

Antimony in Drinking-water

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

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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.

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The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

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Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

AAS	atomic absorption spectrophotometry
APT	potassium antimony tartrate
AST	sodium antimony tartrate
ATO	antimony trioxide
ATP	adenosine triphosphate
CAS	Chemical Abstracts Service
EPA	Environmental Protection Agency (USA)
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer
IUCLID	International Uniform Chemical Information Database
LD ₅₀	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

<i>Compound</i>	<i>CAS No.</i>	<i>Molecular formula</i>
Antimony	7440-36-0	Sb
Antimony trioxide (ATO)	1309-64-4	Sb ₂ O ₃
Potassium antimony tartrate (APT)	28300-74-5	KSbOC ₄ H ₄ O ₆
Sodium antimony tartrate (AST)	34521-09-0	NaSbOC ₄ H ₄ O ₆

1.2 Physicochemical properties (Wiberg, 1985; HSDB, 1990)

<i>Property</i>	<i>Sb</i>	<i>Sb₂O₃</i>	<i>KSbOC₄H₄O₆</i>	<i>NaSbOC₄H₄O₆</i>
Melting point (°C)	630.5	655	100	–
Boiling point (°C)	1635	1425	–	–
Density at 20 °C (g/cm ³)	6.691	–	2.6	–
Vapour pressure at 886 °C (kPa)	0.133	–	–	–
Water solubility (mg/litre)	insoluble	0.017 ¹	readily soluble	readily soluble

¹ Kuroda et al. (1991).

1.3 Organoleptic properties

APT is odourless and has a sweet metallic taste (Hawley, 1981). ATO is both odourless and tasteless.

1.4 Major uses

Elemental antimony is an inflexible metal and therefore has few technical uses. However, it forms very hard and technically interesting alloys with copper, lead and tin.

ATO as a technical product or in technical processes can serve as a flame retardant, as a turbidifier in white enamel and as an initiator or additive in the production of polyethylene terephthalate.

Soluble pentavalent antimony (antimony(V)) compounds (sodium stibogluconate, stibosamine) are used as specific therapeutics against different forms of leishmaniasis and are physiologically tolerated more than trivalent antimony (antimony(III)) compounds (Winship, 1987).

APT (tartar emetic) has been used to induce vomiting in poisoning cases, and antimony compounds such as piperazine antimony tartrate were used as drugs against bilharzia.

1.5 Environmental fate

The emission of antimony into the human environment appears to be exclusively the result of human activity. Most emitted antimony is in the form of ATO, which is released as a result of coal burning or with fly ash when antimony-containing ores are smelted (Nriagu & Pacyna, 1988). Approximately 6400 tonnes of antimony are transported annually to oceans (Bowen, 1979).

The chemical behaviour of antimony is as complex as that of arsenic, its neighbour in the periodic table (Wiberg, 1985). It is speculated that antimony could be a natural co-contaminant with arsenic in some drinking-waters (Gebel, 1999b). Soluble forms of antimony (and arsenic) tend to be quite mobile in water, whereas less soluble species are adsorbed onto clay or soil particles and sediments, where they are mainly bound to extractable iron and aluminium (Crecelius et al., 1975). Although few data address the speciation of antimony in water, those that are available together with thermodynamic predictions indicate that the most favoured form in water will be the pentavalent oxo-anion, $\text{Sb}(\text{OH}_6)^-$ (Mohammad et al., 1990; Cotton et al., 1999).

2. ANALYTICAL METHODS

Antimony can be determined by graphite furnace atomic absorption spectrophotometry (AAS), with a detection limit of 0.8 $\mu\text{g}/\text{litre}$ (EPA Method 204.2). More sensitive determination is possible using inductively coupled plasma mass spectrometry, with detection limits of 0.1 $\mu\text{g}/\text{litre}$ in the presence of three other metals (ICI-Technology, 1996) and 0.02 $\mu\text{g}/\text{litre}$ (EPA Method 6020). Antimony(V) can be differentiated from antimony(III) using *N*-(*p*-methoxyphenyl)-2-furylacrylohydroxamic acid and can be determined separately by electrothermal AAS at concentrations down to 0.01 μg of antimony per litre (Abbassi, 1989).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Atmospheric antimony concentrations of about 0.2 ng/m^3 were reported for the Alps at Jungfrauoch, Switzerland (Dams & de Jonge, 1976). In more densely populated areas of Europe, levels between 0.6 and 32 ng/m^3 were determined in the 1980s (Hurtig, 1990). Concentrations of antimony in air are considered to be lower today because industrial emissions have been significantly reduced by the introduction of dust filters. At present, abrasion of antimony (and other metals) from brakes, tires and street surfaces as well as emission of aerosolic antimony in vehicle exhaust are the main sources of antimony in urban fine dust (Stechmann, 1993). In Göttingen, a medium-sized city in Germany, approximately 176 kg of antimony are emitted annually from the above sources (Plessow et al., 1997).

Exposure of the typical urban population to antimony from air is estimated to be between 60 and 460 ng/day per person (Slooff, 1992).

3.2 Food

Antimony does not bioaccumulate, so exposure to naturally occurring antimony through food is very low. Antimony is present in food, including vegetables grown on antimony-contaminated soils, mostly in the low $\mu\text{g}/\text{kg}$ wet weight range or less.

3.3 Water

Concentrations of antimony in groundwater and surface water normally range from 0.1 to 0.2 $\mu\text{g}/\text{litre}$ (Bowen, 1979). Marine antimony concentrations are approximately 0.15 $\mu\text{g}/\text{litre}$ (Andreae et al., 1981). Antimony is not likely to occur at significantly higher concentrations in natural waters, except in those areas affected by acid mine drainage.

Domestic wastewater is practically free of antimony, in contrast to wastewater from glass or metal processing enterprises (Enders & Jekel, 1994).

Antimony at one time was considered as a possible replacement for lead in solders, but there is no evidence of any significant contribution to drinking-water concentrations from this source. The concentrations in drinking-water appear to be less than 5 $\mu\text{g}/\text{litre}$ (US EPA, 1984; Longtin, 1985).

3.4 Estimated total exposure and relative contribution of drinking-water

Daily oral uptake of antimony ranges from 10 to 70 μg and therefore appears to be significantly higher than uptake via inhalation. Total exposure from environmental sources (air, soil) and food/drinking-water is very low compared with exposure in the workplace (Gebel, 1999a).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The solubility of ATO in synthetic gastric juice has been shown to be 20 mg/litre after 24 h (DuPont, 2001). However, studies on absorption indicate that it is relatively low. Even in soluble forms, antimony is not readily absorbed from the gastrointestinal tract, irrespective of the valence state (Felicetti et al., 1974). Absorption rates between 5% and 20% have been observed in animals (Moskalev, 1959; Waitz et al., 1965; Van Bruwaene, 1982). Examination of four persons after involuntary acute intoxication with APT revealed an absorption rate of 5% (Iffland & Bösche, 1987; Lauwers et al., 1990).

In experimental animals, after absorption, antimony is bound to the red blood cells (Molokhia & Smith, 1969; Felicetti et al., 1974; Gerber et al., 1982; Dieter et al.,

1991) and then transported mainly to the spleen, liver and bone (Casals, 1972) and to some extent into skin and hair (Felicetti et al., 1974; Berman et al., 1988). It is unknown to what extent inorganic and organic antimony(V) may be reduced to antimony(III) *in vivo*. Antimony(III) in the form of antimony trihydroxide (Sb(OH)₃) can easily pass through cell membranes due to its lack of electrical charge. This seems to be the reason for its longer elimination half-time (94 h vs. 24 h) compared with antimony(V) (Stemmer, 1976; Gebel, 1997).

Although there appear to be few data available on the *in vivo* reduction of antimony(V) to antimony(III), it appears that conditions under which this may occur are not the normal physiological conditions found in cells and tissues. Only special conditions of low pH may facilitate the change, and, under normal circumstances, the bulk of any ingested antimony(V) will not be reduced. However, this may occur to a small extent, and the view expressed recently (Frezard et al., 2001; Shaked-Mishan et al., 2001) is that this reduction may be important for the antileishmanial activity of meglumine antimoniate, reduction of antimony(V) to toxic antimony(III) occurring in specific organelles of the leishmania species.

Sb(OH)₃, like As(OH)₃, readily reacts with thiol groups. Both trivalent metal species accumulate *in vitro* in cultured mammalian cells and seem to exert mutually additive or sub-additive toxicity in combined incubation (Felicetti et al., 1974; Buchet et al., 1980; Bailly et al., 1991; Gebel, 1997, 1998; Schaumlöffel & Gebel, 1998). Elimination of antimony(III) and arsenic(III) from cells follows the same ATP-dependent mechanisms and explains the cross-resistance between both trivalent elements in bacterial and mammalian cells (Rosen et al., 1988; Mukhopadhyay et al., 1996; Wang et al., 1996).

Antimony is not an essential element in plants or animals (Fowler & Goering, 1991).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Oral LD₅₀ values reported for APT in experimental animals range from about 115 mg/kg of body weight in rabbits and rats to 600 mg/kg of body weight in mice. ATO is practically non-toxic (LD₅₀ > 20 000 mg/kg of body weight) due to its extremely low solubility in water (Gebel, 1999a).

5.2 Short-term exposure

5.2.1 APT

In a 14-day NTP drinking-water study, APT was tolerated by rats and mice in doses up to 168 and 273 mg of antimony per kg of body weight per day, respectively. Lesions of the forestomach and liver were observed at a dose of 407 mg/kg of body weight per day (NTP, 1992). In contrast, APT administered intraperitoneally to rats and mice in 16-day toxicity studies provoked clear signs of toxicity. In rats, increased

mortality and histopathological lesions in liver and kidney were produced generally at the highest dose levels (11 and 22 mg of antimony per kg of body weight per day). In mice, increased mortality and minimal to mild hepatocellular necrosis were observed at 50 and 100 mg of antimony per kg of body weight per day (NTP, 1992). The large differences in toxicity between the intraperitoneal and the oral exposure routes were due to significant differences in systemic availability and absorption of APT (Lynch et al., 1999).

In a 90-day NTP study in which groups of rats and mice were intraperitoneally injected with APT at doses equal to 0, 1.5, 3.0, 6.0, 12 or 24 mg of antimony per kg of body weight per day, rats were about 4 times more sensitive than mice to APT treatment. They exhibited adverse effects (increased mortality, decreased body weight) at 12 and 24 mg/kg of body weight per day. At 6.0 mg/kg of body weight per day (males) and 12 mg/kg of body weight per day (females), hepatocellular degeneration and/or necrosis occurred in association with dose-related increases in the activities of sorbitol dehydrogenase and alanine aminotransferase. The NOAEL of antimony (APT) resulting from intraperitoneal injection was 3.0 mg of antimony per kg of body weight per day. This would be equivalent to an oral NOAEL of about 15 mg of antimony per kg of body weight per day, assuming 20% absorption (NTP, 1992).

Poon et al. (1998) administered APT in drinking-water for 90 days to Sprague-Dawley rats (15 per sex per dose) at concentrations equivalent to 0, 0.5, 5.0, 50 and 500 mg of antimony per litre. This corresponded to daily antimony intakes of 0.06–45.39 mg/kg of body weight in females and 0.06–42.17 mg/kg of body weight in males. Additional groups of 10 rats per sex were exposed to either 0 or 500 mg of antimony per litre in drinking-water for 90 days and then observed over 4 weeks for reversibility of any antimony-mediated adverse or non-adverse effects. No signs of overt clinical toxicity were observed in any animal. In the high-dose males, a marked but reversible loss of body weight gain occurred, probably in conjunction with distinctly reduced food and water intake at this dose. Based on subtle histopathological changes in the thyroids of males (increased epithelial height, decreased follicular size), the authors identified a NOAEC of 0.5 mg of antimony per litre in drinking-water, which corresponded to a NOAEL of 0.06 mg of antimony per kg of body weight per day.

However, Lynch et al. (1999) questioned the authors' evaluation of the otherwise "generally well designed study," pointing to the reversible/adaptive nature of the "critical" thyroidal and other biochemical and histological observations in this study, the absence of any quantitative dose-response relationship, although a more than 1000-fold dose range was applied, and the high physiological variability and/or treatment-related occurrence of the observed "critical" effects. Moreover, "none of the subtle histological changes recorded by Poon et al. (1998) were detected in the NTP (1992) study." Instead of 0.06 mg of antimony per kg of body weight per day, Lynch et al. (1999) proposed a subchronic NOAEL of 6.0 mg of antimony per kg of body weight per day, which corresponds to 50 mg of antimony per litre in the Poon et al. (1998) drinking-water study. This NOAEL was based on the decreased body weight

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gain and reduced food and water intake observed in that same study at 500 mg of antimony per litre, which is the LOAEC corresponding to a LOAEL of 60 mg of antimony per kg of body weight per day (Lynch et al., 1999).

5.2.2 ATO

In a dose range-finding GLP study, ATO incorporated in the diet of Wistar-derived rats (Alpk:ApfSD) (eight per sex per group) at concentrations of 0, 1000, 5000 or 20 000 mg/kg for 28 days caused significant changes only in two top-dose females. The lesions in kidney and liver were not of marked severity, but the lesion seen in the adrenal capsule was unusual and could be treatment-related. The LOAEC of 20 000 mg of ATO per kg in the diet was equivalent to a daily dose of 1000 mg of antimony per kg of body weight per day (LOAEL), the exact dose depending on the weekly feed consumption/body weight ratio (Central Toxicology Laboratory, 1996).

In a subchronic GLP study, ATO given to Wistar-derived rats (Alpk:ApfSD) (12 per sex per dose) in the diet at concentrations of 0, 1000, 5000 or 20 000 mg/kg for 90 days provoked no toxicologically significant findings in any of the dose groups (Hext et al., 1999). There were no adverse effects on body weight, food consumption or haematological parameters. A number of statistically significant, but inconsistent, biochemical changes were observed, including a decrease in alkaline phosphatase in the plasma at the two highest doses in males and the highest dose in females; an increase in triglycerides in the plasma at the highest dose in males, but with no trend; an increase in cholesterol at the highest dose in females; and an increase in aspartate aminotransferase in the plasma at the highest dose in males. In addition, liver weights were slightly increased at 20 000 mg/kg in animals of both sexes, and urine volume and specific gravity were reduced in the 20 000 mg/kg females. The authors considered none of these changes to be of toxicological significance. At necropsy, no treatment-related findings were made. The NOAEC of 20 000 mg of ATO per kg in the diet was equivalent to a NOAEL of 1685.9 mg of ATO per kg of body weight per day (or 1407.7 mg of antimony per kg of body weight per day).

5.2.3 Comparison between APT and ATO

The large difference in toxicity between ATO antimony and APT antimony is due to the significant difference between bioavailabilities and corresponding systemic exposures. This is not unexpected, in view of the high water solubility of APT and the insoluble nature of ATO.

5.3 Long-term exposure

Early studies on the chronic and subchronic oral toxicity of antimony were carried out using APT. Lynch et al. (1999) extensively reviewed these studies and raised several points of criticism. One of these studies, carried out by Schröder et al. (1970), was the experimental basis on which the provisional guideline value in the second edition of the Guidelines was derived.

5.4 Reproductive and developmental toxicity

Exposure to 250 mg of antimony per m³ in the air for 4 h per day during a 2-month period was reported to cause some adverse effects on the reproductive outcome of rats (Belyeava, 1967). Teratogenicity of antimony(V) dextraneglycoside or of antimony trichloride could not be demonstrated in rats and sheep (James et al., 1966; Casals, 1972; Rossi et al., 1987). However, ¹²⁵Sb was shown to cross the placenta and was also found in the milk of lactating rats (Gerber et al., 1982).

5.5 Mutagenicity and related end-points

ATO was genotoxic in a number of older bacterial mutation assays but not in more recent ones (Lantsch & Gebel, 1997; Elliott et al., 1998). Conflicting results were also obtained with respect to the genotoxicity of antimony in cultured mammalian cells. Positive results were observed with ATO in the *in vitro* cytogenetic assay with human lymphocytes (Elliott et al., 1998) and the sister chromatid exchange assay with V79 cells (Kuroda et al., 1991), but not in the L5178Y mutation assay (Elliott et al., 1998).

The *in vivo* genotoxicity of ATO was extensively investigated by Elliott et al. (1998) using single- and repeat-dose mouse bone marrow micronucleus tests and the rat liver unscheduled DNA synthesis assay. All three studies were negative. In contrast, Gurnani et al. (1992a) reported chromosomal damage by ATO in mouse bone marrow cells after repeat dosing but not after single dosing. This discrepancy between Elliott et al. (1998) and Gurnani et al. (1992a) with respect to repeat dosing may be explained (Elliott et al., 1998) by the “not specified purity” and much higher systemic toxicity of the ATO sample used by Gurnani et al. (1992a). For this reason, and because of the poor water solubility of ATO (17 µg/litre), Elliott et al. (1998) concluded that ATO was not genotoxic *in vivo*.

Different results were obtained with more water soluble antimony compounds. The compounds antimony trichloride and antimony pentachloride were reported to be genotoxic in the rec-assay with *Bacillus subtilis* (Kanematsu et al., 1980; Kuroda et al., 1991). Antimony(III) acetate enhanced the simian adenovirus-7-mediated transformation of Syrian hamster embryo cells (Casto et al., 1979), and enhanced rates of chromosomal breaks in human leukocytes were reported after treatment with APT (Paton & Allison, 1972).

The potency of antimony(III) to induce micronuclei *in vitro* in V79 cells and human lymphocytes was about 1 order of magnitude lower than that of arsenic(III) (Gebel, 1998; Schaumlöffel & Gebel, 1998). The comparable dose levels in human lymphocytes were 0.5 µmol/litre for arsenic(III) and 5 µmol/litre for antimony(III). In contrast to sodium arsenite, antimony trichloride did not induce DNA–protein cross-links in V79 cells and peripheral human lymphocytes (Gebel et al., 1998; Schaumlöffel & Gebel, 1998). The genotoxicity of antimony(III) was also lower than that of arsenic(III) in the test for sister chromatid exchange and in a single-cell gel test reviewed by Gebel (1999a).

In vivo, tartar emetic (APT) and bilharcid (piperazine antimony tartrate), two important antischistosomal drugs, were reported to be genotoxic after acute and subacute application to rats (El Nahas et al., 1982). Seven days after being given orally to Swiss mice, antimony trichloride was reported to cause increased chromosomal aberration rates in bone marrow cells (Gurnani et al., 1992b).

5.6 Carcinogenicity

The greatest concern with regard to the carcinogenicity of antimony compounds relates to the inhalation route. ATO has been found to be carcinogenic to experimental animals in inhalation studies (IARC, 1989) and to cause direct lung damage following chronic inhalation as a consequence of overload with insoluble particulates (Newton et al., 1994).

In contrast, oral lifetime studies with LE rats (Kanisawa & Schröder, 1969; Schröder et al., 1970) or Charles River CD mice (Schröder et al., 1968; Kanisawa & Schröder, 1969), in which animals were exposed to 5 and/or 50 mg of antimony (as APT) per litre in drinking-water, did not give any indication that antimony(III) showed carcinogenic potential by the oral route. However, Lynch et al. (1999) critically reviewed all three studies and concluded that they were not suitable for making a definitive assessment of the carcinogenicity of antimony because they contained many flaws in design and experimental methodology. In addition, the use of these studies as a quantitative starting point to assess the cancer risks associated with oral antimony exposure was deemed to be inappropriate.

6. EFFECTS ON HUMANS

The toxicity of antimony is a function of the water solubility and the oxidation state of the antimony species under consideration (Elinder & Friberg, 1986; Fowler & Goering, 1991). In general, antimony(III) is more toxic than antimony(V), and the inorganic compounds are more toxic than the organic compounds (Stemmer, 1976), with stibin (SbH_3), a lipophilic gas, being most toxic (by inhalation).

Soluble antimony salts, after oral uptake, exert a strong irritating effect on the gastrointestinal mucosa and trigger sustained vomiting. Other effects include abdominal cramps, diarrhoea and cardiac toxicity (Elinder & Friberg, 1986). The minimal lethal dose for oral intoxication by antimony in the form of APT (tartar emetic) is reported in textbooks as 300 mg of APT for a child and 1200 mg of APT for an adult. The acute symptoms are similar to those seen after acute oral intoxication by arsenic (Wirth, 1994).

Chronic respiratory uptake of antimony-containing dusts leads to irritation of the respiratory tract and myocardial and liver damage (Elinder & Friberg, 1986; Winship, 1987).

With respect to possible reproductive effects of antimony in humans, one incomplete study reported that respired antimony compounds could trigger premature births and spontaneous abortions (Belyeava, 1967).

Repeated oral exposure to therapeutic doses of antimony(III) was associated with optic nerve destruction, uveitides and retinal bleeding. Specific symptoms of intoxication are generally accompanied by headache, coughing, anorexia, troubled sleep and vertigo (Stemmer, 1976).

Significant induction of chromosomal aberrations and micronuclei was reported in 15 patients given therapeutic doses of APT (Hashem & Shawki, 1976). In a case-study of a patient suffering from visceral leishmaniasis and treated with meglumine antimoniate (antimony(V)), the authors reported an increase in the number of cells with micronuclei, but no changes in sister chromatid exchange or structural aberrations in chromosomes in the lymphocytes (Hantson et al., 1996). On the basis of these findings, the authors concluded that this compound did not represent a mutagenic or carcinogenic risk to humans.

Inhalation exposure to ATO in workplaces was associated with increased incidences of lung cancer, but not with tumours of other organs (Elinder & Friberg, 1986).

7. GUIDELINE VALUE

Although there is some evidence for the carcinogenicity of certain antimony compounds by inhalation, there are no data to indicate carcinogenicity by the oral route. IARC has concluded that there is inadequate evidence for the carcinogenicity of ATO in humans but sufficient evidence in experimental animals and that there is only limited evidence for the carcinogenicity of antimony trisulfide in experimental animals. ATO was assigned to Group 2B and antimony trisulfide to Group 3 (IARC, 1989).

Antimony trioxide, due to its low bioavailability, is genotoxic only in some *in vitro* tests, but not *in vivo*, whereas soluble antimony(III) salts exert genotoxic effects *in vitro* and *in vivo*.

The most common source of antimony in drinking-water appears to be dissolution from metal plumbing and fittings. The form of antimony in drinking-water is a key determinant of its toxicity, and it would appear that antimony leached from antimony-containing materials would be in the form of the antimony(V) oxo-anion, which is the less toxic form. It is therefore critical that the study selected for guideline derivation be a drinking-water study.

The suggested NOAEL (Lynch et al., 1999) in the subchronic drinking-water study in rats conducted by Poon et al. (1998) was 6.0 mg/kg of body weight per day based on decreased body weight gain and reduced food and water intake. A TDI of 6 µg/kg of body weight can be determined by applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a subchronic study). A guideline

value of 20 µg/litre (rounded figure) can be derived from this TDI by assuming a 60-kg adult drinking 2 litres of water per day and allocating 10% of the TDI to drinking-water. It should be noted that this value could be highly conservative because of the nature of the end-points and the large uncertainty factor; further data could result in a lower uncertainty factor.

There are adequate analytical methods for antimony in drinking-water with detection limits below the guideline value. As the most common source of antimony in drinking-water appears to be dissolution from metal plumbing and fittings, control of antimony from such sources would be by product control. At one time, antimony was suggested as a possible replacement for lead in solders, but there is no evidence that this has occurred. Antimony is not removed from water by conventional treatment processes (EUREAU, 1994). Control would therefore be by source selection or dilution.

The possibility of co-exposure of consumers to arsenic and antimony in drinking-water would necessitate an assessment of the local geological conditions on a case-by-case basis. If both elements were found to be present, case-specific risk evaluations for possible additivity and synergistic effects would need to be performed.

8. REFERENCES

Abbassi SA (1989) Sub-micro determination of antimony(III) and antimony(V) in natural and polluted waters and total antimony in biological materials by flameless AAS following extractive separation with *N-p*-methoxy-phenyl-2-furylacrylohydroxamic acid. *Analytical Letters*, 22:237–255.

Andrae MO et al. (1981) Determination of antimony (III), antimony (V), and methylantimony species in natural waters by atomic absorption spectrometry with hydride generation. *Analytical Chemistry*, 53:1766–1771.

Bailly R et al. (1991) Experimental and human studies on antimony metabolism: their relevance for the biological monitoring of workers exposed to inorganic antimony. *British Journal of Industrial Medicine*, 48:93–97.

Belyeava AP (1967) [The effect produced by antimony on the generative function.] *Gigiena Truda i Professional'nye Zabolevaniya*, 11:32–37 (in Russian).

Berman JD, Gallalee JF, Gallalee JV (1988) Pharmacokinetics of pentavalent antimony (Pentostam) in hamsters. *American Journal of Tropical Medicine and Hygiene*, 39:41–45.

Bowen HJM (1979) *Environmental chemistry of the elements*. London, Academic Press.

Buchet JP, Lauwerys R, Roels H (1980) Comparison of several methods for the determination of arsenic compounds in water and in urine. Their application for the study of arsenic metabolism and for the monitoring of workers exposed to arsenic. *International Archives of Occupational and Environmental Health*, 46:11–29.

Casals JB (1972) Pharmacokinetic and toxicological studies of antimony dextran glycoside (RL-712). *British Journal of Pharmacology*, 46:281–288.

Casto BC, Meyers J, Dipaolo JA (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Research*, 39:193–198.

Central Toxicology Laboratory (1996) *Antimony trioxide: 28 day dietary toxicity study in rats*. Alderley Park, Zeneca (Report No. CTL/L/7222) [cited in IUCLID].

Cotton FA et al. (1999) *Advanced inorganic chemistry*, 6th ed. New York, NY, Wiley.

Creclius EA, Bothner MH, Carpenter R (1975) Geochemistries of arsenic, antimony, mercury, and related elements in sediments of Puget Sound. *Environmental Science and Technology*, 9:325–333.

Dams R, de Jonge J (1976) Chemical composition of Swiss aerosols from the Jungfrauoch. *Atmospheric Environment*, 10:1079–1084.

Dieter MP et al. (1991) Comparative toxicity and tissue distribution of antimony potassium tartrate in rats and mice dosed by drinking water or intraperitoneal injection. *Journal of Toxicology and Environmental Health*, 34:51–82.

DuPont (2001) *Solubility of antimony trioxide in synthetic gastric juice*. Wilton, Redcar, DuPont Polyester Technologies (Report NAM 64).

Elinder CG, Friberg L (1986) Antimony. In: Friberg L, Nordberg GF, Vouk VB, eds. *Handbook on the toxicology of metals*. Amsterdam, Elsevier, pp. 26–42.

Elliott BM et al. (1998) An assessment of the genetic toxicology of antimony trioxide. *Mutation Research*, 415:109–117.

El Nahas S, Temtamy SA, de Hondt HA (1982) Cytogenetic effects of two antimonial antibilharzial drugs: tartar emetic and bilharcid. *Environmental Mutagenesis*, 4:83–91.

Enders R, Jekel R (1994) Entfernung von Antimon(V) und Antimon(III) aus wässrigen Lösungen. Teil I: Mitfällung und Adsorption bei der Flockung mit Eisen(III)-Salzen. [Elimination of Sb(V) and Sb(III) from aqueous solutions. Part I: Coprecipitation and adsorption during flocculation with Fe(III)salts.] *Wasser Abwasser*, 135:632–641.

EUREAU (1994) Implications to water suppliers and householders of the new WHO guidelines for drinking water quality. *Aqua*, 43(6):315–322.

Felicetti SA, Thomas RG, McClellan RC (1974) Metabolism of two valence states of inhaled antimony in hamsters. *Journal of the American Industrial Hygiene Association*, 35:292–300.

Fowler BA, Goering PL (1991) Antimony. In: Merian E, ed. *Metals and their compounds in the environment: occurrence, analysis, and biological relevance*. Weinheim, VCH, pp. 743–750.

Frezard F et al. (2001) Glutathione-induced conversion of pentavalent antimony to trivalent antimony in meglumine antimoniate. *Antimicrobial Agents and Chemotherapy*, 45:913–916.

Gebel T (1997) Arsenic and antimony: comparative approach on mechanistic toxicology. *Chemico-Biological Interactions*, 107:131–144.

Gebel T (1998) Suppression of arsenic-induced chromosome mutagenicity by antimony in V79 cells. *Mutation Research*, 412:213–218.

Gebel T (1999a) Metalle/Antimon. In: Wichmann-Schlipkötter-Fülgraff, eds. *Umweltmedizinisches Handbuch*, 17. Ergänzungslieferung (November 1999). Landsberg, ecomed.

Gebel T (1999b) Arsenic and drinking water contamination [letter]. *Science*, 283:1458–1459.

ANTIMONY IN DRINKING-WATER

Gebel T et al. (1998) Arsenic(III), but not antimony(III), induces DNA–protein crosslinks. *Anticancer Research*, 18:4253–4257.

Gerber GB, Maes J, Eykens B (1982) Transfer of antimony and arsenic to the developing organism. *Archives of Toxicology*, 49:159–168.

Gurnani N, Sharma A, Talukder G (1992a) Comparison of the clastogenic effects of antimony trioxide on mice *in vivo* following acute and chronic exposure. *Biometals*, 5:47–50.

Gurnani N, Sharma A, Talukder G (1992b) Cytotoxic effects of antimony trichloride on mice *in vivo*. *Cytobios*, 70:131–136.

Hantson P et al. (1996) Cytogenetic observations after meglumine antimoniate therapy for visceral leishmaniasis. *Pharmacotherapy*, 16:869–871.

Hashem N, Shawki R (1976) Cultured peripheral lymphocytes: one biologic indicator of potential drug hazard. *African Journal of Medicine and Medical Sciences*, 5:155–163.

Hawley GG (1981) *The condensed chemical dictionary*, 10th ed. New York, NY, Van Nostrand Reinhold.

Hext PM, Pinto PJ, Rimmel RA (1999) Subchronic feeding study of antimony trioxide in rats. *Journal of Applied Toxicology*, 19:205–209.

HSDB (1990) *Hazardous Substances Data Bank*. Bethesda, MD, National Library of Medicine.

Hurtig HW (1990) Die Immissionsbelastung von Böden durch Antimon. [Exposure of soils to antimony.] *VDI-Berichte*, 837:91–102.

IARC (1989) *Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting*. Lyon, International Agency for Research on Cancer, pp. 291–305 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47).

ICI-Technology (1996) *Technical dossier “antimony trioxide.”* Transmitted on November 10, 2000, by A. Sarraf from DuPont Polyester Technologies, Bad Homburg (TDSB203.SAM).

Iffland R, Bösche G (1987) Therapie und klinisch-toxikologische Verlaufskontrolle einer Brechweinstein-Vergiftung durch ein Ameisenvernichtungsmittel bei einem Kind. [Therapy and clinical-toxicological development and control of a child’s poisoning with emetic tartar from an anticide.] *Monatsschrift für Kinderheilkunde*, 135:227–230.

James LF, Lazar VA, Binns V (1966) Effect of sublethal doses of certain minerals on pregnant ewes and fetal development. *American Journal of Veterinary Research*, 27:132–135.

Kanematsu N, Hara M, Kada T (1980) Rec assay and mutagenicity studies on metal compounds. *Mutation Research*, 77:109–116.

Kanisawa M, Schröder HA (1969) Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. *Cancer Research*, 29:892–895.

Kuroda K et al. (1991) Genotoxicity of beryllium, gallium and antimony in short-term assays. *Mutation Research*, 264:163–170.

Lantzsch H, Gebel T (1997) Genotoxicity of selected metal compounds in the SOS chromotest. *Mutation Research*, 389:191–197.

- Lauwers LF et al. (1990) Oral antimony intoxications in man. *Critical Care Medicine*, 18:324–326.
- Longtin JP (1985) *Status report — national inorganics and radionuclides survey*. Cincinnati, OH, US Environmental Protection Agency, Office of Drinking Water.
- Lynch BS et al. (1999) Review of subchronic/chronic toxicity of antimony potassium tartrate. *Regulatory Toxicology and Pharmacology*, 30:9–17.
- Mohammad B et al. (1990) Speciation of antimony in natural waters: The determination of antimony (III) and antimony (V) by continuous flow hydride generation–atomic absorption spectrometry. *Chemical Speciation and Bioavailability*, 2(3):117–122.
- Molokhia MM, Smith H (1969) The behaviour of antimony in blood. *Journal of Tropical Medicine and Hygiene*, 72:222–225.
- Moskalev YI (1959) Materials on the distribution of radioactive antimony. *Medical Radiology*, 4(3):6–13.
- Mukhopadhyay R et al. (1996) Trypanothione overproduction and resistance to antimonials and arsenicals in *Leishmania*. *Proceedings of the National Academy of Sciences of the United States of America*, 93:10383–10387.
- Newton PE et al. (1994) Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. *Fundamental and Applied Toxicology*, 22(4):561–576.
- Nriagu JO, Pacyna JM (1988) Quantitative assessment of worldwide contamination of air, water and soils by trace metals. *Nature*, 333:134–139.
- NTP (1992) *NTP technical report on toxicity studies of antimony potassium tartrate in F344/N rats and B6C3F₁ mice (drinking water and intraperitoneal injection studies)*. Research Triangle Park, NC, National Institutes of Health, National Toxicology Program (NTP Toxicity Report Series No. 11) [cited in Lynch et al., 1999].
- Paton GR, Allison AC (1972) Chromosome damage in human cell cultures induced by metal salts. *Mutation Research*, 16:332–336.
- Plessow A, Plessow K, Heinrich H (1997) Schadstoffbelastung von Straßenkehricht und Sedimenten der Regenwasserkanalisation durch den Straßenverkehr am Beispiel von Göttingen. [Pollution of street sweepings and sediments of the sewerage system by automobiles exemplified with the city of Goettingen (Germany).] *Umweltwissenschaften und Schadstoff-Forschung - Zeitschrift für Umweltchemie und Ökotoxikologie*, 9(6):353–354.
- Poon R et al. (1998) Effects of antimony on rats following 90-day exposure via drinking water. *Food and Chemical Toxicology*, 36(1):21–35.
- Rosen BP et al. (1988) Molecular characterization of an anion pump. The *arsA* gene product is an arsenite(antimonate)-stimulated ATPase. *Journal of Biological Chemistry*, 263:3067–3070.
- Rossi F et al. (1987) Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development in pups. *Teratogenicity, Carcinogenicity, and Mutagenicity*, 7:491–496.
- Schaumlöffel N, Gebel T (1998) Heterogeneity of the DNA damage provoked by antimony and arsenic. *Mutagenesis*, 13:281–286.

ANTIMONY IN DRINKING-WATER

Schröder HA et al. (1968) Zirconium, niobium, antimony and fluorine in mice: Effects on growth, survival and tissue levels. *Journal of Nutrition*, 95:95–101.

Schröder HA, Mitchener M, Nason AP (1970) Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. *Journal of Nutrition*, 100(1):59–68.

Shaked-Mishan P et al. (2001) Novel intracellular Sb^V reducing activity correlates with antimony susceptibility in *Leishmania donovani*. *Journal of Biological Chemistry*, 276:3971–3976.

Slooff W (1992) *Exploratory report. Antimony and antimony compounds*. Bilthoven, Rijksinstituut voor de Volksgezondheid en Milieuhygiene.

Stechmann H (1993) *Charakterisierung kraftfahrzeugspezifischer partikelförmiger Emissionen und Quantifizierung ihrer Beiträge zu Aerosolen und Gewässerverunreinigungen*. Hamburg, Dannecker.

Stemmer KL (1976) Pharmacology and toxicology of heavy metals: antimony. *Pharmacology and Therapeutics Part A*, 1:157–160.

US EPA (1984) *Antimony: an environmental and health effects assessment*. Washington, DC, US Environmental Protection Agency, Office of Drinking Water.

Van Bruwaene RE et al. (1982) Metabolism of antimony-124 in lactating cows. *Health Physics*, 43:733–738.

Waitz JA et al. (1965) Physiological disposition of antimony after administration of ¹²⁴Sb-labeled tartar emetic to rats, mice and monkeys, and the effects of tris(*p*-aminophenyl)carbonium pamoate on this distribution. *WHO Bulletin*, 33:537–546.

Wang Z et al. (1996) Efflux-mediated resistance to arsenicals in arsenic-resistant and -hypersensitive Chinese hamster cells. *Toxicology and Applied Pharmacology*, 137:112–119.

Wiberg N (1985) *Holleman-Wiberg Lehrbuch der Anorganischen Chemie*. [Holleman-Wiberg textbook of inorganic chemistry.] Berlin, De Gruyter.

Winship KA (1987) Toxicity of antimony and its compounds. *Adverse Drug Reactions and Acute Poisoning Reviews*, 2:67–90.

Wirth C (1994) *Wirth/Gloxhuber Toxikologie*. [Wirth/Gloxhuber Toxicology.] Stuttgart, Georg Thieme.