALB/c mice were estimated to absorb about 7% (Gerber *et al.*, 1982). A number of factors are likely to affect the absorption of antimony including chemical form, particle size and solubility, species, age and diet.

No studies were located regarding dermal penetration of antimony compounds. Antimony or its compounds are generally not sufficiently water or lipid soluble to make this a significant avenue of exposure.

Some inhalation uptake is possible since higher antimony excretion has been measured in the urine of antimony process workers (Cooper *et al.*, 1968; Ludersdorf *et al.*, 1987). Absorption of antimony from the respiratory tract is probably a function of particle size, where smaller particles are retained and are likely to be absorbed over a period of time (ATSDR, 1992).

Distribution

Several studies that have monitored the disposition of antimony in experimental animals indicate that antimony mostly concentrates in the skeleton, liver, spleen, lung, fur/pelt, adrenal and thyroid (Westrick, 1953; Van Bruwaene *et al.*, 1982).

Hamsters were exposed to aerosols of trivalent and pentavalent radioactive antimony tartrate. Felicetti *et al.* (1974) found that 90% of initial whole body activity cleared rapidly and that most of the remaining antimony concentrated in the liver, skeleton and pelt. More trivalent antimony concentrated in the liver, while the pentavalent predominated in the skeleton. More trivalent antimony was found in red blood cells than pentavalent.

Otto *et al.* (1947) administered two trivalent antimony compounds (lithium antimony thiomalate and monosodium antimony thioglycollate) intramuscularly and two pentavalent antimony compounds (stibinose and neostibosan) intravenously to 14 male filariasis patients. Trivalent and pentavalent antimony plasma concentrations were sustained for less than 24 hours. For both trivalent compounds, antimony was found inside the red blood cells with very little in plasma, and the converse was observed for both pentavalent compounds.

Gerber *et al.* (1982) measured tissue distribution in pregnant BALB/c mice exposed to radioactively-labeled SbCl_3 in the diet and another group of mice received an intraperitoneal (ip) injection of radioactively-labeled SbCl_3 on day 12 of pregnancy. Mice receiving antimony in the diet had little of the label (7%) absorbed by the gastrointestinal tract, and the organ concentrations

were low. The highest concentration of 0.6% was in the liver, with about 0.35% in uterus and skin and 20% or lower in the thyroid, brain and blood. With ip dosing, approximately half of the label was concentrated in the intestinal tract tissues and bone surfaces. Other tissues received up to 1% of the label and even lower concentrations were found in the placenta and fetus.

Metabolism

Antimony is an element and cannot be catabolized. However, covalent interactions are possible with sulfhydryl or phosphate groups (ATSDR, 1992). There is also the possibility of valence state inter-conversions *in vivo*, but the reports have not been definitive. It is likely that if such inter-conversion occur, they are relatively insignificant.

It has been suggested that only trivalent antimony but not pentavalent antimony enters erythrocytes when patients are injected with antimony pharmaceuticals (Molokhia and Smith, 1969; Otto *et al.*, 1947, Felliciti *et al.*, 1974). Otto and Maren (1950), however, found large amounts of antimony in erythrocytes following intramuscular injection of stibanose (6 mg/kg) in 11 dogs. The authors suggest that pentavalent antimony may have been reduced to the trivalent form *in vivo*. However, a lower dose of pentavalent antimony did not enter red blood cells in the same study. In a study by Goodwin and Page (1943) using polarography to analyze the valence state of antimony in blood and urine of seven humans administered pentavalent antimony intravenously (iv), about 83.5% (average of three subjects) of the administered dose was excreted in the urine as pentavalent and 2.5% as trivalent antimony suggesting a slight reduction potential. Otto and Maren (1950) pointed out, however, that the trivalent antimony found could have been formed during sample preparation in hydrochloric acid for polarographic examination.

Antimony was found conjugated with glutathione and excreted through the bile. Rats administered antimony and depleted of their glutathione resulted in more antimony excreted in the urine and higher levels of antimony in the liver (Bailly *et al.*, 1991).

Excretion

Van Bruwaene *et al.* (1982) administered single oral doses of 21.1 mg of antimony (as $^{124}\text{SbCl}_3$), to three lactating cows. Excretion of antimony in feces totaled 82% of the dose and excretion in urine only totaled about 1% of the dose. The antimony excreted in milk was less than 0.01% of the dose.

Human subjects were administered antimony compounds ip or iv for the treatment of filariasis or schistosomiasis (Otto *et al.*, 1947; Lippincott *et al.*, 1947). Subjects administered potassium antimony tartrate excreted over half the dose within 48 hours (Lippincott *et al.*, 1947). Subjects given pentavalent antimony compounds excreted over half into the urine within 24 hours while those receiving trivalent excreted about 15% during the same period (Otto *et al.*, 1947). A woman ingested an unknown amount of antimony sulfate intended for veterinary use. Due perhaps to clinical intervention, no signs of intoxication were evident. Antimony appeared in the bile, blood and gastric fluid within 20 hours, in the urine it peaked at 20 hours and then dropped rapidly to near baseline levels within 100 hours (Bailly *et al.*, 1991).

TOXICOLOGY

Toxicological Effects in Animals

Acute Effects

Acute oral LD₅₀ values for potassium antimony tartrate (tartar emetic) in mice and rats range from 115 to 600 mg/kg (Bradley and Frederick, 1941; HSDB, 1996) whereas an oral LD₅₀ of 15 mg/kg has been reported for rabbits (HSDB, 1996). The iv and ip LD₅₀ values for antimony and its various compounds in mice, rats, guinea pigs and rabbits are generally somewhat lower ranging from 11 to 329 mg/kg (Bradley and Frederick, 1941, and HSDB, 1997). The toxicity varies among the different antimony compounds. Bradley and Frederick (1941) using antimony compounds “of high purity” with negligible arsenic content, rated antimony trioxide as among the least toxic of five inorganic antimony compounds tested by the ip route. Organic antimony compounds like the tartrate appear to be more toxic than inorganic forms, but this may be due to the higher solubility of the organic forms increasing their apparent uptake.

Antimony is well known for its emetic effects. Flury (1927) determined the most effective emetic doses of six antimony compounds (antimony trioxide, antimony pentoxide, sodium antimonate, potassium antimontate, sodium *meta*-antimonate and potassium antimony tartrate) in dogs. Potassium antimony tartrate was the most effective at 33 mg/kg (about 12 mg/kg). Cats were sensitive to the emetic effects of potassium antimony tartrate at doses of 4.3 or 5.2 mg/kg (Flury, 1927).

Subchronic Effects

Flury (1927) extended his studies by dosing rats (two per test group) to potassium antimony tartrate, antimony trioxide and sodium *meta*-antimonate (NaSbOC₄H₄O₆) in food for 131 days. Dosing was begun in a graduated fashion for the first two compounds, starting with 1 mg/day and increasing over 86 days to 200 mg/day. The last compounds was given from 3 to 1,000 mg/day in a similar pattern. No effects were seen even at the highest doses for antimony trioxide and sodium *meta*-antimonate, but potassium antimony tartrate caused a systemic deterioration and death at 200 mg/day. This corresponds to 485 mg/kg-day based on mean body weight of 155 grams as stated by the author.

Rats were administered potassium antimony tartrate (8 mg/kg-day) or finely granulated antimony metal (8 or 40 mg/kg-day) in the diet for 4 to 12 months, or potassium antimony tartrate or antimony metal for six months with doses increasing up to 100 and 1,000 mg/kg-day with the final dose continued for an additional month (Bradley and Fredrick, 1941). All animals maintained normal growth rates. Pathologic changes were evident upon sacrifice and these included congestion and polymorphonuclear leukocyte infiltration in the liver, congestion with glomerulonephritis and tubular necrosis of the kidney, congested viscera with hemorrhages in the small intestine and congestion of the spleen.

In a recent 90-day study (Zeneca, 1997a), twelve male and female Alpk:AP_iSD (Wistar-derived) rats were fed diets containing 0, 1000, 5000 or 20000 ppm antimony trioxide for 90 days. Mean doses rates in mg antimony trioxide/kg-day for males were: 84.2, 421.2 and 1685.9. Female mean

doses were 97.1, 484.1 and 1878.9 mg antimony trioxide/kg-day. Exposure to antimony trioxide resulted in no mortalities or treatment-related changes in body weight, food consumption, or hematology. At the high dose, elevated levels of alanine aminotransferase (females), aspartate aminotransferase (females) and creatine kinase, plasma triglyceride (males) and plasma cholesterol levels (females) were statistically significant. Absolute and relative liver weights and the number of pituitary cysts were increased in both sexes at the high dose. The authors concluded that the effects noted in the study at the high dose had no toxicological significance.

Genetic Toxicity

Antimony trichloride, antimony pentachloride and antimony trioxide were determined to be mutagenic in the *Bacillus subtilis* (H17 and M45) recombinant assay (Kanematsu and Kada, 1978; Kanematsu *et al.*, 1980). Antimony trioxide was not reported to be mutagenic at concentrations up to 5mg/plate when tested in *S. typhimurium* strains TA98, 100, 1535, 1537 and *E. coli* WP2P and WP2P uvrA with or without S9 (Zeneca, 1996a). Mouse lymphoma cells (L5178Y TK+/-) were exposed to 6.0 to 50 µg/ml of antimony trioxide in the presence or absence of S9 (Zeneca, 1996b); no mutagenic potential was indicated. Potassium antimony tartrate, and sodium antimony tartrate and antimony trioxide induced chromosomal aberrations in cultured human leukocytes and lymphocytes (Paton and Allison, 1972; Hashem and Shawki, 1976; Zeneca, 1996c). Piperazine antimony tartrate and potassium antimony tartrate induced chromosomal aberrations in bone marrow cells of rats injected ip with 2, 8.4 or 14.8 mg/kg of tartar emetic, and 1, 10 or 19.1 mg/kg of biharcid (piperazine antimony tartrate El Nahas *et al.*, 1982). Antimony trioxide suspended in water was given by gavage to mice and monitored for chromosomal aberrations in the bone marrow and clastogenic effects (Gurnani *et al.*, 1992). Chronic exposure daily to 400, 667.67 and 1,000 mg/kg-day for periods up to 21 days induced chromosomal aberrations, but no clastogenic effects. In other mouse bone marrow micronucleus tests with antimony trioxide, no clastogenic effects were observed either with one dose of 5000mg/kg, or with repeated dosing at 400, 667, and 1000 mg/kg-day for 7, 14, 21 days (Zeneca, 1996d, Zeneca, 1997b).

Developmental and Reproductive Toxicity

Potassium antimony tartrate was orally administered to four-year-old ewes at of 2 mg/kg for 45 days or throughout gestation. All ewes administered antimony fed gave birth to normal, full-term lambs. No adverse effects were noted in ewes at necropsy (James *et al.*, (1966). In another study, antimonial drug RL-712 (antimony dextran glycoside) was administered through five intramuscular injections of 125 or 250 mg/kg between days 8 and 14 of gestation. No abnormalities were reported (Casals, 1972).

Hodgson *et al.* (1927) studied the effects of injected sodium antimony tartrate (2.2 mg/kg) using 9 to 16 doses of 50 mg of an unknown organic antimony compound over 16 to 38 days in rabbits. They also injected English white mice (male and female) with 30 to 39 doses of 10 mg of another unknown organic antimony salt over 60 to 77 days. Both female rabbits and mice were reported to exhibit effects on contraception, abortion and fetal damage but no effects on sterility were noted on male mice with these unknown antimony salts.

Rossi *et al.* (1987) reported no gross abnormalities to rat fetuses after exposure of dams to 0.1 and 1 mg/dL of antimony trioxide in drinking water from the first day of pregnancy until weaning. In the Gerber *et al.* (1982) study described previously, no effect was noted on fetuses.

Belyaeva (1967) investigated the reproductive effects of antimony trioxide in female rats following repeated inhalation exposures to 250 mg/m³ dust over a two-month period. Sterility and fewer offspring were noted in exposed rats when compared to the control group.

Chronic Toxicity and Carcinogenicity

Two important chronic studies were conducted by Schroeder *et al.* (1968 and 1970) with potassium antimony tartrate administered by drinking water to animals. Male and female Charles River CD mice received 0 or 5 ppm antimony in drinking water from weaning until death (Schroeder *et al.*, 1968). Mean body weight and water consumption for mice was 0.03 kg and 5 mL/day, respectively as estimated by U.S. EPA (1992b). Based on the reported data and U.S. EPA's estimates, an average dose of 0.83 mg/kg-day antimony can be estimated. Antimony had no effect the first year, but resulted in weight loss in male mice after 18 months ($p < 0.025$) and decreased weight gain in females measured at 12 and 18 months ($p < 0.005$). In female mice, antimony appeared to shorten the median survival by 49 days, and at the 75% survival level the difference was 85 days when compared with controls. However no significant differences were noted in the overall survival rates. Male mice' survival patterns essentially mirrored that of controls. No increases in tumor incidence were noted in exposed animals.

A similar study was performed in groups of 50 male and female Long-Evans rats receiving 0 or 5 ppm in drinking water from weaning until death (Schroeder *et al.*, 1970). An average daily dose of 0.43 mg/kg-day was estimated by U.S. EPA (1992b) based on a mean body weight of 0.35 kg and a water consumption of 30 mL/day. Unlike the results in mice, there was no significant effect on body weight gains, but there was a significant difference in longevity. Mean longevity in days plus or minus (\pm) standard error was 1,160 \pm 27.8 for control males, 1,304 \pm 36 for control females, 999 \pm 7.8 for treated males and 1,092 \pm 30 for treated females. There were negligible effects on body weight. Serum cholesterol levels were increased in male rats but decreased in female rats. Fasting glucose levels were not significantly different in either males or females but non-fasting glucose levels were lower in exposed males and females. Deposition of antimony in kidney, liver, heart, lung and spleen was also observed which increased with age. No increase in tumor incidence was noted. An epidemic of viral pneumonia during the experiment was reported for this colony of rats, but the investigators claimed that they saved enough of the animals to make the results valid.

Antimony compounds might be carcinogenic by the inhalation route. Watt (1983) reported that antimony trioxide induced fibrosis and neoplasms in female rats when inhaled at levels close to the threshold limit value (TLV). Female SDF rats and S-1 miniature swine were exposed to antimony trioxide dust at 1.6 \pm 1.5 or 4.2 mg/m³ for six hours/day, five days/week, for one year followed by another year of observation. Lungs of exposed animals of both species were reported to be mottled and heavier than non-exposed animals and these effects were related to increases in exposure level and exposure time. Only female rats showed neoplasms and mostly at the higher dose (62% incidence). Neoplasms were identified as scirrhous carcinomas, squamous cell carcinomas or bronchoalveolar adenomas.

Groth *et al.*, (1986) exposed three groups (90 males or females/group) of Wistar rats via inhalation to antimony trioxide [mean time-weighted average (TWA) = 45.0 and 46.0 mg antimony] and to antimony ore concentrate (mean TWA = 36.0 and 40.1 antimony ore/m³) or to filtered air for one year followed by about one-half year of observation. Efforts were made to assure as uniform a particle size as possible although the antimony ore was larger in aerodynamic mass median

diameter. The authors noted lung neoplasms (squamous cell carcinomas, bronchioalveolar adenomas, bronchioalveolar carcinomas or scirrhous carcinomas) in both treated female groups, specifically 27% in the antimony oxide and 25% in antimony ore group, but none in the male treated groups. Analysis of antimony content of the lungs of treated animals demonstrated that antimony oxide-exposed males had nearly two times higher levels of antimony than the corresponding females, and the antimony content of oxide-exposed animals was five times more than ore-treated animals.

Subchronic and chronic inhalation toxicity tests were performed with several doses of antimony trioxide dust on Fisher 344 rats (Newton *et al.*, 1994). For the subchronic study the doses were 0.025, 1.08, 4.92 or 23.46 mg/m³ for six hours/day, five days/week for 13 weeks. The chronic study was conducted at levels of 0.006, 0.51 or 4.5 mg/m³, five days/week, for 12 months followed by a one-year observation period. Except for corneal opacities following two weeks exposure, no other clinical effects was noted for either study. Microscopic changes were noted in the lungs of subchronic and chronically exposed animals. These were limited to subacute or chronic interstitial inflammation, granulomatous inflammation, fibrosis and other inflammatory indications. Three carcinomas of the lung were reported, one in a treated male and female and one in the male control group, all within historical incidences.

Toxicological Effects in Humans

Acute Effects

Several incidences of antimony poisoning have been reported with suicide attempts, inadvertent poisonings and with the treatment of leishmaniasis. Dunn (1928) reported an incident where workers began to vomit upon ingestion of approximately 0.53 mg/kg (based on a 70 kg man) after lemonade was contaminated with antimony tartrate. Four adults were admitted to a hospital suffering from severe abdominal cramps, nausea, continuous vomiting and water diarrhea after ingestion of cake in which “tarter emetic” (antimony potassium tartrate) was substituted for cream of tartar. Moderate leukocytosis and hemoconcentration and decreased extracellular volume were noted. All patients exhibited anorexia and asthenia, but no other pathologic signs were found in three patients. Electroencephalogram rhythms were abnormal for two patients. The remaining patient, a 93-year-old man, exhibited severe gastrointestinal bleeding and died from cardiac and respiratory failure. Estimated dose of tarter emetic was 850 mg per person (Lauwers *et al.*, 1990). Kaplan and Korff (1937) reported several instances of “food poisoning” that were traced to antimony extracted by acid contents from enamel-coated vessels. Humans surviving acute exposures appeared to have no lasting sequelae.

Subchronic Effects

Effects on antimony workers have been primarily signs of lung irritation, gastric irritation, pneumoconiosis, fibrosis, metal “fume” fever, cardiac effects and dermal reactions. Antimony dermatitis, commonly known as “antimony spots,” has been known as long as antimony processing has occurred (MacCallum, 1989; Oliver, 1933). Lesions appear on the forearms, wrists, thighs, lower legs and in the flexures, the trunk, back of neck and scrotum but they do not occur on the face, hands or feet. These occur mainly in summer months in workers working in the vicinity of furnaces. White *et al.* (1993) described this dermatitis in three workers melting antimony in the manufacture of brazing rods who were exposed to antimony fumes and antimony

trioxide. Beside skin lesions, nose bleeds were also reported. The TWA was below Occupational Safety and Health Administration (OSHA) limits but was reported to exceed the OSHA Permissible Exposure Limit (PEL).

Antimony pneumoconiosis was described by Karajovic (1958) in a population of antimony miners and smelters in Yugoslavia based on diffuse x-ray opacities. Other respiratory effects noted in workers include impaired airway obstruction, bronchospasm, hyperinflation, coughing and wheezing, although these effects could have been due to other compounds (Cooper *et al.*, 1968; Potkonjak and Pavlovich, 1983).

Cardiac effects have been noted in some studies. Brieger *et al.* (1954) examined workmen in a plant where antimony trisulfide was used in the manufacture of grinding wheels. Antimony levels throughout the plant ranged from 0.58 to 5.5 mg/m³ (0.4 mg/kg antimony trisulfide). About 10% of exposed workers had elevated blood pressure, half of those monitored showed significant changes in their electrocardiograms (EKGs), mostly in the T-wave, and an increase in ulcers was also noted in plant workers.

Another study (Chulay *et al.*, 1985) followed 59 Kenyans treated with 10, 20 or 40 to 60 mg/kg-day of sodium stibogluconate for leishmaniasis. Dose-related increases in EKG abnormalities were noted following 65 courses of antimony treatment over four months. The incidences of EKG abnormalities were 22% (2/9) at 10 mg/kg-day; 52% (25/48) at 20 to 30 mg/kg-day; and 100% (8/8) at 40 to 60 mg/kg-day. The frequency of EKG abnormalities increased in individuals with duration of treatment.

Schroeder *et al.* (1946) administered sodium antimony bis(pyrocatechol-2,4-sulfonate) (Stibophen NF or fuadin) intramuscularly and potassium antimony tartrate by iv daily or on alternate days for about one month to patients treated for schistosomiasis. Estimated doses ranged from 0.24 to 0.89 mg/kg-day. Examination of 315 EKGs from 100 patients revealed that the EKGs did not show major changes indicative of damage.

Developmental and Reproductive Toxicity

Belyaeva (1967) reported disturbances in menstruation and an increase in the number of spontaneous abortions in women exposed to airborne antimony in the workplace. No obvious developmental effects were observed in the children of these women.

Chronic Toxicity and Carcinogenicity

Potkonjak and Pavlovich (1983) reported on the health of 51 workers from a smelting plant exposed to dust of predominantly antimony oxide for from 9 to 31 years (mean 17.91). Measured dust concentration was at 86 mg/m³ (maximum); 80% of the particles were below 5 µm in size. They found definite pulmonary changes (pin-point opacities) characteristic of pneumoconiosis, which they designated as antimonosis. These changes were evident in all workers in the study. Other respiratory signs were evident; chronic coughing, conjunctivitis and upper airway inflammation. No other evidence of systemic toxicity was noted including no electrocardiograph disturbances. No malignancies were noted in the study population.

A survey of mortality at an antimony smelter in England indicated that workers employed prior to 1960 had double the incidence rate of lung cancer over a control worker population (Jones, 1994).

The cohort recruited after 1960 showed either the same or diminished cancer rate levels over the control population. The investigator attributes the result to changes in the processing of antimony which changed from primarily production of antimony alloy to that of antimony trioxide. During this period the type of ore used had also changed to a type that contained more antimony and (implied) less arsenic. The influence of smoking on incidence rates was not accounted for and cannot be ruled out, nor can changes in exposure levels. Jones (1994) proposed that the excess of cancers can be attributed to arsenic exposure and possibly other carcinogens which diminished after 1960 when the type of processing changed.

A recent mortality study, with a large cohort (1,014 men) from a Texas antimony smelter, was conducted by Schnorr *et al.* (1995). Men employed from 1937 to 1971 were evaluated for lung cancer mortality, EKG abnormalities, and heart and lung disease. The population was mostly Hispanic which led to some difficulty in finding appropriate reference groups for comparisons. The results showed slightly elevated rates for lung cancer deaths (1.39 SMR) against an Hispanic surname group (but 0.52 against a white population), ischemic heart disease (0.91, 1.22 and 1.49 SMR against three different comparison groups), and pneumoconiosis or other lung disease (1.22 SMR). The ore smelted was derived primarily from Mexico and other South American countries and the process changed little from when the smelter opened in 1930 to 1979. No exposure data were available until National Institute of Occupational Safety and Health (NIOSH) surveys in 1975 and 1976 showed the geometric means of 50 personal samples were 551 and 747 $\mu\text{g}/\text{m}^3$, respectively. Both mean values are above the OSHA standard of 500 $\mu\text{g}/\text{m}^3$. There was also a positive trend toward increasing lung cancer rates with duration of employment.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The most relevant studies for risk extrapolation for drinking water exposures are the chronic drinking water studies conducted by Schroeder and colleagues (1968, 1970). Unfortunately, only one dose was used for either of the studies conducted in mice and rats and the antimony compound used was the potassium antimony tartrate (primarily because of its greater water solubility). A potentially confounding factor is the epidemic of viral pneumonia reported in the Schroeder *et al.*, (1970) study in rats, since this would influence survival rates which is the critical endpoint for this study. Nevertheless, the antimony may still have resulted in shortened lifespan as suggested in the mouse study.

Because the estimated dose to rats is lower than the mice (0.43 mg/kg-day for rats compared to 0.83 mg/kg-day for mice) and the lifespan was significantly shorter for both male and female rats, the rat study is selected as the most sensitive indicator of toxicity to antimony. In this study (Schroeder *et al.*, 1970), 50 male and female Long-Evans rats were exposed to 0 or 5 mg/L in drinking water from weaning until death (over 1,000 days). Effects noted in treated groups include decrease in longevity, and altered blood glucose and serum cholesterol levels. Based on these effects, a lowest-observed-adverse-effect-level (LOAEL) of 0.43 mg/kg-day is identified.

Carcinogenic Effects

There was no evidence that antimony or its compounds are carcinogenic by the oral route as evidenced by the Schroeder *et al.* (1968 and 1970) studies. U.S. EPA has stated that there is

inadequate evidence for potential of antimony to cause cancer from drinking water (U.S. EPA, 1995). Even by the inhalation route, the evidence is equivocal for antimony carcinogenicity. For the animal studies it is clear that incidence of lung tumors do not correlate with the concentration antimony, and appear in only one gender and species. For worker exposures (Jones, 1994), an elevated incidence of lung cancer was reported for exposures prior to 1960 and not thereafter. This cannot be solely explained due to decreases in airborne concentrations of antimony, because the changes in processing did not necessarily change absolute amounts of antimony dust in the environment. Rather it seems that the changes in processing technology (including ore composition) probably altered the form of airborne dust. Schnorr *et al.* (1995) reported a slight increase in lung cancer rate in an antimony oxide processing plant where little change in processing technology had occurred. Therefore, the epidemiological evaluations have not confirmed that antimony or its forms are directly carcinogenic. Nevertheless even if antimony trioxide is carcinogenic by the inhalation route, it would likely not be relevant for assessing drinking water exposure since the mechanism for inhalation toxicity appears to be related to the localized action of the dust particles.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, in food preparation and for bathing or showering. It is also used in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures. Based on the foregoing information on antimony and its compounds, it can be assumed that these contaminants are not volatile or dermally permeable. Therefore, we conclude that it is unlikely that significant exposures will occur from inhaling or from direct contact, but rather the primary route of exposure will be from drinking water.

The following general equation for noncarcinogenic endpoints is used for calculating the public health-protective concentration (C) of antimony (and its compounds) in drinking water (in mg/L):

$$C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}} = \text{mg/L}$$

where,

- NOAEL = No-observed-adverse-effect-level (a LOAEL of 0.43 mg/kg-day was used in the absence of an NOAEL)
- RSC = Relative source contribution of 40% (0.4)
- UF = Uncertainty factor of 300 (3-fold for LOAEL to NOAEL conversion and a non-severe endpoint, 10-fold for inter-species variation and 10-fold for variation in the human population)
- L/day = Volume of daily water consumption for an adult (2 L/day)
- BW = Body weight for an adult male (70 kg).

There are two factors in these equations which consider exposure. The relative source contribution (RSC) is a factor which is based on an estimate of the contribution of drinking water relative to other sources of exposure to the chemical contaminant. The other sources are food and air. In this case, food is the most significant source of exposure in addition to drinking water. U.S. EPA has selected an RSC of 40% (U.S. EPA, 1995). This is based on the assumption that drinking water

contributes to 40% of the exposure, 50% comes from the diet and 10% is assumed to be contributed by air. These intakes are based on the dietary levels of antimony of 4.5 µg/day estimated from Iyengar *et al.* (1987) and Cunningham and Stroube (1987). Water intakes were based on measured nation-wide concentrations of 0.6 to 4.0 µg/L and inhalation intakes of 0.6 µg/day as based on reports from U.S. EPA's Office of Air Quality and Planning and Standards (U.S. EPA 1991). We agree with U.S. EPA's rationale and also select 40% as the RSC.

The other exposure factor in the equation is the water intake in L/day. This factor represents the amount of tap water that an individual consumes as drinking water, as well as water mixed with beverages and used in cooking. The adult default value for this factor is 2 L/day. For children 1 L/day is used. Since the study used is a lifetime exposure, the water consumption value will be based on an adult intake assumption.

Because an NOAEL cannot be determined directly from the Schroeder *et al.* (1970) study, an NOAEL can be estimated by the common risk assessment practice of selecting the LOAEL and applying an additional UF (usually 10). In the case of antimony, the endpoints of concern are of less public health concern than terata, reproductive effects, neurological effects or other adverse effects that severely impair organ functions. Furthermore, potassium antimony tartrate used in this study is anticipated to be more toxic than the more insoluble antimony forms expected to be present in the water. For these reasons, a UF of three (3) is used to account for the estimation of a NOAEL from an LOAEL, for relatively non-severe endpoints. An additional 10-fold UF was applied for inter-species extrapolation and a 10-fold UF was applied to account for human variability.

Therefore,

$$\begin{aligned} C &= \frac{0.43 \text{ mg/kg} \times 70 \text{ kg} \times 0.4}{300 \times 2 \text{ L/day}} \\ &= 0.02 \text{ mg/L} = 20 \text{ ppb.} \end{aligned}$$

Therefore, OEHHA calculates a PHG of 0.02 mg/L (20 ppb) for antimony in drinking water.

RISK CHARACTERIZATION

The PHG of 20 ppb is about three times higher than the MCL and Maximum Contaminant Level Goal (MCLG) of 6 ppb established by U.S. EPA's National Primary Drinking Water Regulations (U.S. EPA, 1995 based on U.S. EPA, 1992a,b). The selected study remains the same, but some assumptions used in calculating the PHG are different than those U.S. EPA used to determine the MCL and MCLG.

The use of the LOAEL from the Schroeder (1970) study, selected as the critical study for PHG determination, might overestimate the adverse effects presented to humans upon ingestion of water containing antimony at the PHG. The study is limited in that it was conducted at one dose, nevertheless the resultant effects are minimal. Considering that current testing guidelines do not require animals to be followed to their natural death, the decrease in longevity (a critical effect) probably would not be detected in chronic studies conducted under present day protocols which terminate the study after 24 months. Changes in cholesterol or glucose levels are difficult to interpret unless a disease state can be identified, and in this case, none was. In addition, some of

these animals could have been more susceptible to the toxic effects of antimony based on their weakened condition from contracting pneumonia.

The form of antimony used in this study, antimony potassium tartrate, is the most absorbable form of antimony and thus probably would not reflect the absorbability of waterborne compounds of antimony (hydrated pentoxides and trioxides). The limited absorbability of the environmental antimony compounds would limit the potential toxicity of these forms and resultant risks when compared with the more absorbable forms. Current U.S. EPA policy (Dourson *et al.*, 1996) suggests using a three-fold safety factor when estimating an LOAEL from an NOAEL for effects of this magnitude. Antimony appears to directly effect the organism at the site of contact and not necessarily through the disposition of antimony within the organism. In considering the limitations of the data and the lack of severity of the endpoint, an uncertainty factor of three (3), rather than the default value of 10, was used to estimate an NOAEL from this LOAEL.

An additional uncertainty factor of 10 is applied to the PHG calculation for antimony to account for estimates that humans could be 10 times more sensitive than animals to the adverse health effects of antimony compounds. In animal acute and chronic ingestion studies, and in the human case reports described previously, gastric upset and emesis is one of the most consistent signs and also one of the most sensitive signs of toxicity. Emesis, can be considered a defensive response as it prevents further antimony contact with the intestinal tract. Humans appear to be particularly sensitive to the emetic effects of antimony at a dose as low as 0.53 mg/kg (Dunn, 1928) while, the most sensitive animal, the cat, responded at 4.3 mg/kg (Flury, 1927). This in itself reflects a potential 10-fold greater sensitivity in human response to antimony ingestion compared to experimental animals.

The shortened life-span observed in rats in the Schroeder *et al.* (1970) study might have been the result of an increased susceptibility of the intestinal tract of aged rats to the toxic effects of antimony. When the intestinal tract deteriorates with age, toxicity from antimony is more likely. As in the case of the 93-old-man (Lauwers *et al.*, 1990), who succumbed to the same dose of antimony tartrate when his younger companions did not, it might be a result of this greater sensitivity. An additional 10-fold UF is applied to account for human variability. This UF for human variability appears to be supported and could reflect the range of human response to this agent.

There is also uncertainty surrounding the source contribution factor which was based on nationwide measured levels of antimony in food, water and air. However, it is unlikely that the ratio of source contribution would change very much unless humans are residing close by an antimony smelter.

OTHER REGULATORY STANDARDS

A maximum airborne concentration (MAC) TWA 0.1 mg/m³ was established after some health studies of the industry. From 1948 to 1963, the TLV-TWA was 0.5 mg/m³ for antimony and this was later extended to all antimony compounds (ACGIH, 1991). This 0.5 mg/m³ level is also the PEL adopted by OSHA and NIOSH and is standard for all reporting countries (RTECS, 1997). Most regulations concerning antimony were formulated to protect workers in either refining or alloy production (ACGIH, 1991). U.S. EPA's MCL for antimony is 0.006 mg/L (6 ppb) (U.S. EPA, 1995) and the California MCL is also 6 ppb.

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