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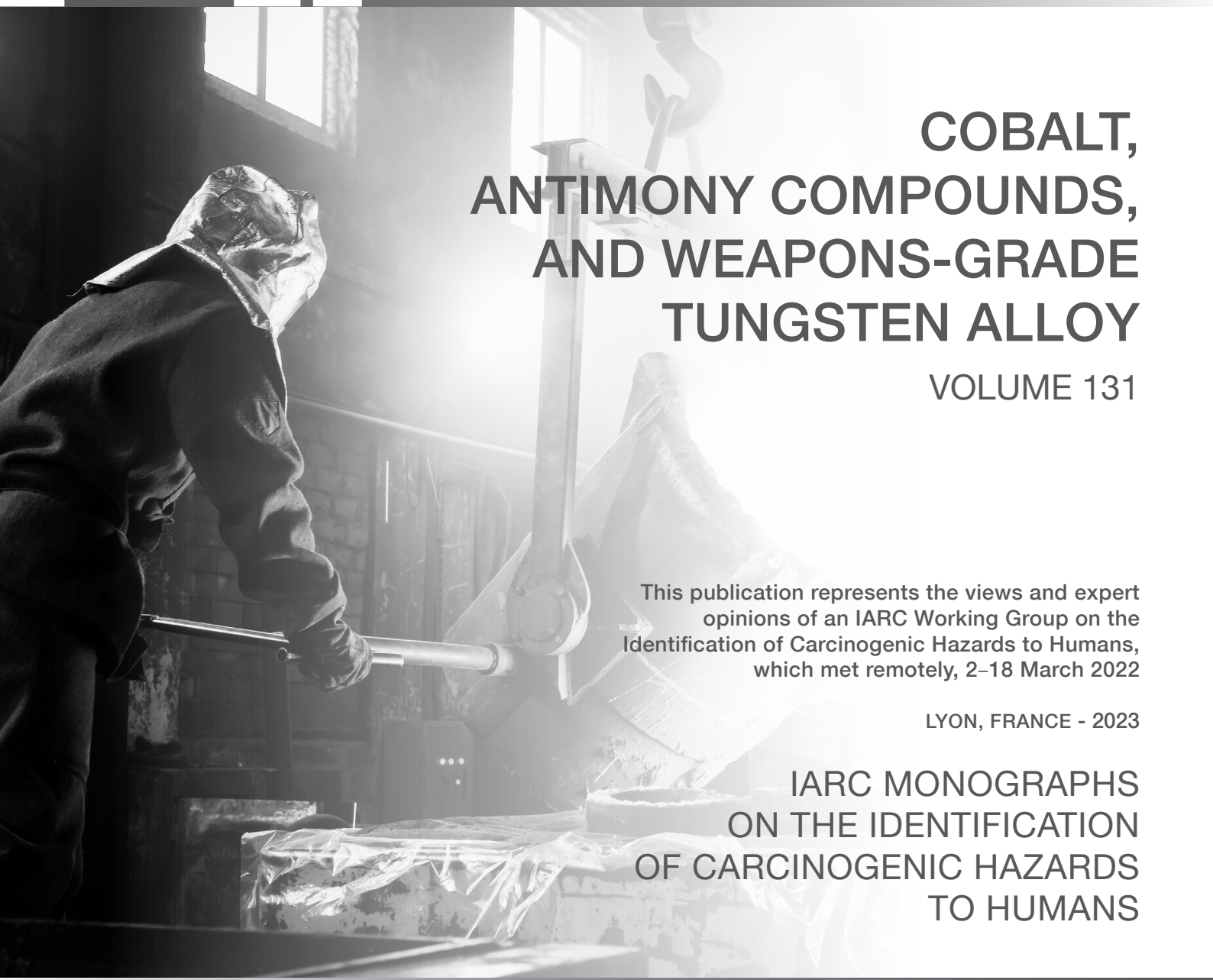

COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

VOLUME 131

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International Agency for Research on Cancer

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TRIVALENT AND PENTAVALENT ANTIMONY

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature, synonyms, trade names, molecular formulae, and relative molecular mass

Multiple agents are considered in this monograph as follows: the trivalent antimony compounds antimony(III) oxide (Sb_2O_3) [antimony trioxide], antimony(III) chloride ($SbCl_3$), antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$ or the anhydrous form $K_2Sb_2(C_4H_2O_6)_2$), antimony(III) sulfide (Sb_2S_3), trivalent antimony(III) ions (Sb^{3+}), and antimony(III) hydride (also known as stibine, SbH_3), and the pentavalent antimony compounds antimony(V) oxide (Sb_2O_5), meglumine antimoniate(V) ($C_7H_{17}NO_5{\cdot}H{\cdot}O_3Sb$), and antimony(V) in sodium stibogluconate ($C_{12}H_{38}Na_3O_{26}Sb_2$). Current and discarded or replaced Chemical Abstracts Service (CAS) registration numbers together with common synonyms and trade names of these agents are presented in Table 1.1. [It is noted by the Working Group that this is a non-exhaustive list of trivalent and pentavalent antimony compounds.]

Antimony(III) oxide can exist in various polymorphs, notably valentinite and senarmontite, with different chemical and physical characteristics. The aqueous speciation of antimony may be complex. The inorganic antimony(III) and antimony(V) species, which tend to predominate under reducing and oxidizing conditions, respectively, may also be variably protonated as a function of pH, complex with a variety of inorganic and organic ligands (notably sulfur-bearing ligands) and they may exist as polynuclear or polymeric moieties even at comparatively low total antimony concentrations (Guo et al., 2020). Many of the agents that commonly occur in the solid phase can exist in forms with various degrees of hydration, polymerization, or protonization. The names of some related agents for antimony(III) potassium tartrate, which also exhibits non-conformational isomerism, are therefore also recorded in Table 1.1. "Meglumine antimoniate(V)" and "antimony(V) in sodium gluconate" are terms that are widely used to refer to mixtures that may have ranges of compositions and molecular constituents of antimony and other compounds. [The Working Group notes that although chemical names may be reported as "synonyms" of a particular agent, such reporting may not always be accurate and relevant papers may be silent on characteristics, such as polymorphism, particle size, or trace element impurities, that may be critical to inform understanding of the reactivity or toxicity of the product overall (Gaultieri, 2017).]

Table 1.1 Registry numbers, synonyms and trade names, molecular formulae, and relative molecular masses for trivalent and pentavalent antimony, antimony metal, and antimonite ore

Chemical name (reference)	CAS No.[a]	Synonyms and trade names	Formula	Relative molecular mass
Antimony(III) oxide (IARC, 1989; ECHA, 2022a; NLM, 2022)	1309-64-4 1327-33-9 1317-98-2 (specific to valentinite) 12412-52-1 (specific to senarmontite)	IUPAC names: diantimony trioxide; (stibanyloxy) stibanediol Antimony trioxide; diantimony trioxide; antimony oxide; antimonous oxide; flowers of antimony Valentinite Trade names: CI 77052; CI Pigment White 11; antimony white; AP 50 Senarmontite	Sb_2O_3	291.50
Antimony(III) chloride (NCBI, 2022d)	10025-91-9 [8007-28-1; 12515-76-3; 39357-85-2; 59922-49-5]	IUPAC names: antimony trichloride (preferred); trichlorostibane (systematic) Antimony chloride; antimony(III) chloride; trichlorostibine; stibine, trichloro-; antimonous chloride; antimony butter; butter of antimony; caustic antimony	$SbCl_3$	228.11
Antimony(III) potassium tartrate (NCBI, 2022a; ECHA, 2022b)	28300-74-5 [1332-41-8; 1332-43-0; 16039-64-8; 26282-95-1]	IUPAC name: potassium antimony(3+) 2,3-dihydroxybutanedioate Tartaric acid, antimony potassium salt, trihydrate; antimony potassium tartrate; tartrated antimony; emetic, tartar; potassium antimonyl tartrate Trade and other names: Tartox	$C_8H_{10}K_2O_{15}Sb_2$; anhydrous form: $K_2Sb_2(C_4H_2O_6)_2$	667.87
Trivalent antimony(III) ions (NCBI, 2021a)	23713-48-6	Antimony(3+); antimony cation (3+); antimony(III) ION; antimony black	Sb^{+3}	121.760
Antimony(III) hydride (Grund et al., 2006; NCBI, 2022b)	7803-52-3	Stibine; stibine; antimony hydride; antimony trihydride; hydrogen antimonide	SbH_3	124.77
Antimony(III) sulfide (NCBI, 2023)	1345-04-6	Diantimony trisulfide, stibnite	Sb_2S_3	339.7
Antimony(V) oxide (NCBI, 2022c)	1314-60-9	IUPAC name: (dioxo-λ^5-stibanyl)oxy-dioxo- λ^5-stibane Antimony(V) oxide; antimony oxide (Sb_2O_5); antimony pentaoxide; antimony pentoxide; antimonic oxide; diantimony pentaoxide; stibic anhydride; Apox S; Nyacol AGO 40	Sb_2O_5	323.52
Meglumine antimoniate(V) (Chemical Abstracts Service, 2021; ChemSrc, 2022)	133-51-7 [161842-96-2]	D-Glucitol, 1-deoxy-1-(methylamino)-,trioxoantimonate(1-); glucitol, 1-deoxy-1-(methylamino)-, compd. with antimonic acid ($HSbO_3$)(1:1), D-; D-glucitol, 1-deoxy-1-(methylamino)-, compd. with antimonic acid ($HSbO_3$)(1:1); glucitol, 1-deoxy-1-(methylamino)-, antimonite(V); antimonic acid ($HSbO_3$), compd. with D-1-deoxy-1-(methylamino)glucitol (1:1) Trade and other names: Glucantime; Glucantim; 2168-rp; Protostib; RP 2168; MFCD01725422; EINECS 205-108-3	$C_7H_{17}NO_5 \cdot H \cdot O_3Sb$[b]	383.995[b]

Table 1.1 (continued)

Chemical name (reference)	CAS No.[a]	Synonyms and trade names	Formula	Relative molecular mass
Antimony(V) in sodium stibogluconate (Chemical Abstracts Service, 2021; NCBI, 2021b; SelleckChem, 2021)	16037-91-5 [35-03-0; 12001-86-4]	D-gluconic acid, 2,4:2′,4′-O-(oxydistibylidyne)bis-,sodium salt, hydrate(1:3:9); D-gluconic acid, 2,4:2′,4′-O-(oxydistibylidyne) bis-, Sb,Sb′-dioxide, trisodium salt, nonahydrate; D-gluconic acid, 2,4:2′,4′-O-[oxybis(oxidostibylidyne)]bis-, trisodium salt, nonahydrate; 1,3,2-dioxantimonane, D-gluconic acid deriv.; 1,3,2-dioxastibinane, D-gluconic acid deriv.; D-gluconic acid, cyclic ester with antimonic acid ($H_8Sb_2O_9$) (2:1), trisodium salt, nonahydrate; antimony gluconate sodium; antimony gluconic acid; antimony sodium gluconate; stibogluconate sodium; SSG Trade and other names: Myostibin; Pentostam; Solustin; Solusurmin; Stibanate; Stibatin; Solyusurmin; Stibinol; Stibanose; Lenocta	$C_{12}H_{38}Na_3O_{26}Sb_2$[c]	909.90[c]

CAS No., Chemical Abstracts Service registry number; CI, Colour Index; IUPAC, International Union of Pure and Applied Chemistry.

[a] Deleted CAS Nos are shown in square brackets.

[b] Meglumine antimoniate(V) is reported by Roberts et al. (1998) to be a complex mixture of compounds rather than a single compound.

[c] Sodium stibogluconate is reported by NCBI (2021b) to be a "D-gluconate adduct of indefinite composition containing between 30% and 34% of antimony(V)"; relative molecular mass is dependent upon degree of protonation and number of waters of hydration.

Molecular formulae and relative molecular masses of the agents under consideration are given in Table 1.1.

1.1.2 Chemical and physical properties of the pure substances

Chemical and physical properties of the agents are presented in Table 1.2. It is noted that many of these properties are dependent upon the polymorphic form of the agent, the particle size, and the level and nature of impurities in specific trade products.

1.1.3 Technical grade and impurities

Purities of commercially available trivalent and pentavalent antimony compounds have been noted to vary from 99% to 99.999% for antimony(III) oxide (ChemicalBook, 2021a; Sigma-Aldrich, 2022a), 98% to > 99% for antimony(III) chloride (NCBI, 2022d), 95% to 99.95% for antimony(III) potassium tartrate (ChemicalBook, 2021b; Sigma-Aldrich, 2022b), 98% to 99% for meglumine antimoniate(V) (ChemSrc, 2022; Albalawi et al., 2021), and > 90% to 99.9% for antimony(V) in sodium stibogluconate (ChemicalBook, 2021c).

1.2 Production and use

1.2.1 Production

Global primary mining production of antimony in 2020 amounted to around 111 000 tonnes, of which most originated in China (61 000 tonnes), the Russian Federation (25 000 tonnes), and Tajikistan (13 000 tonnes), with substantial production greater than 2000 tonnes noted also in Myanmar, the Plurinational State of Bolivia, and Australia (USGS, 2021). Antimony in mined ores is predominantly in the antimony(III) oxidation state. Antimony is a chalcophile element and its ores are dominated by the sulfide minerals stibnite (also known as antimonite; Sb_2S_3) (Filella et al., 2002) and, to a lesser extent, jamesonite ($Pb_4FeSb_6S_{14}$), as well as fahlore, a sulfosalt that is highly compositionally variable (including in sulfur, arsenic, copper, zinc, iron, silver, and mercury) (George et al., 2017), of which tetrahedrite ($Cu_{12}Sb_4S_{13}$) is an antimony-dominated end-member. The antimony(III) oxide polymorphs senarmontite and valentinite are also widely mined (Butterman & Carlin, 2004). Minerals with mixed oxidation-state antimony include cervantite ($Sb(III)Sb(V)O_4$) and stibiconite ($Sb(III)Sb(V)_2O_6(OH)$), such as are mined at the San José antimony mines, northern Mexico (White & Jenaro Gonzáles, 1946). Antimony often, but not exclusively, occurs in complex ores from which it may be removed or extracted as a by-product, made more profitable because antimony is widely considered to be a penalty element (i.e. a contaminant that reduces the value of a metal/metalloid product) in base metal (e.g. copper) concentrates (Lane et al., 2016; Haga et al., 2018). In the USA, recycling contributes to around 15% of national consumption (USGS, 2021) but is largely restricted to the production of antimonial lead for use in alloy production (Butterman & Carlin, 2004). Global recycling rates are estimated to be between 1% and 10% (European Commission, 2020a), although these rates are higher (28%) in the European Union (EU) (Filella et al., 2020). Among several other antimony compounds, the antimony(III) salts of acetic acid, antimony, and antimony-rich lead dross have been classified in the past as High Production Volume chemicals by the Organisation for Economic Co-operation and Development (OECD, 2009), whereas the only antimony compounds listed as such in 2022 were antimony metal and antimony(III) sulfide (OECD, 2022).

Production methods for antimony products are highly variable, depending upon the product and the nature and grade of the source. The overwhelming majority of the world's

Table 1.2 Chemical and physical properties of the pure agents containing antimony

Chemical name	Typical physical description	Melting point (°C)	Boiling point (°C)	Density (g/cm³)	Solubility
Antimony(III) oxide (IARC, 1989; Lide, 1992; National Research Council, 2000; European Commission, 2008; ILO, WHO, 2013)	White, odourless, crystalline powder	656	1550 (sublimes)	5.7–5.9 (valentinite); 5.2 (senarmontite)	Very slightly soluble in cold water; slightly soluble in hot water; soluble in potassium hydroxide, hydrochloric acid, and acetic acid; insoluble in organic solvents; pH-dependent solubility in water is 19.7, 25.6, and 28.7 mg/L at 20 °C and pH 5, 7, and 9, respectively
Antimony(III) chloride (Grund et al., 2006; NCBI, 2022d)	Colourless, orthorhombic, deliquescent	73.4	223	3.14	Very soluble in water: 987 g/100 g water at 25 °C; slightly soluble in ethanol, hydrochloric acid, and tartaric acid
Antimony(III) potassium tartrate (ATSDR, 2019; Lide, 1992)	Colourless crystals	100 (decomposes)	NA	2.6	Slightly soluble in water: 8.3 g/100 mL at 20 °C; soluble in glycerine; insoluble in alcohol
Trivalent antimony(III) ions	Aqueous species, not a phase	NA	NA	NA	See above, depends on matrix composition and nature of mobility controlling phases
Antimony(III) hydride (NCBI, 2022b; ATSDR, 2019)	Colourless gas under ambient conditions	−88	−18	2.204[a]	Slightly soluble in water: 4.1 g/L at 0 °C; soluble in carbon disulfide and ethanol
Antimony(III) sulfide (NCBI, 2022e)	Red or black crystals	550	NA	4.56	Practically insoluble in water
Antimony(V) oxide (Grund et al., 2006; NCBI, 2022c; ATSDR, 2019; ChemicalBook, 2022)	White to yellowish powder	380	NA	3.78	Very slightly soluble in water; soluble in alkalis; practically insoluble in nitric acid
Meglumine antimoniate(V) (ChemSrc, 2022; VWR, 2021)	White to yellow powder[b]	168–170	490.4	1.375	Greater than 0.38 g/100 mL[c]; predicted: 24 g/100 mL in water[d]
Antimony(V) in sodium stibogluconate (ChemicalBook, 2021c; ChemSrc, 2021c; SelleckChem, 2021)	Sodium stibogluconate is a pale yellow solid	673.6	NA	NA	Slightly soluble to soluble in water: 2 g/100 mL at 25 °C, 0.1 g/100 mL at 75 °C; insoluble in ethanol

NA, not available or not applicable.

[a] At −17 °C; density is strongly dependent on pressure and temperature.

[b] VWR page code 22 676 858; product ACRO461141000 (VWR, 2021).

[c] Inferred from Martins et al. (2009).

[d] Predicted solubility based on ALOGPS software (www.vcclab.org/lab/alogps/) (DrugBank, 2021).

production has been located at plants in China, the USA, Kyrgyzstan, France, the Plurinational State of Bolivia, and Belgium, notably including some countries with very limited, if any, mine production (Anderson, 2012). Primary product compounds are typically antimony(0) metal, antimony(III) oxide, or the antimony(V) compound sodium antimonate ($NaSbO_3$), with other antimony products produced from those forms. The dominant production methods include blast-furnace smelting, volatilization roasting, liquation, reduction, leaching/electrowinning, and precipitation (Butterman & Carlin, 2004), all of which typically require prior crushing, grinding, and/or sizing of the ore, and, in some countries, hand-sorting is or has been widespread. Blast-furnace smelting at temperatures of 1300–1400 °C, a dominant production process for 25–40% antimony concentrates, generates antimony(0) metal and relatively large volumes of solid waste, known as "slag" (Anderson, 2012). Volatilization roasting of typically antimony(III) stibnite ores with charcoal or coke at temperatures over 1000 °C, a dominant process for 5–25% antimony ore/concentrates (Anderson, 2012), results in direct recovery of antimony oxides from the produced vapour phase. The production of antimony(III) oxide requires careful control of the process, otherwise less marketable oxides, such as the mixed antimony(III)/antimony(V) oxide, antimony tetroxide (Sb_2O_4), are produced. The process is energy-intensive and releases sulfur dioxide, carbon dioxide, and other volatiles, including those bearing arsenic and mercury. Liquation is typically used for the production of antimony(III) sulfide, whereas reduction, precipitation, and leaching/electrowinning are more indicated for high-grade (45–60% antimony) ores/concentrates and for the production of high-quality antimony(0) metal (Butterman & Carlin, 2004; Anderson, 2012). Revolatilization of antimony(III) oxide or antimony(0) metal is often required to remove lead, arsenic, sulfur, iron, and copper impurities to attain antimony(III) oxide at the purities required for commercial purposes (Butterman & Carlin, 2004).

1.2.2 Uses

Antimony is included on the EU list of critical raw materials (European Commission, 2020b) and within the EU has been used in flame retardants (43%), lead–acid batteries (32%), lead alloys (14%), plastics (catalysts and stabilizers) (6%), and glass and ceramics (5%) (the values refer to usage over the period 2012–2016) (European Commission, 2020a). In the USA, antimony is principally used in flame retardants (42%), metal products (36%), and non-metal products, including ceramics, glass, and rubber products (22%) (USGS, 2021). [Information on major uses outside Europe and North America was unavailable to the Working Group.]

The major use of antimony(III) oxide is as a flame retardant in combination with halogenated compounds, forming pyrolysis-inhibiting halogenated antimonials in a wide variety of products, including "plastics, cable coatings, upholstered furniture, car seats, fabrics and household appliances" (European Commission, 2020a). Antimony(III) oxide is also used as a catalyst in the production of several types of plastic, notably polyethylene terephthalate (PET), which is widely used in plastic bottles used for drinking-water and soft drinks (Martin et al., 2010; Snedeker, 2014). Antimony(III) oxide can be used as a colourant in materials used in the production of food packaging; in plastics, rubber, paints, and enamels (European Commission, 2020a); and as a stabilizer in polyvinyl chloride (European Commission, 2020a). Antimony(III) sulfide is used as a lubricant in brake pads and clutch discs, and as an ammunition primer in explosives (European Commission, 2020a). Antimony(V), in the form of sodium hexahydroxoantimonate ($NaSb(OH)_6$), is used as a degassing agent in the production of glass, as well as in controlling glass colour. Antimony(V) oxide is used as a flame

retardant, including in textiles (Garcia, 1982; Leblanc, 1980; NCBI, 2022c).

Antimony(III) potassium tartrate has been principally used in the treatment of trypanosomiasis, schistosomiasis (Dziwornu et al., 2020), and leishmaniasis (Haldar et al., 2011), although other medicines are now generally preferred. Both meglumine antimoniate(V) and the antimony(V) product sodium stibogluconate are still widely used (McGwire & Satoskar, 2014) as the treatment of first choice (Haldar et al., 2011) for the treatment of leishmaniasis, a disease that is particularly prevalent in Andean Latin America, north Africa, the Middle East, western sub-Saharan Africa, and south Asia (Karimkhani et al., 2016). There is increasing use, or exploration of use, of the delivery of these agents within microspheres (Navaei et al., 2014) or as part of nanoparticulate biocomposites (Gélvez et al., 2018). These developments, together with exploration of alternative treatments, are being driven by concerns about adverse effects of and pathogen resistance to antimony-based medicines (Gélvez et al., 2021).

1.3 Detection and quantification

This section focuses on methods, and the key attributes of those methods, for the detection and quantification of antimony and antimony species in media relevant to assessing exposure and health risks. Antimony may be present in environmental media (e.g. water, air, soil, food, packaging, paint, water pipework, flame retardants, and consumer products) and biological media (e.g. blood, urine, organs, and other tissues) in target organisms.

Although several notable repositories of analytical methods for antimony and other analytes in environmental and biological media exist (see Table 1.3), selection of methods or protocols for the analysis of antimony or antimony speciation is typically made on the basis of a comparison of method characteristics against project-dependent data and data quality objectives (US EPA, 2006). Broader process-dependent controls on data quality include: sampling strategy and representativeness (Gy, 1995), sampling and preservation protocols, selection of analytical instrumentation, analytical and data reduction protocols, and total quality management protocols (Polya & Watts, 2017; APHA/AWWA/WEF, 1999; Ferreira et al., 2014). Yang et al. (2023) highlight the importance of ensuring that contamination from antimony-bearing plastic tubes into aqueous samples presented for instrumental analysis is minimized. Middleton et al. (2016) emphasize the need for adequate sample preparation, notably in the removal of surface contaminants from biological media such as toenail cuttings and hair before digestion.

1.3.1 Elemental analysis of antimony

Elemental analysis of antimony in environmental and biological media has been widely carried out by atomic absorption spectrophotometry (Bureau of Indian Standards, 2003), neutron activation analysis, inductively coupled plasma (ICP) mass spectrometry (ICP-MS), and anodic stripping voltammetry, as well as various colorimetric and titrimetric techniques (IARC, 1989). Electrothermal atomic absorption spectrophotometry (APHA/AWWA/WEF, 1999; Section 3113B) and ICP-MS (APHA/AWWA/WEF, 1999; Section 3125B) are particularly recommended as the analytical methods of choice for water, wastewater, and digests of solid media by the American Public Health Association, American Water Works Foundation, and Water Environment Foundation. The National Institute for Occupational Safety and Health (NIOSH) lists several methods (NIOSH, 2003a, b, c) for the analysis of total antimony in digested air particulates in NIOSH (2022). However, detection limits of as low as around 0.001 µg/g are now achievable after sample (e.g. human hair) digestion followed by instrumental analytical techniques such as ICP

Table 1.3 Analytical methods for the measurement of antimony or antimony chemical species in environmental or biological media[a]

Sample matrix (analyte)	Sample preparation (method)	Analytical technique (method)	LOD[b] (working range)	Comments	Reference
Air (total antimony)	Collection on filter (0.8 µm [pore size] cellulose ester membrane (MCE), or 5.0 µm [pore size] PVC membrane) followed by digestion in aqua regia	ICP-AES (NIOSH Method 7301)	0.192 µg/sample, 7.7 ng/mL ([5–2000 µg/sample])	Validated multi-element method. NIOSH (2017) notes "antimony [does] not form stable solutions in nitric acid when chloride from the PVC filters is present".	NIOSH (2003b)
Air (total antimony)	Collection on filter (0.8 µm [pore size] MCE membrane) followed by hot-block digestion in hydrochloric acid:nitric acid	ICP-AES (NIOSH Method 7303)	0.018 µg/mL (5000–50 000 µg/sample)	Partially validated multi-element method.	NIOSH (2003c)
Air (total antimony)	Collection on filter (MCE membrane, 37 mm diameter, 0.8 µm pore size) followed by microwave digestion in nitric acid	ICP-AES (NIOSH Method 7302)	0.4 µg/sample (2.5–750 µg/sample)	Validated multi-element method.	NIOSH (2014)
Air (total antimony)	Collection on internal capsule, cellulose-acetate dome with inlet opening, attached to 0.8 µm pore size MCE membrane filter and housed within a 2-piece, closed-face cassette filter holder, 37 mm diameter followed by hotplate digestion, microwave digestion, or hot-block extraction with nitric acid, nitric acid:perchloric acid, aqua regia, or nitric acid:hydrochloric acid	ICP-AES (NIOSH Method 7306)	0.11 µg/sample ([0.04–10 000 µg/m^3])	Validated multi-element method.	NIOSH (2015)
Air (total antimony)	Collection on 0.5 µm PVC filter, then treated with a mixture of 5 mL of 37% hydrochloric acid and 1 mL of 70% nitric acid, followed by ultrasonic shock for 30 min, and filtered using a Millipore filter membrane with a 0.22 µm pore size	ICP-MS	4.4 µg/sample	Spike recovery only 84.5%. NIOSH (2017) notes "antimony [does] not form stable solutions in nitric acid when chloride from the PVC filters is present".	Wu & Chen (2017)
Airborne particles (total antimony)	MCE filters (0.8 µm pore size); filters digested with nitric acid, sulfuric acid, and hydrogen peroxide; sampling via wipes and bulk methods also possible	ICP-AES (OSHA Method ID-125G)	4.2 µg/sample (0.28–100 µg/mL)	Validated multi-element method.	OSHA (2002)
Airborne particles (total antimony)	MCE filters (0.8 µm pore size); filters digested to give a final acid concentration of 4% nitric acid and 32% hydrochloric acid; sampling via wipes and bulk methods also possible	ICP-AES (OSHA Method ID-206)	3.5 µg/sample (0.47–100 µg/mL)	Validated multi-element method.	OSHA (1991)

Table 1.3 (continued)

Sample matrix (analyte)	Sample preparation (method)	Analytical technique (method)	LOD[b] (working range)	Comments	Reference
Biological media (inorganic and organic antimony species)	A variety of extraction methods noted including various combinations of: methanol/water, citric acid, sodium hydroxide/acetic acid, EDTA, TBAOH, acetonitrile, chloroform, cellulase, protease, aqua regia, and sulfuric acid	Separation by HPLC, GC, or HG-GC; detection by HPLC-ICP-AES, ES-MS, UV spectroscopy, NMR, HG-GC-ICP-MS, HG-CT-GC-ICP-MS, or HPLC-ES-MS; HPLC-ICP-MS; HPLC-ES-MS/MS		A critical review of published methods. Highlights challenges of achieving quantitative extraction, and of species instability and preservation, during sample processing and analysis.	Hansen and Pergantis (2008)
Biological media (antimony speciation)	Freeze-dried plant material was ground to powder, pressed into 5 mm diameter, 2–3 mm thick pellets under a nitrogen atmosphere	XANES (LODs not reported); quantitative speciation information obtained from plant samples with antimony species concentrations between ~1 and 1600 µg/g	NR	Method provided quantitative information about concentrations of trivalent and pentavalent antimony, and TMSb, in plant roots and shoots.	Ji et al. (2017)
Biological media (total antimony)	Low-temperature (85 °C) digestion with nitric acid followed by careful addition of 30% hydrogen peroxide solution; evaporated to dryness and reconstituted with 5% nitric acid	ICP-MS (USGS NWQL Method B-9001-95)	0.3 µg/L in digest (> 0.01 µg/g)	Multi-element method. Applicable to aquatic biological tissue and aquatic plant material only.	US EPA (1996)
Blood (total antimony)	Preserve 10 mL of sample with heparin; digest in 3:1:1 (v/v/v) nitric acid: perchloric acid: sulfuric acid	ICP-AES (NIOSH Method 8005)	1 µg/100 g blood (10–10 000 µg/100 g blood)	Validated multi-element method.	NIOSH (1994)
Blood (total antimony)	Sample (0.5 mL) microwave digested with 3 mL of 70% nitric acid	ICP-MS	0.06 µg/L	Recovery, 90.0%.	Wu & Chen (2017)
Hair (total antimony)	Sample (0.4 g) washed with 1:200 v/v Triton X-100, acetone and then deionized water. Oven-dried at 75 °C for 24 h and then microwave digested with 70% nitric acid and then diluted with 1% hydrochloric acid and an indium internal standard solution	ICP-MS	0.0004 µg/g	Recovery rate, 81.0%.	Wu & Chen (2017)

Table 1.3 (continued)

Sample matrix (analyte)	Sample preparation (method)	Analytical technique (method)	LOD[b] (working range)	Comments	Reference
Solids (including airborne particles) (antimony speciation)	Extraction with hydroxylammonium chlorhydrate aqueous solution assisted by ultrasound	HPLC-HG-AFS	In extracts: trivalent antimony, 0.9 µg/L; pentavalent antimony, 1.2 µg/L	Extraction efficiencies greater than 90% reported. Relative standard deviations better than 10% for a 6 µg/g certified reference material.	Bellido-Martín et al. (2009)
Solids (antimony speciation)	PET bottle section of size 0.5 cm × 0.5 cm × 0.2 mm used without further preparation	XANES (speciation information obtained from a PET sample with 0.3 µg/g antimony)		Method provided qualitative information about the nature, particularly oxidation state of antimony species in PET.	Martin et al. (2010)
Solids (antimony speciation)	Samples mounted in epoxy resin and polished	XANES with LCF, EXAFS		XANES/LCF used to quantitatively determine antimony speciation in glasses. EXAFS used to identify pentavalent antimony in the aluminium tetrahedral site of anorthite.	Miller et al. (2019)
Tissue (total antimony)	Sample 1 g of tissue; digestion in 3:1:1 (v/v/v) nitric acid:perchloric acid:sulfuric acid	ICP-AES (NIOSH Method 8005; working range; LOD)	0.2 µg/g tissue (2–2000 µg/g tissue)	Validated multi-element method.	NIOSH (1994)
Toenails (total antimony)	Samples washed, air-dried, and then digested in 9:1 nitric acid:hydrochloric acid and diluted with deionized water	ICP-QQQ		Multi-element method.	White et al. (2020)
Urine (total antimony)	Urine samples to be refrigerated for short-term (several days) storage or frozen at ≤ –20 °C (if to be stored for longer)	ICP-DRC-MS (CDC Method 3004.1)	0.04 µg/L (lower)	Multi-element method. Based on Mulligan et al. (1990).	CDC (2006, 2013)
Urine (total antimony)	Sample (10 mL) centrifuged and upper solution mixed with indium internal standard and 1% v/v hydrochloric acid and nitric acid; creatinine measured separately and antimony reported as µg/g creatinine	ICP-MS	0.03 µg/L	Recovery rate, 90.2%.	Wu & Chen (2017)
Water (inorganic antimony species)	Water samples diluted with water or hydrochloric acid	HPLC-HG-AFS	Trivalent antimony, 0.3 µg/L; pentavalent antimony, 0.4 µg/L ([500–5000 µg/L])	Addition of hydrochloric acid noted to result in oxidation of trivalent antimony to pentavalent antimony during storage.	González de las Torres et al. (2020)

Table 1.3 (continued)

Sample matrix (analyte)	Sample preparation (method)	Analytical technique (method)	LOD[b] (working range)	Comments	Reference
Water (inorganic antimony species)	Water samples centrifuged and diluted with 2% nitric acid	HPLC-ICP-OES	Trivalent antimony, 24.9–32.3 µg/L; pentavalent antimony, 36.2–46.0 µg/L (12.5–5000 µg/L for each species)	Recoveries of 90–105%.	Moreno-Andrade et al. (2020)
Water (inorganic antimony species)	Water samples filtered through 0.2 mm pore-size cellulose-acetate membrane, flash frozen, and separated by anion exchange chromatography	AEC-ICP-MS	NR (but species concentrations as low as 0.04 µg/L reported)	Reported quantification of all of trivalent and pentavalent antimony, trithioantimonate, and tetrathioantimonate.	Guo et al. (2020)
Water (inorganic antimony species)	FBA method	FBA-HG-AFS	6 ng/L (100–2000 ng/L)	Recovery rates, 90–114%. Throughput of 54 samples/h.	Lima et al. (2020)
Water (inorganic antimony)	Pre-treatment/concentration with SPE cartridges	HPLC-ICP-MS and FT-ICR MS		Used to identify a new antimony species, trimethylmonothioantimony.	Yin et al. (2022)
Water (total antimony)	Water (or digest of a solid material) diluted with hydrochloric acid and made up to 2% v/v nitric acid	AA (direct aspiration; EPA Standard Method 204.1)	200 µg/L (optimal, 1000–40 000 µg/L)		US EPA (1978a)
Water (total antimony)	Water (or digest of a solid material) diluted with hydrochloric acid and made up to 2% v/v nitric acid	AA (graphite furnace; EPA Standard Method 204.2)	3 µg/L (optimal, 20–300 µg/L)		US EPA (1978b)

AA, atomic absorption; AEC, anion exchange chromatography; AES, atomic emission spectrometry; AFS, atomic fluorescence spectroscopy; CDC, Centers for Disease Control and Prevention; CT, cryotrapping; DRC, dynamic reaction cell; EDTA, ethylenediaminetetraacetic acid; EPA, United States Environmental Protection Agency; EXAFS, extended X-ray absorption fine structure; FBA, flow-batch analysis; FT-ICR, Fourier transform ion cyclotron resonance; GC, gas chromatography; HG, hydride generation; HPLC, high-performance liquid chromatography; HPLC-ES-MS, high-performance liquid chromatography with electrospray mass spectrometry; ICP-AES, inductively coupled argon plasma atomic emission spectroscopy; ICP, inductively coupled plasma; LCF, linear combination fitting; LOD, limit of detection; MCE, mixed cellulose ester; min, minute; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; NMR, nuclear magnetic resonance; NR, not reported; NWQL, National Water Quality Laboratory; OES, optical emission spectrophotometer; OSHA, Occupational Safety and Health Administration; PET, polyethlyene terephthalate; PVC, polyvinyl chloride; QQQ, (triple) quadrupole mass spectrometry; SPE, solid-phase extraction; TBAOH, tetrabutylammonium hydroxide; TMSb, trimethylantimony; USGS, United States Geological Survey; UV, ultraviolet; v, volume; XANES, X-ray absorption near edge structure.

[a] This is not a comprehensive nor a systematically selected list, but rather an indicative list of: (i) methods validated by NIOSH, the United States EPA, OSHA, or other relevant organizations; and (ii) methods illustrating the use and characteristics of different sampling, preparation, and instrumental analytical techniques.

[b] LODs are as reported and would be expected to vary depending upon instrument model, operation conditions, and calibration standard selection.

triple quadrupole mass spectrometry (Nouioui et al., 2018), and field-portable-X-ray fluorescence spectrometry has been demonstrated to be a very effective and rapid screening tool for solid plastic consumer products with antimony concentrations in the range of 100 to 60 000 µg/g (Turner & Filella, 2017). Time-of-flight secondary ion mass spectrometry has been shown to be of value in determining antimony concentrations for particle surface and bulk (Kappen et al., 2017), as well as having the potential to be applied to the analysis of single particles.

1.3.2 Speciation analysis of antimony in air, water, urine, soil, sediment, consumer products, and human tissues

Solid-phase antimony speciation may be determined in bulk samples by X-ray diffraction (Gržeta et al., 2002), when phases are sufficiently crystalline. Although more expensive, neutron powder diffraction, synchrotron-based X-ray diffraction, and X-ray absorption spectroscopy, including X-ray absorption near edge structure and extended X-ray absorption fine structure spectroscopy, collectively provide the means of accurately characterizing bond distances and coordination of antimony in solid phases at a molecular level, and of determining local- and long-range structures (Miller et al., 2019; Mayer et al., 2020). Micro-synchrotron-based X-ray fluorescence together with X-ray absorption near edge structure spectroscopy provides the means of mapping antimony speciation at the micrometre scale in, for example, PET bottles (Martin et al., 2010) and household dusts (Walden, 2010). The isotope ^{121}Sb is suitable for Mössbauer spectroscopy (Gržeta et al., 2002). A variety of extraction methods (e.g. the Bioaccessibility Research Group of Europe Unified Bioaccessibility Method) are used to measure operationally defined solid-phase antimony speciation, for example, to assess bioaccessibility in the gastrointestinal tract (Denys et al., 2012). Smichowski (2008) reviewed methods to determine antimony speciation in extracts of airborne particles. Reviews of methods to determine inorganic and organic speciation of antimony in biological media are available (e.g. see Hansen & Pergantis, 2008).

Aqueous-phase antimony speciation is routinely accomplished by hyphenated techniques involving liquid chromatographic separation of the chemical species followed by detection by atomic fluorescence spectrometry (González de las Torres et al., 2020), ICP-optical emission spectrometry (Moreno-Andrade et al., 2020), or ICP-MS (Guo et al., 2020). ICP-MS and ICP-optical emission spectrometry have typical limits of detection (LODs) of 0.5 and 50 µg/L, respectively, which may be comparable to or higher than concentrations observed in many waters. Sufficient sensitivity, together with challenges regarding comprehensively separating a wide range of antimony species and ensuring their stability during storage before analysis, are key limitations to these techniques (as summarized in Moreno-Andrade et al., 2020). Fang et al. (2020) reported high-resolution imaging of antimony(III) distribution in soil pore waters. Aqueous antimony speciation may be complex, so many methodologies focus on types of species – for example, antimony(III) or antimony(V) – or operationally defined classes of species (e.g. Chen et al., 2020). Independent verification of species otherwise determined by retention time is important (Guo et al., 2020).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence, including dietary and consumer products

Antimony is a naturally occurring element. Its abundance in the Earth's continental crust is estimated to be around 0.2 µg/g . Most antimony deposits are formed by hydrothermal activity. They are found in geological formations of a wide range of ages, although they tend to

be concentrated in the Palaeozoic and Cenozoic, and – particularly in China – predominantly in the Devonian (Grund et al., 2006; Dill et al., 2008; Seal et al., 2017).

Although antimony can exist in various oxidation states – including antimony(–III), antimony(0), antimony(III), antimony(IV), and antimony(V) – in environmental, biological, and geochemical samples, it exists mainly as antimony(III) and antimony(V). Antimony ores are dominated by antimony(III) minerals, the antimony(III) sulfide stibnite, and the antimony(III) oxide valentinite. These compounds of antimony are commonly found in ores of copper, silver, and lead. Oxidation of antimony ores may result in the formation of antimony(V)-bearing minerals such as natrojarosite ($NaFe_3(SO_4)_2(OH)_6$) or iron–antimony (oxy)hydroxides (Álvarez-Ayuso et al., 2022), or mixed antimony(III)–antimony(V) oxide minerals. Antimony – as either antimony(III) or, to a lesser extent, antimony(V) – is also a common minor or trace component of coal and petroleum (Filella et al., 2002). Antimony(V) readily substitutes for aluminium(III) in anorthite feldspar ($CaAl_2Si_2O_8$) (Miller et al., 2019), a very common mineral in the continental crust, meaning that even small concentrations of antimony(V) in anorthite could account for a substantial proportion of all antimony in the continental crust (Miller et al., 2019). Antimony in coal may be in either the antimony(III) or antimony(V) oxidation states, while (coal-derived) fly-ash leachates have similarly been found to contain antimony predominantly as either antimony(III) (Narukawa et al., 2005) or antimony(V) (Miravet et al., 2006). Miravet et al. (2007) measured predominantly antimony(III) in antimony leached from volcanic ash from the Copahue volcano, Argentina.

Releases of antimony, including both antimony(III) and antimony(V) compounds, into the environment occur as a result of natural processes, such as the weathering of rocks, soil runoff, wind-blown dust, volcanic eruptions, sea spray, forest fires, and from biogenic sources, as well as from anthropogenic sources, including mining and the processing of ores, industry (e.g. glass, dyestuff, ceramics, and fire retardants), coal combustion, metal production (e.g. copper), and refuse incineration (Pacyna, 1984; Mok & Wai, 1990; ATSDR, 1992; Slooff et al., 1992). Biological accumulation of antimony is low in algae and no antimony accumulation is produced during deep-water oceanic circulation. The few data available point to antimony accumulation near the soil surface, concentrations decreasing with increasing depth. There is little evidence of biomagnification of antimony in food-chains represented by the soil–vegetation–invertebrate–insectivore pathway of grasslands and little indication of significant accumulation by herbivorous mammals, despite marked contamination of their diets (Filella et al., 2002).

Nriagu (1989) estimated that natural sources of antimony emissions into the air and their median percentage contributions were as follows: wind-borne soil particles [32.5%], volcanoes [29.6%], sea spray [23.3%], forest fires [9.2%], and biogenic sources [12.1%]. However, anthropogenic activities have significantly affected the atmospheric flux of antimony over the past 2000 years (Shotyk et al., 1996; Barbante et al., 2004; Hong et al., 2009). Nriagu (1989) estimated that in 1983, anthropogenic sources contributed 59% of antimony emissions into the air, although this figure is questioned by Shotyk et al. (2005), who estimated that the ratio of anthropogenic to natural antimony emissions may be around 10 or more. Several studies have also indicated a positive correlation between locally increased concentrations of antimony in air, soil, and water and road traffic (European Commission, 2008), while the general population is exposed to low levels of antimony mainly in ambient air and food. Individuals can also be exposed to antimony(III) in PET water bottles or from consumer products containing antimony flame retardants, including textiles, toys, and aircraft

and automobile seat covers (ATSDR, 2019). Table 1.4 summarizes occurrences of antimony in environmental matrices, foodstuffs, drinking-water, and consumer products.

(a) Air

Releases of antimony to the atmosphere occur from natural and anthropogenic sources, which include coal combustion, smelting, and refining as major sources (Belzile et al., 2011). Global atmospheric antimony emissions from anthropogenic activities were estimated to be around 2232 tonnes in 2005 and then decreased gradually to about 1904 tonnes in 2010, with fuel combustion as the major source category. Asia and Europe accounted for about 57% and 24%, respectively, of the global total emissions, with China, the USA, and Japan ranked as the top three emitting countries (Tian et al., 2014). The United Kingdom (UK) Heavy Metals Monitoring Network reported that the mean air concentration of antimony in winter 2017–2018 was 1.84 ng/m^3 (Goddard et al., 2019). Belzile et al. (2011) reviewed published data on ambient air in Europe, North and South America, Asia, Oceania, Atlantic and Pacific Ocean islands, and the Arctic area. They found that air concentrations of antimony varied from a few picograms per cubic metre in remote areas to a few nanograms per cubic metre in urban areas and that values were much higher at contaminated sites (e.g. at a site close to a lead smelter, the average was 146 ng/m^3, with a range of 5.2–1210 ng/m^3).

Atmospheric particulate matter (PM) has also been found to be enriched with antimony. Pinto et al. (2015) reported that antimony is predominantly associated with PM with diameters less than approximately 2.5 μm ($PM_{2.5}$), indicating that antimony originates mainly from anthropogenic sources, such as industry and road traffic. Higher antimony levels in high-density traffic areas probably result from emissions from automobile engines and the abrasion of tyres, brake linings, and other automotive components that use antimony alloys (Belzile et al., 2011). Ramírez et al. (2020) have reported that the main sources contributing to antimony in PM smaller than approximately 10 μm (PM_{10}) are unidentified industry (62%), road dust (14%), fossil-fuel combustion and forest fires (12%), the iron and steel industry (7%), and traffic emissions (4%). A recent study reported that the annual average air PM_{10} mass concentration of antimony was 1.31 ng/m^3 at urban sites in Grenoble, France (Borlaza et al., 2021).

(b) Soil

Antimony occurs naturally as a trace element in soil, with its main source being the weathering of soil parent materials. Contamination of the soil leads to increased concentrations of antimony. Most of the antimony released into the environment is released to land (ATSDR, 2019). The soil concentration of antimony varies greatly because of variations in background concentrations, which reflect mineralization and parent material differences, and varying degrees of anthropogenic influence. Observed concentrations can be scale-dependent, and spatial distributions can be highly heterogeneous. Antimony contamination in soils occurs frequently on and around mining and smelting sites, often co-occurring with arsenic (Wilson et al., 2010).

On the basis of a national geochemical survey of soil in the USA, Smith et al. (2013) reported that the mean concentration of antimony was 0.84 mg/kg, while the range was from below the LOD (< 0.05 mg/kg) to 630 mg/kg. The average antimony concentration in the surface soils of the Bosten Lake Basin in central Asia was 1.05 mg/kg (Ma et al., 2019). However, in a region with geogenic antimony contamination (i.e. naturally occurring antimony) in Kutahya, Türkiye, the mean soil concentration of antimony was found to be 13.5 mg/kg (Guney et al., 2019).

Filella et al. (2002) reviewed published data on soils and found that antimony concentrations

Table 1.4 Occurrence of antimony in environmental matrices, foodstuffs, drinking-water, and consumer products

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Environmental samples in air, soil, water, and sediment							
Air, PM_{10} samples	United Kingdom, 25 sites, winter 2017/2018	123	1.84 (0.13–8.02) ng/m³	1.21 ng/m³	ICP-MS (0.002 ng/m³)	Monitoring sites around the United Kingdom Heavy Metals Monitoring Network; strong correlations were observed between Sb, Ba, and Cu concentrations	Goddard et al. (2019)
Air, PM_{10}, urban sites	Grenoble, France, 2017–2018	~390	Annual mean: 1.31 (25th, 0.33; 75th, 0.93) ng/m³		ICP-MS (NR)	Annual means: As, 0.33 ng/m³; Pb, 4.42 ng/m³; Cr, 1.65 ng/m³; Cd, 0.07 ng/m³; Cu, 8.5 ng/m³; Ni, 0.91 ng/m³	Borlaza et al. (2021)
Soil	USA, 2007–2010	4841	0.84 (< 0.05–630; SD, 9.1) mg/kg	0.57 (25th, 0.37; 75th, 0.80) mg/kg	ICP-MS (0.05 mg/kg)	National geochemical survey; means: Pb, 25.8 mg/kg; Cr, 36 mg/kg; Cd, 0.3 mg/kg; Cu, 17.9 mg/kg; Ni, 17.7 mg/kg; Sr, 159 mg/kg	Smith et al. (2013)
Soil	Bosten Lake Basin, central Asia, NR	48	1.05 (0.68–1.47; SD, 0.20) mg/kg		ICP-MS (0.05 mg/kg)	Means: As, 9.86 mg/kg; Pb, 17.1 mg/kg; Cr, 49.6 mg/kg; Cd, 0.15 mg/kg; Cu, 17.9 mg/kg; Ni, 23.1 mg/kg; Hg, 20.6 ng/g	Ma et al. (2019)
Soil	Kutahya, Türkiye, NR	53	13.5 (0.44–76.0) mg/kg		ICP-MS (NR)	Means: As, 182 mg/kg; Hg, 108 µg/kg	Guney et al. (2019)
Soil, around coal mines	Anhui, China, NR	33	4.0 (2.9–7.7) mg/kg		ICP-OES (0.0084 mg/kg)		Qi et al. (2011)
Soil, abandoned arsenic-containing mine	Hunan, China, 2019	190	6.5 (1.1–76.9; SD, 9.6) mg/kg	3.5 mg/kg	ICP-OES (NR)	Means: As, 394 mg/kg; Pb, 44.3 mg/kg; Sr, 232 mg/kg	Ran et al. (2021)
Soil, mining area	Zijiang River basin, Hunan, China, 2017	135	18.1 (3.8–251.0; SD, 32.7) mg/kg	9.7 mg/kg	ICP-OES (NR)	Means: As, 8.9 mg/kg; Cr, 90.3 mg/kg; Pb, 29.5 mg/kg	Zhang et al. (2019)
Soil, near mining areas	Central China, 2013	54	36.7 (9.6–111) mg/kg		AAS (NR)	Means: Cd, 0.472 mg/kg; Pb, 193 mg/kg; As, 89.0 mg/kg	Fan et al. (2017)
Soil, former mining sites	Sudetes, Poland, NR	6	(12.8–195) mg/kg		ICP-MS (NR)	As, 56–50 000 mg/kg	Lewińska et al. (2018)

Table 1.4 (continued)

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Soil, mining and smelting area	Hunan, China, NR	9	(100.6–5045) mg/kg		ICP-AES (0.63 µg/L)		He (2007)
Soil, mining area	Hunan, China, 2012	29	3061 (74.2–16 389; SD, 3715) mg/kg		ICP-MS (NR)	Means: As, 216 mg/kg; Cd, 1.93 mg/kg; Pb, 48.3 mg/kg; Cu, 23.6 mg/kg	Li et al. (2014)
Soil, shooting range	Alaska, USA, 2010–2015	12	(< LOD to 281.3) mg/kg		ICP-MS (5.9 mg/kg)	As, 12.9–21.0 mg/kg; Cr, 114–150 mg/kg; Pb, 19.5–16 410 mg/kg	Barker et al. (2019)
Soil, shooting range	Østre Toten, Norway, 2010	9	(40–123) mg/kg		ICP-MS (0.06 µg/L)	Pb, 356–1112 mg/kg; Cu, 41–88 mg/kg	Okkenhaug et al. (2016)
Soil, shooting ranges	Norway, 6 locations, NR	18	(< 0.001–830) mg/kg		ICP-MS (0.05 µg/L)	Pb, 20–13 000 mg/kg; Cu, 10–5200 mg/kg	Mariussen et al. (2017)
Soil, shooting ranges	Switzerland, 7 locations, NR	7	(500–13 800) mg/kg		ICP-MS (0.04 µg/L)		Johnson et al. (2005)
River water	Bytomka River, Poland, 2014–2015	60		0.91 (range, 0.36–1.78) µg/L	ICP-MS (0.05 µg/L)	Middle part of the river current below the water surface	Jabłońska-Czapla & Zerzucha (2019)
River-bottom sediments	Bytomka River, Poland, 2014–2015	60		33.6 (range, 5.9–98.1) mg/kg		Top 0–5 cm of river-bottom layer	
Surface water	Lowland dam reservoir, Poland, 2018	20		1.01 (range, 0.67–1.58) µg/L	ICP-MS (0.01 µg/L)	As: median, 1.96 µg/L	Jabłońska-Czapla & Grygoyć (2020)
Bottom sediments	Lowland dam reservoir, Poland, 2018	25		1.86 (range, 0.32–3.30) mg/kg		As: median, 33.4 mg/kg	
Surface water, mineralized areas	Alaska, USA, 2005–2007	2	(2.7–4.2) µg/L		ICP-MS (~5 µg/L)	Background (upstream) concentration	Ritchie et al. (2013)
Streambed sediments	Alaska, USA, 2005–2007	2	(91–968) mg/kg			Background (upstream) concentration	
Groundwater	Bangladesh, nationwide 1998–1999	112	(0.0015–1.8) µg/L		ICP-MS (0.0015 µg/L)	Water from tubewells; As, 0.0007–0.64 mg/L	Frisbie et al. (2002)

Table 1.4 (continued)

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Groundwater	England and Wales, nationwide (23 areas), NR	989	0.18 (< 0.05–3.43) µg/L	< 0.05 µg/L	ICP-MS (0.05 µg/L)	As: mean, 3.2 µg/L; median, < 1 µg/L	Shand et al. (2007)
Groundwater	Ibadan metropolis, Nigeria, 2016	210	13.5 ± 15.0 to 33.2 ± 36.8 µg/L		ICP-OES (NR)	Suggesting influence of geogenic factors; As, 2.17 ± 3.49 to 33.8 ± 37.2 µg/L	Etim (2017)
River water, mining areas	Nandan, China, NR	27	727 ± 820 µg/L		ICP-MS (NR)	River water of mine; As, 185 µg/L; Pb, 34 µg/L; Sr, 752 µg/L	Li et al. (2018)
River water further downstream from mining areas	Nandan, China, NR	6	192 ± 100 µg/L			River water (further downstream); As, 15 µg/L; Pb, 1 µg/L; Sr, 518 µg/L	
Sediments, mining areas	Nandan, China, NR	27	5942 ± 7337 mg/kg			Sediment in mining area; As, 11 577 mg/kg; Pb, 3406 mg/kg; Sr, 323 mg/kg	
Sediments, further downstream from mining areas	Nandan, China, NR	6	1696 ± 879 mg/kg			Sediment (further downstream); As, 5045 mg/kg; Pb, 2168 mg/kg; Sr, 229 mg/kg	
Discharge water, shooting ranges	Norway, 6 locations, NR	7	(0.34–65) µg/L		ICP-MS (0.05 µg/L)	Pb, 1.9–176 µg/L; Cu, 11–415 µg/L	Mariussen et al. (2017)
Subsurface soil water, shooting range		19	0.4 ± 0.33 to 150 ± 93 µg/L			Pb, 3.0–2500 µg/L; Cu, 1.3–900 µg/L	
Food and drinking-water							
Potable water	Greece, 19 locations, 2012	74	(< 0.01–2.12) µg/L		ICP-MS (0.01 µg/L)	Significant correlation: Sb/As (r = 0.61)	Andra et al. (2014)

Table 1.4 (continued)

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Water bottled in PET	Brands of bottled water from 28 countries, NR	132		0.33 (range, 0.001–2.57) µg/L	ICP-MS (NR)		Krachler & Shotyk (2009)
Water bottled in PET	Japan, NR	170	0.43 ± 0.52 µg/L		ICP-MS (0.2 µg/L)		Suzuki et al. (2000)
Water bottled in PET	Ontario, Canada, 2005	12	0.16 ± 0.09 µg/L		ICP-SF-MS (0.03 ng/L)	Natural water	Shotyk et al. (2006)
		3	0.16 ± 0.03 µg/L			Deionized water	
	Germany, 2005	6	0.36 ± 0.05 µg/L		ICP-SF-MS (0.03 ng/L)	Brand A	
		3	0.63 ± 0.02 µg/L				
		6	0.26 ± 0.02 µg/L			Brand B	
		6	0.30 ± 0.04 µg/L			Brand C	
	Brands of bottled water from 11 other European countries, 2005	35		0.343 µg/L	ICP-SF-MS (0.03 ng/L)		
Water bottled in PET	Türkiye, 2007	70	0.47 (0.29–1.23) µg/L	0.38 µg/L	ICP-MS (0.004 µg/L)	As: 1.71 (0.12–30.6) µg/L; median, 0.44 µg/L	Güler & Alpaslan (2009)
Water bottled in PET	Hungary, NR	37	0.26 ± 0.16 µg/L		ICP-SF-MS (0.7 ng/L)	Still mineral water	Keresztes et al. (2009)
		29	0.40 ± 0.22 µg/L			Sparkling mineral water	
Water bottled in PET	Monterrey, Mexico, NR	12	1.05 (0.28–2.30) µg/L		HG-AFS (0.113 µg/L)		Chapa-Martínez et al. (2016)
Water bottled in PET	Poland, NR	30	0.37 (0.08–1.15) µg/L	0.28 µg/L	ICP-MS (0.061 µg/L)	Flavoured bottled drinking-waters	Lorenc et al. (2020)
		12	0.39 (0.20–0.61) µg/L	0.43 µg/L		Functional bottled drinking-waters	
Water bottled in metals	Germany, NR	1	24.4 µg/L		ICP-MS (NR)	Pewter hip flask; consists of Cu–Sb alloy	Krachler & Shotyk (2009)
		1	5.0 µg/L			Stainless-steel flask	
Canned meat	Lublin, Poland, 2017	14	0.0268 (0.0028–0.0724) µg/g		ICP-MS (0.023 ng/g)		Kowalska et al. (2020)

Table 1.4 (continued)

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Canned fish		16	0.0377 (0.0014–0.0830) μg/g				
Various foods Milk and dairy products	Secondary school students, Hong Kong Special Administrative Region, China, 2000	100		< 0.001 (range, < 0.001–0.009) μg/g 0.001 (range, 0.0004–0.004) μg/g	ICP-MS (0.001 μg/g)	Cooked cereal and cereal products, vegetables, fruits, meat, poultry, eggs and their products, and seafood	Cheung Chung et al. (2008)
Rice grain	Zijiang River basin, including a mining area, China, 2017	135	0.027 ± 0.055 μg/g	0.007 (range, 0.002–0.408) μg/g	ICP-MS (0.001 μg/g)	Mean: Cu, 2.013 μg/g); Ni, 1.332 μg/g; Cr, 0.571 μg/g; Cd, 0.283 μg/g; As, 0.241 μg/g; Pb, 0.145 μg/g	Zhang et al. (2020)
Brown rice	Central China, near mining areas, 2013	54	5.175 (1.987–10.320) μg/g		AAS (NR)	Cd, 0.103 μg/g; Pb, 0.131 μg/g; As, 0.524 μg/g	Fan et al. (2017)
Wild fish	Gaotang Lake in the coal-mining area, China, NR	28	0.017 μg/g (range, 0.015–0.018 μg/g) in crucian carp to 0.040 μg/g (range, 0.018–0.083 μg/g) in common carp		AFS (0.5 ng/g)	Wet-weight basis; 6 fish species, including crucian carp, bighead carp, silver carp, tilapia, common carp, and grass carp; Cu, 2.47 μg/g; Cr, 1.60 μg/g; Pb, 0.122 μg/g; Co, 0.060 μg/g; As, 0.048 μg/g; Cd, 0.029 μg/g; Hg, 0.018 μg/g in common carp	Cheng et al. (2019)
Total diet study	Adults, Hong Kong Special Administrative Region, China, 2010–2011	600	≤ 0.004 μg/g		ICP-MS (0.001 μg/g)	Total diet study; 150 most commonly consumed food items were selected	Chen et al. (2014)
Total diet study	France, NR	998	≤ 0.0024 μg/g		ICP-MS (0.001 μg/g)	First total diet study; 300 individual food items	Leblanc et al. (2005)
Total diet study	France, 2007–2009	1319	≤ 0.0089 μg/g		ICP-MS (0.001 μg/g)	Second total diet study; 212 individual food items	Arnich et al. (2012)

Table 1.4 (continued)

Sample type	Location and collection date	No. of samples	Concentration of antimony		Analytical method (LOD)	Co-exposures and other relevant information	Reference
			Mean (range or percentile) or ± SD	Median (range or percentile)			
Consumer products							
Children's toys	Lebanon, NR	30	9.0 (< LOD to 159; SD, 31.2) µg/g		NR	Plastic toys	Korfali et al. (2013)
		23	2.1 (< LOD to 10 µg/g; SD, 6.2) µg/g			Modelling clays	
Cosmetics	Araraquara, Brazil, NR	3	12.7 ± 0.2 µg/g		AAS (0.3 µg/g)	Orange blush	Barros et al. (2016)
		3	14.5 ± 1.2 µg/g			Pink blush	
		3	9.1 ± 0.9 µg/g			Purple eye shadow	
Cosmetics	Spain and Germany, NR	12	(< 0.0013–75.6) µg/g		ICP-OES (0.0013 µg/g)	Kohl eyeliners; As, < 0.0008–12.6 µg/g; Pb, 1.73–410 807 µg/g; Cd, 0.0006–20.75 µg/g	Navarro-Tapia et al. (2021)
Cigarettes	France, NR	6	(1.2–1.5) ng/mL		ICP-MS (LOQ 0.1 ng/mL)	E-cigarette liquids	Beauval et al. (2017)
		96	(< 0.11–0.47) pg/mL puff		ICP-MS (LOQ 0.11 pg/mL puff)	Aerosols from 1 model of e-cigarette	

AAS, atomic absorption spectroscopy; AES, atomic emission spectroscopy; AFS, atomic fluorescence spectrometry; As, arsenic; Ba, barium; Cd, cadmium; Cr, chromium; Cu, copper; e-cigarette, electronic cigarette; Hg, mercury; HG, hydride generation; ICP, inductively coupled plasma; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; Ni, nickel; NR, not reported; OES, optical emission spectrometry; Pb, lead; PET, polyethylene terephthalate; PM_{10}, particulate matter, inhalable particles with diameters 10 µm and smaller; Sb, antimony; SD, standard deviation; SF-MS, sector field mass spectrometry; Sr, strontium.

ranged from 1.1 to 360 µg/g dry weight in areas around a smelter. Studies in and around mining areas have also reported mean soil concentrations of antimony ranging from 4.0 to 36.7 mg/kg (µg/g) (Qi et al., 2011; Fan et al., 2017; Zhang et al., 2019; Ran et al., 2021). Soil concentrations of antimony ranged from 12.8 to 195 mg/kg at former mining sites in the Sudetes in south-western Poland (Lewińska et al., 2018), and from 100.6 to 5045 mg/kg in a mining and smelting area in Hunan, China (He, 2007). Concentrations of antimony also averaged 3061 mg/kg in highly polluted soils of the mining area in Hunan, China (Li et al., 2014).

Soil contamination by antimony released from corroding ammunition or bullets also occurs, because antimony is used as a hardening agent in lead bullets (Ackermann et al., 2009; Hockmann et al., 2014; Melo et al., 2014). Several studies have reported that average soil concentrations of antimony in shooting ranges can be up to 13 800 mg/kg (Johnson et al., 2005; Okkenhaug et al., 2016; Mariussen et al., 2017; Barker et al., 2019).

(c) Water and sediments

The presence of antimony in ground- and surface water results primarily from rock weathering, soil runoff, and anthropogenic sources (Filella et al., 2002; Seal et al., 2017), including from mining and smelting, shooting ranges, and road-bound traffic dust from brake pads and tyres (ATSDR, 2019).

Filella et al. (2002) reviewed published data for fresh water, marine waters, and estuaries and found that typical concentrations of total dissolved antimony were usually < 1.0 µg/L in non-polluted waters, while the data for sediments revealed a range from < 0.05 µg/g dry weight in uncontaminated areas to 12 500 µg/g dry weight in areas around a smelter. Antimony is not considered to be a highly reactive element in oceans, with concentrations of the order of 200 ng/L (Filella et al., 2002). Studies on water and sediments at the bottom of bodies of water have also reported that median concentrations of antimony were 0.91 µg/L in water and 33.6 mg/kg in sediment of the Bytomka River, Poland (Jabłońska-Czapla & Zerzucha, 2019), and 1.01 µg/L in water and 1.86 mg/kg in sediment of the Kozłowa Góra dam reservoir, Poland (Jabłońska-Czapla & Grygoyć, 2020). Ritchie et al. (2013) reported that in Alaska, USA, the background (upstream) concentrations of antimony in Stampede Creek and Slate Creek surface waters and sediments from mineralized areas ranged between 2.7 and 4.2 µg/L and 91 and 968 mg/kg, respectively.

WHO reported that antimony concentrations in groundwater, surface water, and drinking-water were typically < 0.001, < 0.2, and < 5 µg/L, respectively (WHO, 2017). Frisbie et al. (2002) similarly found that the concentrations of antimony in groundwaters ranged from 0.0015 to 1.8 µg/L in Bangladesh. Shand et al. (2007) also reported antimony concentrations in the ranging from 0.1 to 1.0 µg/L in the majority of groundwaters in the UK.

However, antimony concentrations of > 100 µg/L in surface waters have been found near mining operations in various countries (Bolan et al., 2022). Etim (2017) reported mean concentrations of antimony in groundwater ranging between 13.5 and 33.2 µg/L in the shallow groundwater system of Ibadan metropolis, south-western Nigeria, suggesting an influence of geogenic factors. In China, the mean concentration of dissolved antimony in mining areas was 727 µg/L in river waters and 5942 mg/kg in sediments. The highest dissolved antimony concentration (5475 µg/L) in river water was found at the outfall of antimony ore flotation drainage (Li et al., 2018). The concentration ranges of antimony in discharge water and subsurface soil water were 0.34–65 and 0.4–150 µg/L, respectively, at six shooting ranges located in Norway (Mariussen

et al., 2017). Conventional water treatment processes do not remove antimony (WHO, 2017).

(d) Food and drinking-water

Belzile et al. (2011) reviewed published data on drinking-water and found that antimony concentrations in drinking-water were < 1.0 µg/L, except for some bottled waters that contained antimony at higher concentrations under extended storage conditions. Of 19 geographical locations in Greece, antimony concentrations in potable water systems were < 1.0 µg/L at 17 locations, 1.27 µg/L in Oreokastro, and 2.12 µg/L in Filippoi, Kavala (Andra et al., 2014).

Antimony(III) oxide is widely used as a building-block catalyst in the production of PET, with the resin containing residual antimony ranging from 200 to 300 mg/kg (Carneado et al., 2015). Previous studies have reported a wide range of antimony concentrations in water packaged in plastic PET bottles (0.001–2.6 µg/L; Suzuki et al., 2000; Shotyk et al., 2006; Güler & Alpaslan, 2009; Keresztes et al., 2009; Krachler & Shotyk, 2009; Chapa-Martínez et al., 2016; Lorenc et al., 2020), and in stainless steel and pewter flasks (5.0 and 24.4 µg/L, respectively) (Krachler & Shotyk, 2009). Some studies have also identified leaching of antimony from plastic PET bottles under certain environmental conditions (high temperatures, sunlight, and increased storage time outdoors), with concentrations in bottled water reaching as high as 2.6–14.4 µg/L, depending on conditions (Westerhoff et al., 2008; Cheng et al., 2010; Hureiki & Mouneimne, 2012; Fan et al., 2014; Al-Otoum et al., 2017).

In terms of food, Belzile et al. (2011) reviewed published data and found that concentrations in food are generally well below 1.0 µg/g on a dry-weight basis, suggesting that there should be little concern in terms of antimony uptake from food. Studies have also reported that the mean concentrations of antimony in canned meat and fish sold at a hypermarket in Lublin, Poland, were 0.027 and 0.038 µg/g, respectively (Kowalska et al., 2020). Median concentrations of antimony in food samples analysed did not exceed the LODs (0.001 µg/g for solid food and 0.1 µg/L for liquid food) in a diet study of secondary-school students conducted in Hong Kong Special Administrative Region, China (Cheung Chung et al., 2008). Mean concentrations of antimony in food samples analysed did not exceed 0.004 µg/g in the first Hong Kong Total Diet Study (TDS) (Chen et al., 2014), 0.0024 µg/g in the first French TDS (Leblanc et al., 2005), and 0.0089 µg/g in the second French TDS (Arnich et al., 2012). In rice grain gathered at the Zijiang River basin (including a mining and smelting area), China, mean concentrations of antimony were found to be 0.027 µg/g (range, 0.002–0.408 µg/g; Zhang et al., 2020). One study reported a high concentration of 5.175 µg/g (range, 1.987–10.320 µg/g) in brown rice gathered near mining areas in central China (Fan et al., 2017). In wild fish caught in Gaotang Lake, China, which is in a coal-mining area, mean concentrations of antimony ranged between 0.017 µg/g (range, 0.012–0.024 µg/g) and 0.040 µg/g (range, 0.018–0.083 µg/g) on a wet-weight basis (Cheng et al., 2019).

(e) Consumer products

Antimony(III) oxide is used as a plastic catalyst and in flame retardants, commonly in combination with brominated compounds, such as decabromodiphenyl oxide. As a flame retardant, it is used in plastics, paints, textiles, adhesives, and rubbers (Jayjock et al., 2015). As a fastener, opacifier, or a fining agent, antimony is also found in paints and enamels for ceramics and glassware, and in paint pigments in plastic materials (Turner & Filella, 2020). Antimony(III) oxide is found in several consumer products in which it is used for non-flame-retardant purposes, including children's toys, children's jewellery, and several PET product types, such as food trays and water bottles (Jayjock et al., 2015). Antimony is found also in cosmetics (Barros et al., 2016; Navarro-Tapia et al., 2021).

Jayjock et al. (2015) reviewed published data on consumer products, showing that concentrations of antimony varied from a few micrograms per gram in carpets or bedding to 30% (300 000 µg/g) in rubber and other elastomers. It was also reported by Butterman & Carlin (2004) that rubber and other elastomers are flame-retarded with halogen compounds and between 5% to as much as 30% antimony(III) oxide. However, the concentration of antimony in polyvinyl chloride straps, which infants might swallow, was found to be between 0.389 and 0.722 µg/g. Other studies have reported that the mean concentration of antimony was 9.0 µg/g in plastic toys and 2.1 µg/g in modelling clays for children (Korfali et al., 2013). In cosmetics, the concentration of antimony was found to range from < 0.0013 to 75.4 µg/g (Barros et al., 2016; Navarro-Tapia et al., 2021).

Antimony was found in liquids used in electronic cigarettes (range, 1.2–1.5 ng/mL) and in the aerosols that they produce (range, < 0.11–0.47 pg/mL puff); however, it was not found in smoke emitted by conventional cigarettes (Beauval et al., 2017).

1.4.2 Occupational exposure

Inhalation of airborne dust is considered to be the most significant route of occupational exposure to antimony. However, oral exposure through hand-to-mouth contact and direct dermal contact with antimony dust (e.g. direct handling, either by contamination of skin surfaces or by dermal deposition of airborne dust) are also concerns (ATSDR, 1992, 2019; European Commission, 2008; Saerens et al., 2019). Occupational exposure to antimony appears to be highest for workers involved in the production, formation, and processing of antimony and antimony(III) oxide. Workers in battery-formation areas in lead storage battery plants may also be exposed to high levels of antimony dust and stibine (see also Table 1.5, Table 1.6, Table 1.7, and Table 1.8).

Exposures may include a combination of several antimony compounds. In the atmosphere, the predominant forms of antimony are considered to be antimony(III) oxide and other oxides (to a lesser extent). In contrast, when dissolved in aqueous media, antimony is largely in the pentavalent-positive (+V) oxidation state. In addition, interconversion is possible in the environment as well as in vivo. Thus, studies on antimony exposure in workers have focused on antimony in general and not on specific valence states or species of antimony (Saerens et al., 2019).

The EU has reported on occupational exposure concentrations estimated on the basis of typical and worst-case inhalation, via personal air sampling and dermal-exposure scenarios in common occupational settings with antimony(III) oxide exposure, using data from measurements and modelling by RISKOFDERM (risk assessment of occupational dermal exposure to chemicals) (European Commission, 2008; Table 1.5). Only 1 of the 12 dermal-exposure scenarios (exposure in processing as a flame retardant in textiles) was modelled using RISKOFDERM. For dermal exposure in production of antimony(III) oxide, there was a sufficient number of measurements. For the other dermal-exposure scenarios, analogous/surrogate data were used. The highest inhalation exposure was estimated to occur during the production of antimony(III) oxide, particularly during the conversion process, followed by the final handling process in cases in which workers did not use respiratory protective equipment. In cases in which the workers used respiratory protective equipment, the highest exposure level was found to occur during raw material handling of flame retardants, in the production of plastics, and in the formulation stage for flame retardants in textiles. The highest dermal exposure was estimated to occur during the processing of flame retardants in textiles, followed by final

Table 1.5 Occupational exposure to antimony(III) oxide via inhalation and dermal exposure based on measured and modelled data in occupational settings in several European countries

Occupational setting	Process	Inhalation exposure (mg/m³)				Dermal exposure (µg/cm² per day)	
		Median (typical)		90th percentile (RWC)		Median	90th percentile
		With RPE[a]	Without RPE	With RPE[a]	Without RPE		
Production of antimony(III) oxide	Conversion[b]	0.027	0.54	0.15	2.9	5.2	16
	Refuming[c]	0.012	0.23	0.047	0.94	12	22
	Final handling[d]	0.040	0.79	0.110	2.1	18	31
Use as catalyst in production of PET	Powder handling	0.002	NA	0.026	NA	3.4[e]	5.8[e]
Use as flame retardant in production of plastics	Raw-material handling	0.13	NA	0.57	NA	6.8[e]	12[e]
Use as flame retardant in textiles	Formulation	0.13[f]	NA	0.57[f]	NA	4.5[g]	7.8[g]
	Processing	< 0.001	NA	0.001	NA	11[h]	72[h]
	Further handling	Negligible	NA	Negligible	NA	0.08	0.35
Use in pigments, paints, coatings, and ceramics	Loading and mixing[i]	0.036[f]	NA	0.16[f]	NA	2.3[g]	3.9[g]
Use as flame retardant in production of rubber	Formulation	0.051[f]	NA	0.22[f]	NA	2.3[g]	3.9[g]
	Processing	0.064[j]	NA	0.14[j]	NA	1.8[a]	3.1[a]
Use in production of crystal glass	Cutting	0.003[k]	NA	0.015[k]	NA	3[l]	11[l]

NA, not applicable; PET, polyethylene terephthalate; RPE, respiratory protective equipment; RWC, realistic worst case.

[a] With the use of RPE, the assigned protection factor was 10 for a P2 mask and 20 for a P3 mask. Use of RPE was mandatory in all surveyed plants. The median exposure level was called "typical" and the 90th percentile exposure level "worst case" exposure.

[b] Refers to conversion of antimony metal to antimony oxides and covers work tasks like loading of furnace with antimony ingots, supervision of operating conditions, and routine inspections and adjustments.

[c] Refuming (if crude antimony metal feedstock is used) is done to adjust the chemical and physical properties of the product. This is achieved by feeding the material through a furnace which has a free flow of air into the transfer ducting.

[d] Final handling covers all kind of work tasks at places where the final product, antimony(III) oxide, is handled, like weighing, packaging etc.

[e] Surrogate data extrapolated from data measured during bag filling at a plant producing antimony(III) oxide.

[f] Contains analogous/surrogate data measured during raw-material handling in the plastics sector.

[g] Recalculated from dermal exposure values of antimony(III) oxide production.

[h] Exposure levels were estimated from the model RISKOFDERM.

[i] Loading and mixing covers emptying of big bags, mixing, etc.

[j] Extrapolated from exposure to antimony(III) oxide measured in rubber fumes and rubber-process dust in the British rubber industry.

[k] Analogous data from the lead Risk Assessment Report (LDAI, 2006) were used.

[l] Analogous data on lead exposure (Wheeler & Sams, 1999) for estimation of dermal exposure to antimony(III) oxide were used.

From European Commission (2008).

Table 1.6 Antimony concentrations in samples of air, blood, urine, and hair of metal-exposed workers and administrative staff, by type of industry, in Taiwan, China

Type of industry	No. of samples	Mean concentration of antimony ± standard deviation[a]			
		Air (mg/m³)	Blood (µg/L)	Urine (µg/g creatinine)	Hair (µg/g)
Glass-manufacturing plant					
Workers	55	0.14 ± 0.01	0.78 ± 0.21	5.60 ± 1.24	0.10 ± 0.01
Administrative staff	20	0.007 ± 0.001	0.60 ± 0.11	2.55 ± 0.71	0.06 ± 0.01
Antimony(III) oxide-manufacturing plant					
Workers	14	2.51 ± 0.57	3.88 ± 1.10	27.15 ± 6.00	5.66 ± 3.66
Administrative staff	9	0.04 ± 0.01	1.07 ± 0.87	2.09 ± 0.55	0.04 ± 0.004
Engineering plastic-manufacturing plant					
Workers	22	0.21 ± 0.06	2.17 ± 0.48	7.48 ± 1.30	0.32 ± 0.05
Administrative staff	13	0.004 ± 0.001	0.49 ± 0.05	1.86 ± 0.55	0.04 ± 0.004
Total					
Workers	91	0.52 ± 0.88	1.61 ± 1.25	9.28 ± 6.31	1.00 ± 2.35
Administrative staff	42	0.012 ± 0.015	0.602 ± 0.0140	2.26 ± 0.68	0.048 ± 0.041

[a] Measurement results were significantly different between workers and administrative staff ($P < 0.001$) for all plants and all sample types.
From Wu & Chen (2017).

Table 1.7 Measurement of antimony in human biological specimens from workers in various types of industries at different production stages

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or ± SD	Median (range)		
Smelting						
Non-ferrous smelter producing antimony(V) oxide and sodium antimoniate, Belgium, NR	Urinary Sb	26	12.3 ± 5.0 µg/g creatinine 11.3[a] ± 1.56 µg/g creatinine		Wet process; end-of-shift sampling.	Bailly et al. (1991)
	Urinary Sb	14	110 ± 76 µg/g creatinine 91[a] ± 1.90 µg/g creatinine		Dry process; end-of-shift sampling.	
Secondary smelting of Pb for birdshot production, Italy, NR	Urinary Sb	18	5.9 (0.1–19.8) µg/L	2.8 µg/L	14 production workers, 2 technical employees, and 2 warehouse workers. End-of-shift sampling.	Lovreglio et al. (2018)
Production of antimony compounds						
Production of Sb_2O_3, Newcastle, United Kingdom, NR	Faeces	6	[2215] (1290–3510) ppm [µg/g] in dry faeces		Packaging department.	Oliver (1933)
Production of Sb_2O_3, Republic of Korea, 1995	Urinary Sb	11	182.7 ± 40.2 µg/g creatinine		Oxidation process; end-of-shift sampling.	Kim et al. (1997)
	Urinary Sb	10	137.1 ± 54.6 µg/g creatinine		Packing process; end-of-shift sampling.	
Production of Sb_2O_3, Republic of Korea, NR	Urinary Sb	12	410.8[a] ± 4.1 µg/g creatinine		Workers directly exposed to Sb_2O_3 through manufacturing processes.	Kim et al. (1999)
	Urinary Sb	22	112.5[a] ± 2.2 µg/g creatinine [b]		Workers in the same factory producing Sb_2O_3 as a major product, but not near the sources of Sb.	
Glass manufacturing						
Glass manufacturing containing Sb_2O_3, Germany, NR	Blood Sb	109		1.0 (0.4–3.1) µg/L	End-of-shift sampling; Pb, 250 (70–680) µg/L.	Lüdersdorf et al. (1987)
	Urinary Sb	109		1.9 (0.2–15.7) µg/L	End-of-shift sampling; Pb, 38 (7–110) µg/L.	
Textile industry						
Industrial plant producing fireproof textiles containing Sb_2O_3, Italy, NR	Urinary Sb	24	0.46 (0.16–1.77) µg/L		Finishing and intermediate inspection operators; end-of-shift sampling.	Iavicoli et al. (2002)
	Urinary Sb	15	0.18 (0.10–0.29) µg/L		Jet operators; end-of-shift sampling.	

Table 1.7 (continued)

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or ± SD	Median (range)		
Polymerization process of polyester fibre containing Sb_2O_3, Egypt, NR	Urinary Sb	22	13 (10–19) µg/L			El Shanawany et al. (2017)
Battery industry						
Production of lead batteries containing Sb_2O_3 and SbH_3, Germany, NR	Blood Sb	7		2.6 (0.5–3.4) µg/L	Grid-casting area, exposure to Sb_2O_3.	Kentner et al. (1995)
	Urinary Sb	7		3.9 (2.8–5.6) µg/g creatinine	Grid-casting area; end-of-shift sampling.	
	Blood Sb	14		10.1 (0.5–17.9) µg/L	Formation area, exposure to Sb_2O_3 and SbH_3.	
	Urinary Sb	14		15.2 (3.5–23.4) µg/g creatinine	Formation area; end-of-shift sampling.	
LBRWs and ERWs, Ghana, NR	Urinary Sb	64	0.75[a] (0.05–17) µg/g creatinine		First morning void sampling; LBRW; As, 75 µg/L[a]; Ni, 3.1 µg/L[a]; Pb, 1.8 µg/L[a]; Se, 24 µg/L[a]; Cr, 0.25 µg/g creatinine.[a]	Dartey et al. (2017)
	Urinary Sb	64	0.16[a] (0.03–7.6) µg/g creatinine		First morning void sampling; ERW; As, 101 µg/L[a]; Ni, 2.9 µg/L[a]; Pb, 1.1 µg/L[a]; Se, 32 µg/L[a]; Cr, 0.23 µg/g creatinine.[a]	
E-waste recycling industry						
Recycling workers, Sweden, 2007–2009	Blood Sb	50		2.2 (1.8–3.8) µg/L	Ni, 0.99 µg/L; Mn, 11 µg/L.	Julander et al. (2014)
	Urinary Sb	53		0.18 (0.054–0.9) µg/L	First morning void sampling; Ni, 1.8 µg/L; Mn, 11 µg/L.	
Recycling workers, Germany, 2017–2018	Urinary Sb	49	0.26[a] (0.15–2.4) µg/L	0.15 µg/L	End-of-shift sampling[a]; As, 1.96 µg/L; Cd, 0.16 µg/L; Cr, 0.10 µg/L; Co, 0.32 µg/L; Ni, 0.74 µg/L; Hg, 0.38 µg/L.	Gerding et al. (2021)
Firefighting						
Firefighters, Florida, USA, 2009	Urinary Sb	20	0.063 µg/g creatinine[a]	0.059 (0.027–0.285) µg/g creatinine	Department A, firefighters did not wear trousers made from Sb-containing fabric.	CDC (2009); de Perio et al. (2010)
	Urinary Sb	41	0.054 µg/g creatinine[a]	0.048 (0.017–0.366) µg/g creatinine	Department B, firefighters did wear trousers made from Sb-containing fabric.	

Table 1.7 (continued)

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or ± SD	Median (range)		
Firefighters, New York, USA, 2001	Urinary Sb	318	0.203 µg/L[a]		All firefighters.	Edelman et al. (2003)
	Urinary Sb	95	0.381 µg/L[a]		Special operation command firefighters (i.e. rescue, squad, and marine units).	

As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; ERW, electronic repair worker; Hg, mercury; LBRW, lead battery repair worker; Mn, manganese; Ni, nickel; NR, not reported; Pb, lead; ppm, parts per million; Sb, antimony; SD, standard deviation; Se, selenium.

[a] Geometric mean (geometric SD).

[b] Mean urine Sb concentration was significantly different ($P < 0.01$) from the mean value for workers who were directly exposed to Sb_2O_3.

Table 1.8 Occupational exposure to antimony measured in the air in various types of industries at different production stages

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or mean ± SD μg/m³	Median (range) μg/m³		
Smelting						
Non-ferrous smelter producing Sb_2O_5 and sodium antimoniate, Belgium, NR	Personal air, Sb dusts	26	86 ± 78 68 ± 1.94[a]		Wet process (handling a solution or a wet paste containing Sb); one whole work shift sampling.	Bailly et al. (1991)
	Personal air, Sb dusts	14	927 ± 985 594 ± 2.62[a]		Dry process (grinding, sieving, and packaging dry Sb products); one whole work shift sampling.	
Production of antimony compounds						
Production of Sb_2O_3, USA, 1960	Stationary air, Sb dusts	28	138 000		Bagging area.	Cooper et al. (1968)
Production of Sb_2O_3, Republic of Korea, 1995	Personal air, total Sb dusts	11	(8.3–40.0)		Oxidation process; whole 8 h work shift sampling.	Kim et al. (1997)
	Personal air, respirable Sb dusts	11	(2.0–3.8)		Oxidation process; whole 8 h work shift sampling.	
	Stationary air, total Sb dusts	11	22.3 ± 4.4		Oxidation process; whole 8 h work shift sampling.	
	Stationary air, respirable Sb dusts	11	2.8 ± 0.4		Oxidation process; whole 8 h work shift sampling.	
	Personal air, total Sb dusts	10	(22.3–402.5)		Packing process; whole 8 h work shift sampling.	
	Personal air, respirable Sb dusts	10	(1.7–5.0)		Packing process; whole 8 h work shift sampling.	
	Stationary air, total Sb dusts	10	280.6 ± 64.2		Packing process; whole 8 h work shift sampling.	
	Stationary air, respirable Sb dusts	10	3.4 ± 0.6		Packing process; whole 8 h work shift sampling.	
Production of Sb_2O_3, Republic of Korea, NR	Personal air, Sb dusts	12	766 ± 1850[a]		Workers directly exposed to Sb_2O_3 through manufacturing processes; more than 4 h sampling.	Kim et al. (1999)
	Personal air, Sb dusts	22	NT		Workers in the same factory producing Sb_2O_3 as a major product, but not near the sources of Sb.	

Table 1.8 (continued)

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or mean ± SD µg/m³	Median (range) µg/m³		
Glass manufacturing						
Glass manufacturing containing Sb_2O_3, Germany, NR	Personal air, Sb dusts	4	(< 50–840)		Batch bunker; 2 h sampling.	Lüdersdorf et al. (1987)
	Personal air, Sb dusts	4	< 50		Melting area; 2 h sampling.	
	Stationary air, Sb dusts	4	(40–290)		Batch bunker; 2 h sampling.	
	Stationary air, Sb dusts	4	(< 5–5)		Melting area; 2 h sampling.	
Textile industry						
Industrial plant producing fireproof textiles containing Sb_2O_3, Italy, NR	Personal air, Sb dusts	26	0.12 ± 0.11		Finishing and intermediate inspection operators; whole 8 h work shift sampling.	Cavallo et al. (2002)
	Personal air, Sb dusts	15	0.052 ± 0.038		Jet operators; whole 8 h work shift sampling.	
Industrial plant producing fireproof textiles containing Sb_2O_3, Italy, NR	Personal air, Sb dusts	24	0.11 ± 0.07		Finishing and intermediate inspection operators; whole 8 h work shift sampling during 5-day period.	Iavicoli et al. (2002)
	Personal air, Sb dusts	15	0.05 ± 0.04		Jet operators; whole 8 h work shift sampling during 5-day period.	
Battery industry						
Production of lead batteries containing Sb_2O_3 and SbH_3, Germany, NR	Personal air, Sb dusts	7		4.5 (1.2–6.6)	Grid-casting area, exposure to Sb_2O_3; over 3 h sampling.	Kentner et al. (1995)
	Personal air, Sb dusts and volatile SbH_3	14		12.4 (0.6–41.5)	Formation area, exposure to Sb_2O_3 and SbH_3; over 3 h sampling.	
E-waste recycling industry						
Recycling workers, Sweden, 2007–2009	Personal air, Sb dusts	77	0.21 ± 2.3[a] (0.0041–1.1)		Inhalable fraction according to EN 481; 10 h work shift, sampling during 5 h. Geometric means: Pb, 7.0 µg/m³; Ni, 0.49 µg/m³; Cr, 0.45 µg/m³; Cd, 0.18 µg/m³; Co, 0.07 µg/m³; As, 0.04 µg/m³; Hg, 0.01 µg/m³.	Julander et al. (2014)

Table 1.8 (continued)

Occupational group/job type, location, and time period	Monitoring method	No. of samples	Antimony concentration		Comments	Reference
			Mean (range) or mean ± SD μg/m³	Median (range) μg/m³		
Recycling workers, Germany, 2017–2018	Personal air, Sb dusts	40	0.091[b]	0.075 (0.051–0.34)	Inhalable fraction; during disassembly work. Geometric means: As, 0.033 μg/m³; Cd, 0.017 μg/m³; Cr, 0.20 μg/m³; Co, 0.041 μg/m³; Ni, 0.27 μg/m³; Hg, 0.47 μg/m³.	Gerding et al. (2021)
	Stationary air, Sb dusts	21	0.067[b]	0.062 (0.047–0.17)	Inhalable fraction; during disassembly work. Geometric means: As, 0.031 μg/m³; Cd, 0.009 μg/m³; Cr, 0.12 μg/m³; Co, 0.035 μg/m³; Ni, 0.11 μg/m³; Hg, 0.46 μg/m³.	
	Personal air, Sb dusts	4	0.076[b]	0.077 (0.064–0.088)	Respirable fraction; during disassembly work. Geometric means: As, 0.025 μg/m³; Cd, 0.008 μg/m³; Cr, 0.077 μg/m³; Co, 0.021 μg/m³; Ni, 0.076 μg/m³.	
	Stationary air, Sb dusts	12	0.064[b]	0.062 (0.047–0.14)	Respirable fraction; during disassembly work. Geometric means: As, 0.033 μg/m³; Cd, 0.007 μg/m³; Cr, 0.110 μg/m³; Co, 0.034 μg/m³; Ni, 0.08 μg/m³.	

As, arsenic; Cd, cadmium; Cr, chromium; Co, cobalt; e-waste, electronic and/or electrical waste; Hg, mercury; Ni, nickel; NR, not reported; NT, not tested; Pb, lead; Sb, antimony; SD, standard deviation.

[a] Geometric mean ± geometric SD.

[b] Geometric mean.

handling in the production of antimony(III) oxide (see Table 1.5) (European Commission, 2008).

The French National Institute for Research and Occupational Safety (INRS) provided data for air measurements of antimony in industrial sectors and job titles (INRS, 2022). By industrial sector, the manufacture of chemicals and chemical products showed the highest arithmetic mean (AM) value in the breathing zones of workers from personal air sampling (AM, 5.66 mg/m^3), followed by the manufacture of textiles (AM, 0.222 mg/m^3), the wholesale and retail trade (repair of motor vehicles and motorcycles) (AM, 0.145 mg/m^3), and the manufacture of rubber and plastic products (AM, 0.095 mg/m^3) (Table 1.9). By job title, plant and machine operators and assemblers had the highest arithmetic mean value (AM, 0.566 mg/m^3), followed by cleaners and helpers (AM, 0.235 mg/m^3) (Table 1.10).

In a cross-sectional study, Wu & Chen (2017) reported antimony exposure among employees in industries in Taiwan, China. In total, 91 workers and 42 office administrators (all men) from two glass-manufacturing plants, one antimony(III) oxide-manufacturing plant, and two engineering plastic-manufacturing plants were recruited. Table 1.6 shows antimony levels in samples of stationary air, blood, urine, and hair, by industry type for workers and administrative staff. The mean (± standard deviation, SD) antimony concentration in the air samples measured for the antimony(III) oxide-manufacturing plant was the highest (2.51 ± 0.57 mg/m^3), being approximately 18 times that for the glass-manufacturing plants (0.14 ± 0.01 mg/m^3) and 12 times that for the engineering plastic-manufacturing plants (0.21 ± 0.06 mg/m^3). The antimony concentrations in the blood, urine, and hair of workers at the antimony(III) oxide-manufacturing plant were also the highest. The antimony concentrations in the blood, urine, and hair of employees were significantly correlated with the concentrations in air samples, with coefficients of 0.713, 0.870, and 0.865 ($P < 0.01$), respectively. The measured antimony concentrations in air and in blood, urine, and hair samples were significantly lower among administrative staff than among workers ($P < 0.001$).

Several scenarios or situations regarding exposure to antimony and antimony compounds in occupational settings are summarized below. Detailed data relating to human tissues, air, and/or biological monitoring are shown in Table 1.7, Table 1.8, and Table 1.11. Occupational exposure may arise in various industrial sectors such as in smelting, the production of antimony compounds and of other metals, glass manufacture, textile production, battery manufacture, and electronic and/or electrical waste (e-waste) processing. Workers may be exposed to various antimony compounds in the workplace and may also have co-exposure to other agents, including arsenic, chromium, lead, cadmium, selenium, nickel, cobalt, and mercury (see Table 1.7, Table 1.8, and Table 1.11). Specifically, in the processing of mined materials, co-exposures may be expected to commonly include arsenic, lead, and silica, among other agents (see Table 1.4). The potential for co-exposure to known or suspected human carcinogens (IARC, 2022) has been reported in various occupational studies (see Table 1.12) [Exposure assessments involving detailed characterization of antimony speciation and co-occurrence of other agents, notably in airborne dusts, were limited.]

(a) Smelting

Smelter workers in northern Sweden were compared with a group of individuals from a nearby area who had no occupational exposure. The individuals studied consisted of a group of 76 deceased men who worked as copper-smelter workers at the Rönnskär smeltery and who died after April 1975. As controls, 25 age-matched men were selected from rural (Burträsk and Jörn) and urban (Stockholm) areas. In the lung tissue of exposed workers, median antimony

Table 1.9 Distribution of air concentrations of antimony dust in industrial sectors, 2000–2020, French National Institute for Research and Occupational Safety

Industrial sector	Antimony concentration in personal air (mg/m^3)				Antimony concentration in stationary air (mg/m^3)			
	N	AM	Median	IQR	N	AM	Median	IQR
Manufacture of textiles	10	0.222	0.012	< LOQ–0.252	8	0.008	NA	NA
Manufacture of chemicals and chemical products	26	5.66	1.37	0.356–6.22	10	0.814	0.677	0.568–1.09
Manufacture of rubber and plastics products	27	0.095	< LOQ	< LOQ–0.016	14	0.003	< LOQ	< LOQ to < LOQ
Manufacture of other non-metallic mineral products	14	0.009	< LOQ	< LOQ to < LOQ	4	NA	NA	NA
Manufacture of basic metals	23	0.007	< LOQ	< LOQ–0.007	60	0.003	< LOQ	< LOQ–0.004
Manufacture of fabricated metal products, except machinery and equipment	76	0.01	0.004	< LOQ–0.011	11	0.003	< LOQ	< LOQ–0.005
Manufacture of computer, electronic, and optical products	11	< LOQ	< LOQ	< LOQ to < LOQ	11	< LOQ	< LOQ	< LOQ to < LOQ
Manufacture of electrical equipment	10	0.013	0.008	< LOQ–0.017	26	0.012	< LOQ	< LOQ–0.014
Manufacture of machinery and equipment	20	0.005	0.001	< LOQ–0.008	18	0.002	< LOQ	< LOQ–0.001
Manufacture of other transport equipment	19	0.005	< LOQ	< LOQ–0.003	10	< LOQ	< LOQ	< LOQ to < LOQ
Water supply; sewerage, waste management, and remediation activities	79	0.008	< LOQ	< LOQ–0.005	62	0.004	< LOQ	< LOQ to < LOQ
Construction	10	0.005	< LOQ	< LOQ to < LOQ	NA	NA	NA	NA
Wholesale and retail trade: repair of motor vehicles and motorcycles	16	0.145	0.01	0.002–0.038	10	0.009	< LOQ	< LOQ–0.006
Financial and insurance activities	24	< LOQ	< LOQ	< LOQ to < LOQ	17	0.006	< LOQ	< LOQ to < LOQ
Administrative and support service activities	22	0.001	< LOQ	< LOQ to < LOQ	NA	NA	NA	NA
Human health and social work activities	35	0.004	< LOQ	< LOQ to < LOQ	NA	NA	NA	NA
Arts, entertainment, and recreation	9	0.029	NA	NA	1	NA	NA	NA

AM, arithmetic mean; IQR, interquartile range; LOQ, limit of quantification; N, number of measurements; NA, not applicable.
From INRS (2022).

Table 1.10 Distribution of air concentrations of antimony dust according to job title, 2000–2020, French National Institute for Research and Occupational Safety

Job title	Antimony concentration in personal air (mg/m³)				Antimony concentration in stationary air (mg/m³)			
	N	AM	Median	IQR	N	AM	Median	IQR
Environmental protection professionals	5	< LOQ	NA	NA	6	< LOQ	NA	NA
Technicians and associate professionals	29	0.004	< LOQ	< LOQ–0.006	9	0.007	NA	NA
Clerical support workers	8	0.01	NA	NA	NR	NR	NR	NR
Craft and related trades workers	166	0.012	<LOQ	<LOQ–0.005	59	0.013	< LOQ	< LOQ to < LOQ
Building and related trades workers, excluding electricians	13	0.005	< LOQ	< LOQ to < LOQ	NR	NR	NR	NR
Metal, machinery, and related trades workers	90	0.019	0.003	< LOQ–0.009	47	0.014	< LOQ	< LOQ–0.002
Handicraft and printing workers	16	0.011	< LOQ	< LOQ–0.018	12	< LOQ	< LOQ	< LOQ to < LOQ
Food-processing, wood-working, and garment and other craft and related trades workers	47	0.002	< LOQ	< LOQ to < LOQ	NR	NR	NR	NR
Plant and machine operators, and assemblers	85	0.566	0.007	< LOQ–0.047	56	0.067	< LOQ	< LOQ–0.01
Elementary occupations	64	0.028	< LOQ	< LOQ–0.004	30	0.003	< LOQ	< LOQ–0.001
Cleaners and helpers	7	0.235	NA	NA	NR	NR	NR	NR
Labourers in mining, construction, manufacturing, and transport	8	0.009	NA	NA	1	NA	NA	NA
Garbage collectors and other unskilled workers	49	0.002	< LOQ	< LOQ–0.001	29	0.002	< LOQ	< LOQ–0.001

AM, arithmetic mean; IQR, interquartile range; LOQ, limit of quantification; N, number of measurements; NA, not applicable; NR, not reported.
From INRS (2022).

Table 1.11 Measurement of antimony in human tissue samples from workers in the smelting and mining industries

Occupational group/job type, location, and time period	Sample type	No. of samples	Antimony concentration		Co-exposures (ng/g wet weight) and other relevant information	Reference
			Mean (range) (ng/g dry weight)	Median (ng/g wet weight)		
Smelting						
Copper smelter, Sweden, 1930–1982	Lung	76	NR	280	Death after April 1975: Cr, 410; Cd, 162; Pb, 140; As, 38; Se, 151; Co, 16	Gerhardsson et al. (1985)
Copper or lead smelter, Sweden, 1930–1980s	Lung	85	NR	260	Death after April 1975: Cr, 450; Cd, 166; Pb, 140; As, 35; Se, 152; Co, 17	Gerhardsson et al. (1988)
Production of antimony compounds and other metals						
Uranium miners, Germany, 1957–1992	Lung	6	NR (218–1180)	NR	Underground workers: As, 136–956; Cr, 2.7–41.2; Co, 157–525; Se, 410–1180	Wiethege et al. (1999)
	Lung	7	NR (40–340)	NR	Other workers: As, 17–95; Cr, 1.1–3.1; Co, 46–86; Se, 420–880	

As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; NR, not reported; Se, selenium.

Table 1.12 Occupational co-exposures with antimony in various processes

Process	Agent to which co-exposure was reported (IARC classification[a])							Study design	
	Arsenic (Group 1)	Cadmium (Group 1)	Chromium[b] (Group 1)	Nickel (Group 1)	Lead[c] (Group 2A)	Polonium-210[d] (Group 1)	Asbestos (Group 1)	Case–control studies	Cohort studies
Antimony smelting	✓				✓				Jones (1994); Schnorr et al. (1995)
Tin smelting	✓	✓			✓	✓			Binks et al. (2005); Jones et al. (2007)
Glass production	✓	✓	✓	✓	✓		✓	Wingren & Axelson (1987, 1993)	

[a] IARC (2022)
[b] Chromium(VI).
[c] Lead compounds, inorganic.
[d] Internally deposited α-particle-emitting radionuclides.

concentrations were approximately 9 and 15 times as high as those in the control group (280 ng/g wet weight compared with 32 ng/g wet weight in Burträsk and Jörn, and 19 ng/g wet weight in Stockholm), respectively (Gerhardsson et al., 1985). An additional study was conducted on 85 deceased smelter workers who worked at the same smeltery, which continued collection of tissues after the study of Gerhardsson et al. (1985), and a similar or the same mean concentration (260 or 280 ng/g wet weight) was found in lung tissue (Gerhardsson et al., 1988; Gerhardsson & Nordberg, 1993).

Another study of non-ferrous-smelter workers involved in the production of antimony(V) oxide and sodium antimonate reported that the mean (± SD) antimony concentration in the personal air of dry-process workers (927 ± 985 μg/m^3) (involved in grinding, sieving, and packaging dry antimony products) was approximately 11 times that of wet-process workers (86 ± 78 μg/m^3) (handling a solution or a wet paste containing antimony). The mean concentration of antimony in urine samples from dry-process workers was approximately 9 times that of wet-process workers. In addition, a significant correlation ($r = 0.86$, $P < 0.0001$) was found between personal air concentrations and increased antimony concentrations in urine (Bailly et al., 1991).

(b) Production of antimony compounds and other metals

In eastern Germany, antimony was found in the lung tissue of uranium miners exposed to ^{222}Rn and dust, even when they had stopped working more than 20 years before death. The antimony concentrations in individuals working underground (range, 218–1180 ng/g dry weight) were also higher than the reference values (range, 190–320 ng/g dry weight) (Wiethege et al., 1999).

Oliver (1933) investigated workers at an antimony-processing plant in Newcastle-upon-Tyne, UK. Six men were engaged in oxide manufacture, four of whom had done the job for 13 years but had been antimony smelters for many years before oxide production began. The two other men had worked with antimony for 2 and 3 years. Examination of faeces indicated that antimony intake had occurred, with concentrations of antimony ranging from 1290 to 3510 ppm [mg/kg] in dry faeces. The mean antimony concentration in four men employed for 13 years [2377.5 mg/kg] was higher than that of two men employed for 3 years or less [1890 mg/kg]. [The Working Group noted that this study was of limited informativeness because of its small sample size and when the assessment was made.]

At an antimony(III) oxide-manufacturing plant in Texas, USA, workers were exposed to crude ore and, primarily, antimony(III) oxide. The mean air concentration was 138 mg/m^3 in the area concerned with bagging operations and 0.08–75 mg/m^3 in other locations (Cooper et al., 1968).

At an antimony(III) oxide-manufacturing plant in Kyeonggi-do, Chungnam, Cheonnam, Republic of Korea, there were two workplaces where the processing of antimony(III) oxide occurred according to the work type (oxidation and packing). The workers in the oxidation area were exposed to antimony fumes during the process of antimony oxidation and exposed to antimony(III) oxide-product dusts while packing the powders into bags in the packing area. The packing area had local ventilation, but the oxidation area did not. The mean concentrations of antimony in personal air in the packing area (range, 22.3–402.5 μg/m^3) were higher than those in the oxidation area (range, 8.3–40.0 μg/m^3). The mean (± SD) stationary air concentration of total antimony dust in the packing area (280.6 ± 64.2 μg/m^3) was approximately 13 times as high as that in the oxidation area (22.3 ± 4.4 μg/m^3). However, the mean air concentrations of antimony in respirable dust and urine samples collected from workers between the packing and oxidation areas did not differ significantly (Kim et al., 1997).

Workers directly exposed to antimony(III) oxide at a manufacturing facility were compared with those at the same facility who did not work near sources of antimony. A second control group of volunteers without occupational exposure to antimony was also examined. The mean concentration of antimony in personal air for the exposed workers was 766 μg/m^3, and personal exposure concentrations for the control workers and volunteer controls were not measured. The geometric mean antimony concentrations in urine were 410.8, 112.5, and 27.8 μg/g creatinine for the exposed workers, control workers, and volunteer controls, respectively (Kim et al., 1999).

In workers at a factory where birdshot was produced by a secondary smelting of lead, the mean urinary antimony concentration was 5.9 μg/L in exposed workers. All measurements were higher than the LOD for exposed workers, whereas only 22% of measurements for the control group were higher than the LOD (Lovreglio et al., 2018).

(c) Glass manufacture

The production of glass involves the use of antimony. Exposure to antimony oxides occurs primarily in sectors of the glass industry where traditional, non-mechanized techniques are used, such as in the production of crystal and other art glasses (IARC, 1993). The stationary air concentration of antimony dust was 2 μg/m^3 or less in the glass-manufacturing department of a plant that produced hypodermic syringes from glass containing small amounts of antimony (Burroughs & Horan, 1981).

Lüdersdorf et al. (1987) reported that the mean stationary air concentrations of antimony at two glass-producing factories were between < 5 and 290 μg/m^3. The personal air concentrations of antimony that the workers were exposed to were between < 50 and 840 μg/m^3. The median antimony concentrations in blood and urine samples collected from exposed workers were 1.0 and 1.9 μg/L, respectively. Median antimony concentrations in blood and urine samples collected from unexposed controls were 0.6 and 0.4 μg/L, respectively. In analyses of antimony concentrations in blood samples collected from workers in four subgroups (i.e. melters, batch mixers, craftsmen, and glass washers), statistically significant differences were observed for the batch mixers (median, 1.1 μg/L) and glass washers (median, 1.1 μg/L) when compared with unexposed controls ($P < 0.05$), but not when compared with the melters (median, 0.8 μg/L) and craftsmen (median, 0.7 μg/L). In urine, higher values were found almost exclusively in samples from individuals working as batch mixers (median, 5.0 μg/L), and statistically significant differences ($P < 0.05$) were observed compared with the melters (median, 0.9 μg/L), craftsmen (median, 0.9 μg/L), and glass washers (median, 1.2 μg/L).

(d) Textile industry

Exposure to antimony has been reported in the textile industry, including among workers in an industrial plant producing fireproof textiles for car upholstery in Italy. Finishing operators unloaded fabric from the transportation trolleys and prepared it for finishing. Once per week, they prepared the antimony(III) oxide-based flame/fire-retardant suspension by mixing fireproofing and binding products. This mixture was then pumped automatically into a tank and used to impregnate the fabric. On the day of sampling, they were assisted by an intermediate inspection operator who checked the product after finishing with the flame retardant and sometimes sampled the textile. At the same time, jet operators were dyeing the raw textiles approximately 20 m away from the finishing plant. The concentrations of antimony in personal air and the urine samples collected from workers were significantly higher among the finishing and intermediate inspection operators than among the jet operators ($P < 0.05$) (Cavallo et al., 2002; Iavicoli et al., 2002), see Table 1.7 and Table 1.8. [Data from the study by

Iavicoli et al, (2002) pertinent to the absorption, distribution, metabolism, and excretion of antimony are detailed in Section 4.1.3(a)]. In Kafr El Dawwar, Beheira, Egypt, workers exposed to antimony(III) oxide while working on the polymerization of polyester in a polyester fibre plant were surveyed (antimony(III) oxide is used as a catalyst in polymerization). The mean concentrations of antimony in urine samples were 13 μg/L in the workers and less than the LOD (< 10 μg/L) in controls (El Shanawany et al., 2017).

(e) Battery industry

At a lead battery-production facility in Germany, workers in the grid-casting and formation areas were surveyed regarding the significance of exposure to antimony and antimony(III) oxide. Antimony(III) oxide dust arose during the casting of the plates during the skimmings of the melt. Stibine was generated while charging the battery plates at the formation area, particularly at the end of the charging process or upon overcharging. The workers in the formation area were exposed to both stibine and antimony(III) oxide, but the casters were exposed only to antimony(III) oxide. The median antimony exposure concentrations of workers in the formation area were approximately 3 to 4 times as high (personal air, 12.4 μg/m^3; blood, 10.1 μg/L; urine, 15.2 μg/g creatinine) as those of workers in the casting area (personal air, 4.5 μg/m^3; blood, 2.6 μg/L; urine, 3.9 μg/g). Median antimony concentrations in blood and urine samples from workers in both the formation and casting areas were considerably greater than the values for occupationally non-exposed individuals (blood, < 1 μg/L; urine, < 0.5 μg/L) (Kentner et al., 1995).

Antimony concentrations in urine samples from lead battery- and electronic-repair workers in Kumasi, Ghana, were measured. The job tasks of the lead battery-repair workers included the charging of lead batteries, the breaking of batteries to replace damaged batteries and the repair of lead plates, and replacement of the lead terminals of batteries by welding. The main job tasks of the electronic-repair workers were dismantling, soldering, and welding, and the reassembly of electronic equipment, including televisions, radios, video players, and computers. The geometric mean urinary antimony concentrations were approximately 5 times as high for the lead battery-repair workers (0.75 μg/g creatinine) as for the electronic-repair workers (0.16 μg/g creatinine) (Dartey et al., 2017).

(f) E-waste recycling industry

Julander et al. (2014) reported antimony exposure levels of recycling workers at three companies involved in e-waste recycling in Sweden. The workers recycled goods such as television sets and computers, electronic tools, toys, and small and large household appliances, and their main tasks were the dismantling, handling, inspection, and transportation of goods. The geometric means of personal air inhalable fraction antimony concentrations were 0.21 μg/m^3 for recycling workers and 0.0085 μg/m^3 for unexposed office workers. The median antimony concentrations in blood and urine samples collected from recycling workers were 2.2 μg/L and 0.18 μg/L, respectively, and 2.2 μg/L and 0.12 μg/L for unexposed office workers. The concentration in the personal air inhalable fraction correlated with concentrations of antimony in both blood ($r = 0.49$; $P = 0.019$) and urine ($r = 0.49$; $P = 0.017$) samples. No significant differences were detected between blood and urine samples from recycling workers and the unexposed office workers.

At the e-waste recycling workshops – where recycling workers mainly performed disassembly of cathode ray tubes and liquid crystal display screens, and sorting of small electronic devices such as consumer electronics – the geometric mean antimony concentrations in urine samples from recycling workers and unexposed controls were 0.26 and 0.36 μg/L, respectively. The difference between the two groups was not significant

(Gerding et al., 2021). [The Working Group noted the lack of occupational exposure data on antimony in e-waste recycling activities in low- and middle-income countries.]

(g) Firefighters

Antimony(III) oxides and antimony(V) oxides have been used as flame retardants in textiles, and uniforms made from fabric containing antimony are commonly worn by firefighters in the USA. NIOSH surveyed the exposure levels of firefighters to antimony and reported that the geometric mean urinary antimony concentrations for firefighters who did not wear trousers made from antimony-containing fabric (department A), firefighters who wore trousers made from antimony-containing fabric (department B), and the general population were 0.063, 0.054, and 0.126 µg/g creatinine, respectively. Means of the log-transformed antimony concentrations in urine samples from participants in departments A and B did not differ significantly; nevertheless, they were significantly lower than that of the general population ($P < 0.001$) (CDC, 2009; de Perio et al., 2010).

Elevated antimony concentrations were reported in urine samples collected from firefighters after they had attended the collapse of the World Trade Center in New York, USA, on 11 September 2001. The adjusted geometric mean (adjusted for covariates of age, race, creatinine, and log cotinine using analysis of covariance) was 0.203 µg/L for all 318 firefighters and 0.165 µg/L for 47 controls. A significant difference was observed between firefighters and controls ($P < 0.01$). By unit assignment, urinary antimony concentrations were 0.381 µg/L for 95 special operations command firefighters (i.e. rescue, squad, and marine units) and 0.169 µg/L for 195 other exposed firefighters (e.g. ladder and engine); the difference was statistically significant ($P < 0.01$) (Edelman et al., 2003).

1.4.3 Exposure of the general population, including biomonitoring levels

Exposure of the general population to a variety of forms of antimony may occur through multiple routes, given the natural occurrence of antimony in the environment, its emission from industrial plants, and its use in the manufacture of certain consumer products and medicines (ATSDR, 2019) (see Section 1.4.1 of the present monograph). Exposure to antimony may result from the ingestion of food and drinking-water (Belzile et al., 2011), the inhalation of PM containing antimony in ambient air (e.g. among those residing in close proximity to urban and industrial sources of antimony pollution) (Cao et al., 2016), contact with consumer products for which manufacture involves the use of antimony (e.g. polymers such as those used in food and drink packaging) (Belzile et al., 2011), and through the treatment of leishmaniasis (Miekeley et al., 2002).

Concerning the antimony species to which general populations are exposed, as discussed in Section 1.1.2 and Section 1.4.1 of the present monograph, antimony naturally occurs in multiple valence states, a variety of forms are used in industrial applications, and antimony is used for the treatment of leishmaniasis, which is particularly relevant to low- and middle-income countries with a high prevalence of the disease. [The Working Group noted that most of the general-population exposure data reviewed consisted of measurements of total antimony concentrations (e.g. in urine), which reflect exposure to any of the individual agents within the scope of this evaluation. For population-based studies, without information on the exposure source, it is difficult to attribute total antimony concentrations to a particular agent.]

Measurement of the total antimony concentration in urine is routinely used to assess recent exposures to different forms of antimony. Among the participants surveyed by the United States

National Health and Nutrition Examination Survey (NHANES) (CDC, 2021) in three later cycles – 2011–2012, 2013–2014, and 2015–2016 (> 2500 people/cycle) – median urinary antimony concentrations ranged from 0.041 (in 2013–2014) to 0.047 µg/L (in 2011–2012), a decrease compared with concentrations observed in the six earlier cycles conducted between 1999–2000 and 2009–2010, in which median concentrations ranged from 0.13 (in 1999–2000) to 0.05 µg/L (in 2009–2010). The 95th percentiles of urinary antimony concentrations for both sexes between 2011 and 2016 ranged from 0.188 to 0.201 µg/L. In the 2015–2016 NHANES cycle, median total urinary antimony concentrations were 0.053 and 0.042 µg/L for male and female participants, respectively, and 0.063, 0.060, and 0.044 µg/L in the age groups 6–11, 12–19, and ≥ 20 years, respectively (ATSDR, 2019). The 95th percentile of total antimony concentrations in spot urine samples collected from 5576 members of the Canadian general population (age, 3–79 years), surveyed from 2009 to 2011 as part of the Canadian Health Measures Survey, was 0.17 µg/L (Saravanabhavan et al., 2017). While there was a paucity of antimony biomonitoring data from general populations in low- and middle-income countries, the 95th percentile of total antimony concentrations in spot urine samples collected from 357 adults from western Kenya, recruited between 2016 and 2019, was 0.46 µg/L (Watts et al., 2021). The urinary antimony concentrations in all the population-based surveys described in this section were considerably lower than those reported in exposed workers (e.g. Table 1.6 and Table 1.7 in Section 1.4.2 of this monograph).

Other studies have quantified antimony concentrations in whole blood, plasma, and other tissues in the general population. The median total antimony concentration in plasma from 419 participants from a Spanish population was 2.23 µg/L, and a positive correlation was observed with age (Henríquez-Hernández et al., 2020). Hoet et al. (2021) reported an upper reference limit for total antimony in blood of < 0.08 µg/L, which was the method LOD for their study of a population in Belgium. Stojsavljević et al. (2021) did not detect (limit of quantification, 0.057 ng/g) antimony in a study of placental tissues taken after placental delivery in a survey of 105 healthy pregnant White women in Serbia.

Several population-based dietary surveys have provided estimates of total antimony intakes using the TDS method. These include Yaoundé, Cameroon (mean dietary exposure estimate, MDE, 0.014–0.034 µg/kg body weight (bw) per day, lower bound–upper bound) (Gimou et al., 2014), France (MDE, 0.03–0.04 µg/kg bw per day) (Arnich et al., 2012), Hong Kong Special Administrative Region, China (MDE, 0.016–0.039 µg/kg bw per day) (Chen et al., 2014), northern Italy (MDE, 0.050 µg/kg bw per day) (Filippini et al., 2020), and the UK (adults, MDE, 0.032–0.033 µg/kg bw per day; toddlers, age 1.5–4.5 years: 0.075–0.077 µg/kg bw per day; young people, age 4–18 years, 0.049–0.050 µg/kg bw per day; elderly people, 0.027 µg/kg bw per day) (Rose et al., 2010). Therefore, all the aforementioned population-based studies have reported mean dietary intakes well below the tolerable daily intake (TDI) of 6 µg/kg bw per day for drinking-water derived by WHO (WHO, 2003).

Elevated concentrations of antimony in biological specimens and estimated daily intakes have been reported in specific populations. These include patients being treated for leishmaniasis with antimony(V) (Miekeley et al., 2002), people living near mining areas (Wu et al., 2011; Ye et al., 2018; Guo et al., 2021a), cigarette smokers and e-cigarette users (Badea et al., 2018; Olmedo et al., 2021), and those exposed to second-hand smoke (Richter et al., 2009). For example, adults living in close proximity to an antimony mine in Xikuangshan, Hunan, China – the world's largest antimony mine – were estimated to have antimony intakes of 554 µg per day assuming a body weight of 60 kg [9.23 µg/kg bw per day],

which exceeds the WHO TDI of 6 µg/kg bw per day (Wu et al., 2011). Co-exposure to arsenic is also often present in such populations (Wu et al., 2011; Fan et al., 2017; Guo et al., 2021a). Although antimony is known to migrate from PET drinking bottles (Makris et al., 2013), the amount released does not appear likely to result in daily intakes that exceed the WHO TDI of 6 µg/kg bw per day. Estimates accounting for recommended daily water consumption were shown to be dependent on time (duration of storage) and temperature, ranging from 19 ng/kg bw per day [0.019 µg/kg bw per day] for a 72 kg adult after 1 month of storage at 6 °C to 259 ng/kg bw per day [0.26 µg/kg bw per day] for a 10 kg child after 12 months of storage at 40 °C (Zmit & Belhaneche-Bensemra, 2019).

1.5 Regulations and guidelines

1.5.1 Exposure limits and guidelines

(a) Occupational exposure limits

The occupational exposure limit (Table 1.13) in the USA for antimony and its compounds (CAS No. 7440-36-0, measured as antimony) in air is 0.5 mg/m^3 as a time-weighted average (TWA) over an 8-hour (Occupational Safety and Health Administration, OSHA; American Association of Governmental Industrial Hygienists) or up to 10-hour (NIOSH) work shift (OSHA, 2021), broadly as recommended by NIOSH (1978) on the basis of a working lifetime of exposure with a 40-hour work week. Similar limits are prescribed for Canadian Jurisdictions (e.g. Ontario) (Ontario Ministry of Labour, Training and Skills Development, 2020), although "ALARA" (as low as reasonably achievable) is indicated for the production of antimony(III) oxide by the Ontario Ministry of Labour, Training and Skills Development (2020). Lower limits exist in Sweden (0.25 mg/m^3), Latvia, and Romania (0.20 mg/m^3), and Japan (0.1 mg/m^3) (International Antimony Association, 2021; IFA, 2021a), while a lower limit of 0.02 mg/m^3 is under consideration by NIOSH and OSHA in the USA (International Antimony Association, 2021). The German Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA 2021b, c) reports 8-hour occupational exposure limits separately for antimony(III) oxide (CAS No. 1309-64-4) and antimony(III) hydride (CAS No. 7803-52-3) for more than 20 jurisdictions. German Technical Rules for Hazardous Substances (TRGS 900) have indicated an occupational exposure limit of 0.006 mg/m^3 for respirable antimony in the form of antimony(III) oxide or antimony(III) sulfide (BAuA, 2018; International Antimony Association, 2021). OSHA (2021) also reports a value for antimony of 50 mg/m^3 for "immediately dangerous to life or health", a parameter "established (1) to ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment and (2) to indicate a maximum level above which only a highly reliable breathing apparatus, providing maximum worker protection, is permitted" (NIOSH, 2019).

(b) Air, water, soil, consumer products, and food

For non-occupational settings, selected regulatory and/or screening values for air, water, soil, food, pharmaceuticals, and toys are summarized in Table 1.14.

Ontario, Canada, set a 24-hour ambient air quality concentration target for antimony of 25 µg/m^3 (Government of Ontario, 1990).

WHO (2003) has published a guideline value of 20 µg/L for total antimony in drinking-water, and this remains the WHO guideline value in 2022. The United States Environmental Protection Agency (US EPA) has recommended a maximum contaminant level for antimony in drinking-water in the USA of 0.006 mg/L (i.e. 6 µg/L) (Office of the Federal Register, 2021; US EPA, 2021). Canada has adopted the same maximum admissible concentration (Health Canada, 2019).

Table 1.13 Occupational exposure limits for antimony and antimony compounds in various countries

Country	Antimony and its compounds (except stibine) CAS No. 7440-36-0 (as Sb)		Antimony(III) oxide CAS No. 1309-64-4 (as Sb)		Antimony(III) hydride (stibine) CAS No. 7803-52-3	
	Limit value		Limit value		Limit value	
	8 h (mg/m³)	Short-term (mg/m³)	8 h (mg/m³)	Short-term (mg/m³)	8 h (mg/m³)	Short-term (mg/m³)
Australia	0.5		0.5		0.51	
Austria	0.5[a]	1.5[a]	0.1[b]	0.4[b]	0.5	2.5
Belgium	0.5				0.52	
Canada (Ontario)	0.5		ALARA[c]	ALARA[c]		
Canada (Quebec)	0.5		0.5		0.51	
China	0.5					
Denmark	0.5	1.0			0.25	0.5
Finland	0.5		0.5			0.26[d]
France	0.5				0.5	
Germany (AGS)			0.006[e]	0.048[d]		
Hungary	0.5	2	0.1	0.4	0.5	2
Ireland	0.5					
Japan (JSOH)	0.1					
Japan (MHLW)			0.1			
Latvia	0.2	0.5[d]	1			
New Zealand	0.5		0.1		0.51	
Norway	0.5				0.25	
Poland	0.5				0.5	1.5[d]
Romania	0.2	0.5[d]			0.2	0.5[d]
Singapore	0.5		0.5		0.51	
Republic of Korea	0.5		0.5		0.5	
Spain	0.5				0.5	
Sweden	0.25[a]		0.25[f]		0.3	
Switzerland	0.5[a]		0.1[b]		0.5	0.5
The Netherlands	0.5				0.5	
USA (NIOSH)	0.5				0.5	
USA (OSHA)	0.5				0.5	
United Kingdom	0.5		0.5		(0.52)[g]	(1.6)[g]

AGS, Ausschuss für Gefahrstoffe [Committee on Hazardous Substances]; ALARA, As Low as Reasonably Achievable; CAS No., Chemical Abstracts Service Registry Number; JSOH, Japanese Society of Occupational Health; MHLW, Ministry of Health, Labour and Welfare; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration.

[a] Inhalable fraction.

[b] Inhalable aerosol.

[c] Exposure by all routes should be carefully controlled to levels as low as possible.

[d] 15-minute average value.

[e] Respirable fraction.

[f] Inhalable dust.

[g] The United Kingdom Advisory Committee on Toxic Substances has expressed concern that, for the OELs shown in parentheses, health may not be adequately protected because of doubts that the limit was soundly based.

From IFA (2021a, b, c).

Table 1.14 Environmental regulations and guidelines for antimony and antimony compounds

Regulation/guideline	Country or location	Value and units	Reference
Air			
24 h Local Air Quality Regulation Standard 24 h Ambient Air Quality Criteria target Annual Ambient Air Quality Criteria target	Canada, Ontario	25 µg/m^3 0.6 µg/m^3 0.12 µg/m^3	Government of Ontario (1990) CAREX Canada (2022)
Water			
WHO guidelines for drinking-water quality	World	20 µg/L	WHO (2003)
Guidelines for Canadian drinking-water quality	Canada, Ontario	0.006 mg/L	Health Canada (2019)
European Council directive on the quality of water intended for human consumption	European Union	5 µg/L	European Council (1998)
Standards for drinking-water quality, national standard of the People's Republic of China	China	5 µg/L	Standardization Administration of the People's Republic of China (2006)
Australian drinking-water guidelines 6, version 3.4, updated October 2017	Australia	3 µg/L	NHMRC, NRMMC (2017)
National standards for drinking-water quality	Pakistan	≤ 5 µg/L	Government of Pakistan (2008)
National primary drinking-water regulations	USA	6 µg/L	US EPA (2021)
Soil			
Soil screening values	United Kingdom	37 mg/kg dry weight (as Sb)	Martin et al. (2020)
Canadian soil quality guidelines	Canada	20 mg/kg (agricultural, parkland) 40 mg/kg (commercial, industrial)	Canadian Council of Ministers of the Environment (2007)
Food			
European Food Safety Authority Scientific Panel opinion	European Union	40 µg/kg of food (as Sb)	EFSA (2004)
Consumer products			
Permitted daily exposure as impurity in pharmaceuticals	USA	120 µg/g; 1200 µg/day (oral) 9 µg/g; 90 µg/day (parenteral) 2 µg/g; 20 µg/day (inhalation)	USP (2017)
Permitted concentration in toy materials	Sweden	45 mg/kg (dry, brittle, powdery, or flexible toy material) 11.3 mg/kg (liquid or sticky toy material)	KIFS (2017)

Sb, antimony.

In the EU (European Council, 1998) and China (Standardization Administration of the People's Republic of China, 2006), regulatory maximum concentrations of antimony in drinking-water (in the EU, water intended for human consumption is defined as "cover[ing] all water either in its original state or after treatment, intended for drinking, cooking, food preparation or other domestic purposes, regardless of its origin and whether it is supplied from a distribution network, from a tanker, or in bottles or containers; and all water used in any food-production undertaking for the manufacture, processing, preservation or marketing of products or substances intended for human consumption") are 5 µg/L (European Commission, 2018), although it is recognized that this longstanding regulatory value is lower than the WHO (2003) guideline value. Australia (NHMRC, NRMMC, 2017) has an even lower guideline value of 3 µg/L. In contrast, many low- and middle-income countries have either adopted a default WHO (2003) or earlier guideline value in their regulations (e.g. Pakistan, ≤ 5 µg/L) (Government of Pakistan, 2008), or do not seem to have any explicit regulatory value for antimony in drinking-water (e.g. India and Bangladesh) (Bureau of Indian Standards, 2012; PHED, 2015). WHO (2018) noted that 76 out of 104 countries and territories considered have set a regulatory/guideline value, with 62 of them setting a value lower than the WHO guideline value, the median value (set by 50 countries) being 5 µg/L.

The UK Environment Agency reported a soil screening value for total antimony of 37 mg/kg (dry weight) based on soil ecotoxicity (Martin et al., 2020). The Canadian Council of Ministers of the Environment (2007) reported use-dependent soil quality guidelines for Canada of 20 mg/kg for agricultural and residential or parkland uses, and 40 mg/kg for commercial and industrial uses. Bolan et al. (2022) cited highly variable values for the bioavailability of antimony in soils depending on the nature and distribution of antimony phases, indicating the future utility of chemical species-dependent soil quality guidelines for antimony.

The European Food Safety Authority recommended a restriction of 0.04 mg/kg of antimony(III) oxide as antimony in food (EFSA, 2004), on the basis of a 10% allowance of a WHO (2003)-recommended TDI for antimony of 0.006 mg/kg bw per day. According to Norwegian Ministry of Health and Care Services (2021) regulations, food-contact plastic materials and articles must not release antimony in quantities giving rise to antimony concentrations in excess of 0.04 mg/kg food.

The United States Pharmacopeia (USP, 2017) indicated limits of 120, 9, and 2 µg/g for total antimony as a trace impurity in pharmaceuticals to be administered via oral, parenteral, and inhalation routes, respectively, on the basis of recommended permitted daily exposures of 1200, 90, and 20 µg per day for each of those routes, respectively (USP, 2017).

To limit migration of antimony from toys, the Swedish Chemicals Agency has set regulations on the upper permissible concentrations of antimony in toys of 45 mg/kg for dry, brittle, powdery, or flexible toy material, and 11.3 mg/kg for liquid or sticky toy material (KIFS, 2017).

Notwithstanding concerns over toxicity, antimony(III) oxide continues to be used as a flame retardant because of the poorer performance of potential substitutes, notably aluminium trihydrate and magnesium hydroxide (European Commission, 2020a).

1.5.2 Reference values for biological monitoring

A summary of selected reference values for human exposure biomonitoring is given in Table 1.15. Saravanabhavan et al. (2017) reported a reference value (RV95) for total antimony in urine of 0.17 µg/L (95% confidence interval, CI, 0.15–0.19 µg/L) (children and adults) on the

basis of the 95th percentile of observations made of a Canadian population. Equivalent reference values have also been reported for populations in Germany (children, 0.3 µg/L; Schulz et al., 2009; adults, 0.2 µg/L; Göen et al., 2020, Heitland & Köster, 2006), Italy (0.095 µg/L; Aprea et al., 2018), the UK (0.26 µg/L; Morton et al., 2014), Belgium (0.236 µg/L; Hoet et al., 2013), and France (0.32 µg/L; Fréry et al., 2011; 0.41 µg/L, Nisse et al., 2017). The International Labour Organization and WHO (ILO, WHO, 2006) indicated that pregnant women should not be exposed to antimony (i.e. the urinary antimony concentration should not exceed the non-exposed reference limit of 0.8 nmol/L [0.1 µg/L]).

1.6 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

1.6.1 Epidemiological studies of cancer in humans

The Working Group identified 16 key studies of cancer in humans for which a critical appraisal of exposure assessment methods was undertaken; these included 8 cohort studies and 8 case–control studies. Of these studies, two case–control studies investigated exposure to antimony(III) oxide, one prospective and one retrospective cohort study investigated antimony-containing ores, two retrospective cohort studies investigated antimony-containing feedstock from smelting, and the remaining studies either did not, or did not intend to, specify the specific agent (this last group being population-based – rather than occupationally based – investigations). The critiques undertaken for each study in relation to different aspects of exposure assessment, in addition to the identification of the specific agent under investigation, are tabulated in Table S1.16 (Annex 1, Supplementary material for Section 1, Exposure Characterization, web only, available from: https://publications.iarc.fr/618).

(a) Exposure assessment methods

(i) Cohort studies

Several investigations were conducted on workers employed at a tin smelter in the UK (Binks et al., 2005; Jones et al., 2007), an antimony smelter in the UK (Jones, 1994), and an antimony smelter in south Texas, USA (Schnorr et al., 1995). The tin smelter in the UK, in operation from 1937 through 1991, processed tin ore concentrates and raw ore as feedstock to produce high-purity tin, lead, copper, cadmium, antimony, and silver; after 1967, the smelter underwent major upgrades, including the introduction of ventilation systems (Binks et al., 2005; Jones et al., 2007). At the antimony smelter in the UK, work practices and raw materials changed over time, including the sourcing of the ore, although most of the sulfide ore came from South Africa and contained about 60% antimony and up to 0.5% arsenic (Jones, 1994). At the antimony smelter in the USA, there was little change in process operations from 1930 until it closed in 1979; the primary source of ore was composed mainly of antimony oxide or antimony sulfide (Schnorr et al., 1995). Schnorr et al. (1995) presented summaries by operation of 8-hour area (n = 12) and personal sampling (n = 50) measurements for antimony and arsenic collected in 1975 and 1976, respectively. Overall, the surveys showed that personal exposures to antimony for workers involved in various operations at the smelter exceeded the OSHA permissible exposure limit (PEL) of 500 µg/m^3 for antimony; all measured exposures were below the OSHA standard for arsenic at the time (OSHA PEL, 500 µg/m^3). Across operations, personal exposures (n = 6) were highest for antimony (range, 90–3100 µg/m^3; geometric mean, 1498 µg/m^3) and arsenic (range, 8–37 µg/m^3; geometric mean,

Table 1.15 Biomonitoring guidance and reference values for antimony and antimony compounds

Regulatory/guideline or reference value	Country/ location	Value and units	Reference
Urine			
Occupational biomonitoring reference value (biological reference value, end-of-shift after several previous shifts)	Germany	0.2 µg/L	Göen et al. (2020)
Federal Environment Agency biomonitoring reference value for children	Germany	0.3 µg/L	Schulz et al. (2009)
Biomonitoring reference value RV95 for adults	Belgium	0.236 µg/L	Hoet et al. (2013)
	Italy	0.095 µg/L	Aprea et al. (2018)
	France	0.32 µg/L or 0.25 µg/g creatinine	Fréry et al. (2011)
	United Kingdom	0.26 µg/L	Morton et al. (2014)
Biomonitoring reference value RV95 for children and adults	Canada	0.17 µg/L	Saravanabhavan et al. (2017)
	USA	0.18 µg/g creatinine (survey 2015–2016)	CDC (2021)
Biomonitoring reference value for men, 75th percentile	Wuhan, China	0.19 µg/L (spot)	Wang et al. (2019a)
Blood			
Reference values for adults (non-fasting sample)	Belgium	< 0.08 µg/L[a]	Hoet et al. (2021)
Serum			
Biomonitoring reference value RV95 for urban and rural men and women	Andalusia, Spain	2.29–2.4 µg/L	Henríquez-Hernández et al. (2020)

RV95, 95th percentile of the substance of interest at a specific time point rounded off within its 95% CI.

[a] Reference limit is below the limit of detection.

19 μg/m³) among workers operating the oxide furnace. [The OSHA PEL for arsenic is currently 10 μg/m³.]

These prospective and retrospective cohort studies applied standard methods in comparing all-cause or cause-specific mortality rates of male worker populations with national and regional population rates (Jones, 1994; Schnorr et al., 1995; Binks et al., 2005). Cohorts were restricted to include workers employed for at least 3 (Jones, 1994; Schnorr et al., 1995) or 12 months (Binks et al., 2005). Jones (1994) also categorized the cohort into four occupational groups (antimony workers, maintenance workers, zircon workers, and others) and computed standardized mortality ratios (SMRs) for each group, stratified by initial employment before and after 1 January 1961. In addition, for lung cancer mortality, Binks et al. (2005) and Jones (1994) performed subcohort analyses using quantitative (i.e. time-related) variables (e.g. years of employment, years since entering employment, and date of first employment). In a follow-up study of lung cancer mortality among workers assessed previously by Binks et al. (2005), an exposure assessment was conducted that relied on over 20 000 occupational hygiene measurements from area and personal sampling conducted between 1972 and 1991 (with lead most often measured) to estimate annual average levels of antimony and other contaminants in seven process areas of the smelter (Jones et al., 2007). For earlier periods dating back to 1937, three extrapolation methods were applied by: applying the mean of the three earliest years for which data were available, applying a linear increasing trend from baseline values to values higher by two-fold in the early 1940s, and applying a linear increasing trend to values higher by two-fold in 1960 and subsequently declining to one half of the baseline in 1937. Under each scenario, this exposure matrix (with three dimensions: time, jobs, and exposure level) was coupled to work histories obtained from personnel records to generate estimates of cumulative exposures to antimony (mg year/m³). Cumulative exposures to other contaminants (arsenic, cadmium, lead, and polonium-210) were also computed.

Two population-based cohort studies relied on measurements of metals in spot urine samples collected from adults (age, ≥ 20 years) participating in the United States Centers for Disease Control and Prevention NHANES 1999–2014 survey to assess associations between metal exposures and cancer mortality. The earlier study assessed the impact of antimony on mortality with no assessment of exposures to other metals (Guo et al., 2016), whereas the later study assessed the impact of 10 metals including cobalt, antimony, and tungsten (with creatinine concentration added as a continuous covariate to the regression models that were applied) (Duan et al., 2020). In addition to models that assessed each metal separately, Duan et al. (2020) assessed the metal mixture using weighted quantile sum (WQS) analyses.

In the Sister Study (a cohort of 50 884 women in the USA, recruited between 2003 and 2009, who had a sister who had received a diagnosis of breast cancer), modelled estimates of metal (antimony, cobalt, arsenic, cadmium, chromium, lead, manganese, mercury, nickel, and selenium) concentrations in air (μg/m³) at the census tract-level from the 2005 US EPA National Air Toxics Assessment (NATA) were linked to participants' geocoded residences at baseline (White et al., 2019). In addition, the metal mixture was assessed using WQS regression. In another investigation of the Sister Study cohort that applied a race/ethnicity-stratified case–cohort study design, concentrations of 15 metals, including antimony and cobalt, were measured in toenail cuttings collected at baseline (Niehoff et al., 2021). Two exposure metrics were applied: a continuous variable with results reported for an interquartile range increase in metal concentration and tertiles. A quantile-based g-computation

approach was used to assess metal mixtures in a model, with each metal categorized into tertiles.

(ii) Case–control studies

Two case–control studies (Wingren & Axelson, 1987, 1993) investigated the risk of death from stomach, colon, and lung cancer in relation to occupational exposure to antimony in the glass-working industry in Sweden in the context of antimony(III) oxide exposure (the agent present in this industry). Both studies used the registered title of occupation recorded on individuals' (men aged ≥ 45 years) death certificates collected from 11 parishes and supplemented them with information collected from questionnaires completed by seven glassworks in the same parishes. These questionnaires included questions on the consumption of metals, both at the time the study was conducted and 25 years earlier. In the earlier of these two analyses (Wingren & Axelson, 1987), three exposure definitions were investigated: any glasswork employment, six categories of glassworkers by task, and exposure categories according to metal consumption (with antimony grouped with arsenic and lead). In the later study (Wingren & Axelson, 1993), the same data were used, but analyses were presented for individual metals, with exposure categorized as employment in a glassworks with no, low, or high consumption.

Three case–control studies used multi-element biomonitoring to assess antimony exposure: one in Poland investigated plasma concentrations of antimony in relation to *BRCA1*-related breast cancer incidence among women who were *BRCA1* mutation carriers (Kotsopoulos et al., 2012), and two studies investigated urinary antimony concentrations in relation to thyroid cancer incidence in Shenzhen, China (Liu et al., 2021) or breast cancer incidence in northern Mexico (Mérida-Ortega et al., 2022). None of these studies investigated a specific scenario of exposure to antimony, instead measuring total antimony (with more than 10 other elements) at a single time point in biological specimens. In the study by Kotsopoulos et al. (2012), blood draws were undertaken for 79% of participants with breast cancer after diagnosis but before treatment, and in the studies by Liu et al. (2021) and Mérida-Ortega et al. (2022), urine samples were collected from all participants around the time of interview, which was post-diagnosis for cases.

Two case–control analyses conducted as part of the same study in Spain investigated residential proximity to point sources of antimony and other pollutants in relation to incidence of colorectal cancer (García-Pérez et al., 2020) and stomach cancer (García-Pérez et al., 2021). The current residential addresses of study participants were geocoded, and distances to facilities on the European Pollutant Release and Transfer Register with information about antimony releases to water, air, and soil were calculated and categorized into different buffers (within 1, 1.5, 2, 2.5, or > 3 km). To account for a minimum latency period of 10 years for these cancers, only facilities that were in operation at least 10 years before recruitment were included. In a case series [case–case comparison study] (Kresovich et al., 2019) of 696 women with a breast cancer diagnosis (2005–2008) enrolled in the Breast Cancer Care in Chicago study, exposures were assessed using modelled estimates of ambient air levels of antimony at the census tract-level from the 2002 US EPA NATA that were linked to the geocoded residences of participants in the same year.

(b) Critical review of exposure assessment

(i) Cohort studies

In the prospective and retrospective occupational cohort studies conducted on workers exposed to antimony (Jones, 1994; Schnorr et al., 1995; Binks et al., 2005), the time-dependent exposure variables (e.g. years of employment) were probably computed with little error. However, limitations in the use of these metrics are that they are not specific to a particular contaminant

and do not account for differences in the magnitude of exposure. Schnorr et al. (1995) presented industrial hygiene data that had been collected in 1975 and 1976 as part of a NIOSH evaluation, although they were not used in the analysis. Personal sampling data indicated that employee exposures to antimony in most operations at the smelter exceeded the PEL on the days that were sampled. There were also exceedances (based on the OSHA PEL at the time) for arsenic among workers operating the oxide furnace. The study of lung cancer mortality among workers at a tin smelter in the UK (Jones et al., 2007), the same cohort as assessed in Binks et al. (2005), relied on historical occupational hygiene measurements from area and personal sampling to generate a job-exposure matrix (JEM), which was coupled to worker histories for estimating cumulative exposures to antimony. To assess the uncertainty in the exposure assessment, three different approaches were applied to model exposures during periods for which no industrial hygiene data were available. Notwithstanding these advantages, the JEM was limited by variability in the quality and quantity of the exposure data over the 20-year period, the use of measurements that may have been collected under "worst-case" sampling strategies (probably resulting in exposure estimates that were biased high), and the use of area samples, which probably underestimated personal exposures.

Both population-based cohort studies of adults (age, ≥ 20 years) participating in NHANES used measurements of metals in spot urine samples (with creatinine correction) to assess associations between antimony (Guo et al., 2016) and cobalt, antimony, and tungsten (Duan et al., 2020), and cancer prevalence and mortality. Because cobalt, antimony, and tungsten have relatively short half-lives in urine, one limitation of the exposure assessments in these two studies was that a single urine sample was used; hence, the measured concentrations may have reflected recent rather than long-term exposure relative to the total exposure period of interest. Further, the exposure estimates were probably imprecise due to intra-individual variation in urinary antimony concentrations over time (Wang et al., 2019a). A key difference between these NHANES studies relates to their assessment of co-exposures. Whereas the earlier study focused on antimony alone (Guo et al., 2016), the later study assessed a metal mixture (cobalt, antimony, tungsten, and seven other metals) using WQS analyses (Duan et al., 2020).

Both of the studies that were conducted among the Sister Study cohort in the USA assessed metals both individually and as mixtures (White et al., 2019; Niehoff et al., 2021). The exposure metrics in the study by White et al. (2019) linked modelled census tract-level estimates of outdoor air levels of antimony and cobalt from the US EPA NATA for a single year to residential addresses at enrolment. Hence, the exposure assessment failed to capture temporal trends in outdoor air levels of metals and did not account for variation in levels within census tracts. Further, there was no consideration of residential mobility, although a sensitivity analysis, restricted to women who did not move during the follow-up period, was conducted. Another investigation of the Sister Study cohort used toenail cuttings to assess exposures to cobalt and antimony (together with 13 other metals) (Niehoff et al., 2021). Toenails as an exposure biomarker offer advantages as they are non-invasive and typically represent exposures to metals 3–12 months before sampling (Gutiérrez-González et al., 2019) as compared with the shorter exposure window reflected in urine samples. However, in the study by Niehoff et al. (2021), antimony measurements from cuttings collected at baseline may not have represented exposures during the at-risk period for all women, because follow-up ranged from 0.1 to 13.5 years (average follow-up, 7.5 years) and a relatively weak intrapersonal temporal correlation of 0.18 in toenail cutting measurements taken an average of 7.6 years apart has

been observed in this study population (O'Brien et al., 2019). Other general considerations with the use of toenails as biomarkers of metal exposures are that they are highly susceptible to exogenous contamination and require adherence to rigorous preparatory and cleaning protocols before analysis (Middleton et al., 2016).

(ii) Case–control studies

Both of the glassworks studies conducted in Sweden (Wingren & Axelson, 1987, 1993) were limited by the same exposure assessment methodology. Individuals were linked by occupation to glassworks in the same geographical area from which only qualitative estimates on antimony exposure were available. No direct, individual-level exposure assessments were undertaken. While the later of the two analyses was separated by exposure to individual metals, correlations between antimony and other metals – particularly lead – were too strong to allow the interpretation of antimony-specific results.

The case–control studies conducted in Poland (Kotsopoulos et al., 2012) and China (Liu et al., 2021), in which the exposure assessments consisted of total antimony measurements for plasma and urine samples, respectively, were both subject to the same major limitations. Primarily, total antimony measurements were assessed on a single occasion – after diagnosis for all participants recruited by Liu et al. (2021) and for 79% of the participants recruited by Kotsopoulos et al. (2012) – meaning that reverse causation could not be ruled out.

The case–control study conducted in Spain in relation to colorectal cancer (García-Pérez et al., 2020) and stomach cancer (García-Pérez et al., 2021) used the same proxy exposure assessment approach for both cancers, using geospatial data to calculate residential proximities to point sources of antimony pollution. The industries included on the register were required to report pollutant releases to water, air, and soil, implying several possible exposure routes that could be considered. While the timing of exposures implied that they occurred at least 10 years before participants received a diagnosis, the proxy nature of this exposure assessment probably resulted in non-differential exposure misclassification. The study by Kresovich et al. (2019) was also probably subject to non-differential misclassification, because the exposure assessment relied on area-level modelled estimates of outdoor air levels of antimony linked to participants' residential addresses.

1.6.2 Mechanistic studies in humans

The Working Group identified 23 key mechanistic studies for which a critical appraisal of exposure assessment methods was undertaken, of which three investigated exposures to meglumine antimoniate(V), seven investigated antimony(III) oxide (one included antimony(V) oxide), two investigated antimonite ore (one included an aforementioned antimony(III) oxide study), and the remaining studies either did not, or did not intend to, specify the specific agent. The critiques undertaken for each study in relation to different aspects of exposure assessment and, where possible, the specific agents investigated are tabulated in Table S1.17 (Annex 1, Supplementary material for Section 1, Exposure Characterization, web only, available from: https://publications.iarc.fr/618).

(a) Exposure assessment methods

Three studies (Hantson et al., 1996; Torrús et al., 1996; Costa et al., 2018) investigated exposure of patients with leishmaniasis to treatment with meglumine antimoniate(V) and subsequently assessed genotoxic (Hantson et al., 1996) and pro-inflammatory (Torrús et al., 1996; Costa et al., 2018) end-points. In all three studies, known doses of meglumine antimoniate(V) were administered for a known duration at known intervals relative to outcome measurements.

In a study by Guo et al. (2018), whole-blood samples were collected via venepuncture during routine health examinations, to assess associations between cobalt and antimony concentrations in plasma and thyroid hormones among a relatively large sample of pregnant women in China. Linear regression analyses were applied using natural log-transformed thyroid hormone levels as the dependent variable and tertiles of blood metal concentrations as the independent variable. Co-exposures were investigated if models assessing metals individually produced statistically significant results ($P < 0.05$); logistic regression results for simultaneous assessment of multiple metals were presented for the association between metals (manganese, nickel, and antimony) and free thyroxine (FT4). In another study (Kirmizi et al., 2021), exposures to antimony and seven other metals were investigated in fasting blood samples collected from women recruited from gynaecology outpatient clinics, who had or did not have polycystic ovary syndrome (PCOS). Differences in mean metal levels between women with and without PCOS were assessed using Student *t*-tests, and Spearman's correlation analysis was used to assess relationships between metals and glucose metabolism parameters and oxidative, antioxidative, and pro-inflammatory markers.

Five studies employed biomonitoring of total antimony concentrations with simultaneous determination of one or more other elements in urine samples from the general population (Tellez-Plaza et al., 2014; Scinicariello & Buser, 2016; Domingo-Relloso et al., 2019), men attending a fertility clinic (Wang et al., 2016), and women early in pregnancy (Margetaki et al., 2021), and investigated associations with a myriad of mechanistic end-points. In the majority of these studies, cross-sectional associations were explored between antimony concentrations in single spot urine samples (or the average of two closely timed samples) (Wang et al., 2016) and end-points measured in biological specimens collected on the same occasion. In one study (Tellez-Plaza et al., 2014), prospective associations were also investigated between total antimony in spot urine samples and oxidative stress markers in blood samples collected ~10 years later. Except for the study by Margetaki et al. (2021), in which urinary concentrations were adjusted for specific gravity, creatinine correction was applied to account for urinary dilution. Another unique aspect of this study was that Margetaki et al. (2021) assessed the potential for co-exposures to cadmium and lead using Bayesian kernel machine regression (BKMR).

Several studies conducted among workers with occupational exposure to antimony and other metals to assess associations with mechanistic end-points have used a variety of different exposure assessment methods (i.e. area sampling, personal sampling in the breathing zones of workers, and/or biomonitoring). A cross-sectional study evaluated associations between antimony(III) oxide exposures, assessed using personal air sampling, and genotoxic parameters (micronucleus formation and sister-chromatid exchange) in peripheral lymphocytes among two groups of men ("high" exposure group, $n = 17$; "low" exposure group, $n = 6$) working at an industrial plant producing fireproof textiles (Cavallo et al., 2002). In this study, multiple personal exposure measurements were collected over a work week (Monday to Friday) with the antimony(III) oxide-based flame retardant applied on Thursday; an earlier study by Iavicoli et al. (2002) indicated that sampling was conducted over the entire work shift "in most cases" or was divided into two 4-hour subsamplings. Differences in markers of oxidative DNA damage were compared between exposure groups, as well as with an unexposed group ($n = 23$). Another study employed area sampling along with biomonitoring to assess associations between antimony and immunological markers – leukocytes, lymphocytes, monocytes, and serum immunoglobulin (Ig)G, IgA, and IgE levels – among 91 workers and 42 office

administrators (all men) at glass-, antimony(III) oxide-, and engineering plastic-manufacturing factories (Wu & Chen, 2017). In this study, air samplers were deployed at work sites and administrative offices during work shifts (5–7 hours in duration), and hair, blood, and first-void urine samples were collected. By factory, differences in average antimony concentrations in samples of air, blood, urine, and hair were observed between workers and administrative staff.

An early occupational study of workers at an antimony plant processing crude ore (stibnite) into antimony(III) oxide reported on assessments for pneumonoconiosis, along with results of area air sampling and biological monitoring of antimony in urine samples (concentrations reported without adjustment for creatinine concentrations) (Cooper et al., 1968). Five studies (Kim et al., 1999; Goi et al., 2003; El Shanawany et al., 2017; Riffo-Campos et al., 2018; Bai et al., 2021) used spot urinary concentrations to assess associations between antimony exposure and mechanistic end-points among workers with suspected occupational exposure to antimony. Kim et al. (1999) investigated differences in immunological end-points between workers (n = 12) exposed to antimony dusts and fumes during the production of antimony(III) oxide and both unexposed workers (n = 22) from the same factory and unexposed controls (n = 33) not employed in the factory. Higher antimony exposure among workers was supported by significantly ($P < 0.01$) elevated geometric mean total antimony concentrations in spot urine test samples relative to the other two groups, previous physician diagnoses of dermal manifestations that resolved after withdrawal from antimony-exposed tasks, and antimony concentrations detected in workplace air (although this was not assessed for either of the two "unexposed" groups). In a similar design, El Shanawany et al. (2017) compared genotoxicity and oxidative stress end-points between 25 workers exposed to antimony(III) oxide at a polyester-production facility and 25 non-exposed controls. Exposures between these groups were further assessed by comparing mean total antimony concentrations in spot urine test samples. El Shanawany et al. (2017) also used duration of employment as an exposure metric.

In a cross-sectional study that collected spot urine samples, investigators assessed associations between antimony exposures, along with 22 other metals and polycyclic aromatic hydrocarbon (PAH) metabolites (with creatinine correction), and mosaic loss of chromosome Y (mLOY) among 888 coke-oven plant workers (all men) (Bai et al., 2021). Three different regression methods were applied including generalized linear models, least absolute shrinkage and selection operator (LASSO) regression, and BKMR to account for mixtures. Deng et al. (2019) also used LASSO analysis in a study that examined associations between antimony and 22 other metals in urine samples (collected either pre- or post-shift) and microRNA (miRNA) expression levels among 122 workers at a coke-oven plant – working at the top, side, or bottom of the coke oven – at a steel factory in China and 238 workers from other locations (e.g. offices) presumed to be unexposed. Another cross-sectional study examined associations between antimony in urine (from a single sample and with no correction for dilution) and lysosomal enzymes in plasma among 26 art-glass workers and 50 unexposed controls (all men) (Goi et al., 2003). While urinary levels of arsenic were also measured, there was no assessment for co-exposures in the statistical analyses. Riffo-Campos et al. (2018) investigated associations between urinary levels of antimony and three other metals (arsenic, cadmium, and tungsten) (with creatinine correction) and subclinical atherosclerosis among 73 workers (all men) at a car assembly plant, assessed during follow-up visits. Correlation analysis was performed to assess relationships between metal exposures and the atherosclerosis markers. In addition, DNA Infinium Methylation 450 K data were available

for a smaller (n = 23) subset of participants who provided blood samples after fasting for assessment of DNA methylation markers [timing of blood draw, i.e. at baseline or during a follow-up visit, is unclear]. Relationships between differentially methylated regions with respect to subclinical atherosclerosis in coronary, carotid, and femoral territories, metal concentrations, sociodemographic variables, and different cell types were assessed using a big-data approach (i.e. bump hunter methodology). A cross-sectional study quantified pro-inflammatory markers and immune responses of antimony miners (Lobanova et al., 1996) and compared them with a group of "unexposed" gold miners. Qualitative occupational status was the primary exposure metric. The quantification of antimony in dust was reported to have been undertaken previously, but limited information was presented. A cross-sectional study (Potkonjak & Pavlovich, 1983) examined lung inflammation in a group of smelters exposed to dust consisting of up to 88% antimony(III) oxide and antimony(V) oxide, in addition to lower concentrations of silica, ferric oxide, and arsenic oxide. Qualitative occupational status was the primary exposure metric, with no exposure contrast or control group available. However, end-points were compared between those with more than and less than 9 years of employment.

Finally, a cross-sectional study (Alrashed et al., 2021) conducted among participants in a case–control study on recurrent pregnancy loss investigated the association between genotoxicity and oxidative stress markers and spot concentrations of total antimony in blood. Continuous metrics were used to investigate associations. The sources of antimony exposure and the specific agents that participants were exposed to were not specified.

(b) Critical review of exposure assessment

The three studies investigating mechanistic end-points in relation to exposure to treatment with meglumine antimoniate(V) in patients with leishmaniasis (Hantson et al., 1996; Torrús et al., 1996; Costa et al., 2018) all had no major limitations as the exposure assessment consisted of known antimony(V) exposure doses, durations, and timing relative to outcome measurements.

The five studies investigating associations between spot urinary concentrations of total antimony due to environmental sources and mechanistic end-points (Tellez-Plaza et al., 2014; Scinicariello & Buser, 2016; Wang et al., 2016; Domingo-Relloso et al., 2019; Margetaki et al., 2021), in addition to the cross-sectional study that measured antimony concentrations in spot blood samples (Alrashed et al., 2021), all shared common limitations. Except for one study (Tellez-Plaza et al., 2014), all associations investigated were cross-sectional, with the timing of exposure assessment the same as that of outcome measurements. None of the studies assessed co-exposures, except that of Margetaki et al. (2021), which assessed cadmium and lead in addition to antimony using BKMR, and that of Alrashed et al. (2021), which quantified (but did not adjust for) arsenic. Because all studies measured urinary antimony concentrations in populations that were not knowingly exposed to elevated levels of antimony, e.g. through occupation or medication use, no information was available on the sources or durations of the exposures to antimony. While urinary total antimony is an appropriate biomarker for recent exposure, the exposure assessments in these studies that relied on measurements made at single time points provided little information about long-term exposure or temporal variability. In one of two cross-sectional studies that collected blood samples (Kirmizi et al., 2021), co-exposures to arsenic, chromium, cadmium, mercury, lead, copper, and zinc were also measured. In the

other study (Guo et al., 2018), co-exposures to arsenic, selenium, manganese, and nickel were considered when the models for metals, assessed one at a time, produced statistically significant ($P < 0.05$) results. However, like the aforementioned studies, these investigations were cross-sectional, and antimony concentrations in blood (like urinary antimony concentrations) reflect recent exposure (ATSDR, 2019).

The investigation by Cooper et al. (1968) of workers exposed to antimony at an antimony plant that processed crude ore reported air levels of antimony in bagging operation areas and other locations, but provided few details except that the exposure assessment was conducted in 1966 and covered many locations and different environmental conditions. Measurements of antimony in urine samples collected from workers were also reported but were not corrected for creatinine concentrations. A key strength of the study by Cavallo et al. (2002) of workers exposed to antimony(III) oxide was the collection over the work week of personal exposure measurements in the breathing zone using accepted sampling and analysis methods. While different numbers of samples were collected for the two exposure groups compared because of differences in shift schedules (with more samples collected for workers in the lower exposure group), additional details would be needed to determine how this may have influenced the results. No other exposures were assessed in this study.

Ten other occupational studies (Potkonjak & Pavlovich, 1983; Lobanova et al., 1996; Kim et al., 1999; Goi et al., 2003; El Shanawany et al., 2017; Wu & Chen, 2017; Guo et al., 2018; Riffo-Campos et al., 2018; Deng et al., 2019; Bai et al., 2021) benefited from knowledge of potential exposures to antimony in specific workplaces. Goi et al. (2003) classified art-glass workers on the basis of their use of arsenic trioxide (As_2O_3) or antimony(III) oxide. The contrasts between total antimony concentrations in spot urine samples from exposed workers and unexposed comparison groups in the studies by Kim et al. (1999) and El Shanawany et al. (2017) provided evidence of ongoing or recent exposure among the worker groups. The study by Kim et al. (1999) further benefited from information on previous diagnoses of dermal manifestations attributed to antimony exposure among exposed workers and antimony concentrations measured in their workplace air, although no comparison air measurements were available for the "unexposed" groups. The study by Wu & Chen (2017) was also multifaceted in its exposure assessment, conducting area monitoring and biological monitoring by collecting blood, urine, and hair samples. However, there was little information about the area monitoring; no information was provided regarding over what time period monitoring was conducted (e.g. on a single day or several days in a single week) or how many air samplers were deployed at each location. Notwithstanding the strengths described, these studies had limitations. Except for one study by Riffo-Campos et al. (2018), study designs were cross-sectional, with the exposures and end-points of interest assessed at the same time, which limited the inferences that could be drawn. Furthermore, reliance on single measurements of antimony in urine or blood provides little information about long-term exposure and, due to within-worker variability in exposure, probably resulted in imprecise exposure estimates. Thus, these assessments may not reflect average exposures and probably introduced non-differential exposure misclassification. In addition, only three (Guo et al., 2018; Deng et al., 2019; Bai et al., 2021) of the eight studies assessed the potential for confounding effects attributable to co-exposures to other metals by applying methods for assessing mixtures in the statistical analyses that were performed. A strength of the study by Riffo-Campos et al. (2018) was the application of a big-data approach (bump hunter methodology) to assess relationships between differentially methylated DNA regions with respect to subclinical atherosclerosis in

coronary, carotid, and femoral territories, metal concentrations, sociodemographic variables, and different cell types among a subgroup of workers (Riffo-Campos et al., 2018). Both Lobanova et al. (1996) and Potkonjak & Pavlovich (1983) provided compelling evidence of probable high antimony exposures among the workers investigated and, in the case of Lobanova et al. (1996), an "unexposed" group of miners was used for comparison. However, both studies were limited by a lack of quantitative exposure contrasts and the high likelihood of co-exposures in both mining and smelting operations.

2. Cancer in Humans

This section comprises a review of the evidence from the studies of cancer in humans exposed to antimony. In the previous evaluation by the *IARC Monographs* programme in 1989, the available data were inconclusive for the evaluation of the carcinogenicity of antimony(III) oxide and antimony(III) sulfide in humans (IARC, 1989). No studies of cancer in humans were included in that evaluation; therefore, all the available studies of cancer in humans are evaluated for the first time in the present volume. The epidemiological evidence for evaluation of the carcinogenicity of trivalent antimony consists of a relatively small number of population-based studies and studies of occupational exposure. The studies of occupational exposure included one of glassworkers (Wingren & Axelson, 1993), two of antimony-smelter workers (Jones, 1994; Schnorr et al., 1995), and one of tin-smelter workers (Jones et al., 2007). There were two retrospective case–control studies using residential distance from industrial sources emitting antimony as the exposure metric, one for colorectal cancer (García-Pérez et al., 2020) and one for stomach cancer (García-Pérez et al., 2021). Studies within a large prospective cohort of women with a sister who had received a diagnosis of breast cancer (the Sister Study) examined breast cancer risk in relation to baseline residential antimony air pollution levels (White et al., 2019) and breast cancer risk in relation to antimony concentrations in toenail cuttings (Niehoff et al., 2021). A small study compared plasma antimony concentrations between *BRCA1* mutation carriers with breast cancer and controls (Kotsopoulos et al., 2012). Another study compared estimated antimony levels in residential air for women with estrogen receptor-negative and progesterone receptor-negative (ER/PR-negative) breast cancer and for women with estrogen receptor-positive and/or progesterone receptor-positive (ER/PR-positive) breast cancer (Kresovich et al., 2019). There were four studies of urinary concentrations of antimony measured in spot urine samples. Two of these were case–control studies on thyroid and breast cancer (Liu et al., 2021; Mérida-Ortega et al., 2022), and two were general population-based studies on the association with total cancer mortality (Guo et al., 2016; Duan et al., 2020).

Workers in smelting processes are exposed to antimony(III) oxide and antimony(III) sulfide. After detailed review of the occupational cancer studies, it was unclear whether there was any exposure to pentavalent antimony among workers in smelting operations. While the types and routes of antimony exposure measured from biological samples cannot be easily determined, these measures probably represent all routes of exposures, including ingestion through diet or hand-to-mouth contact, as well as the inhalation of agents in workplace air. No epidemiological studies have yet considered exposures to pentavalent antimony, i.e. that would occur through injection of drugs for the treatment of leishmaniasis.

The outcomes examined in occupational studies were exclusively related to cancer mortality rather than incidence. For lung cancer, for which survival time tends to be shorter than

for other cancers, this is a reasonable proxy for lung cancer incidence. However, this is not the case for many other types of cancer and is particularly problematic when evaluating all types of cancers combined, which comprise a heterogeneous group of outcomes. The case definitions for the incidence studies tended to be more precise and based on histological confirmation.

2.1 Cancer of the lung and other parts of the respiratory tract

See Table 2.1.

Four occupational studies investigated lung cancer mortality among workers with potential exposure to antimony. Two cohort studies were conducted among antimony-smelter workers – one in north-eastern England, UK, (Jones, 1994) and another in Texas, USA (Schnorr et al., 1995). A further study of cohort of tin-smelter workers in Humberside, UK, included analyses by duration of service (Binks et al., 2005) but did not contribute to the present evaluation, because it was not specific to antimony exposure. However, a later study of the same cohort estimated antimony exposure on the basis of air sampling and personal monitoring data (Jones et al., 2007). A case–control study of glass blowers in Sweden, in which exposure assessment was based solely on job title (Wingren & Axelson, 1987), lacked risk estimation specific to antimony exposure and was considered uninformative.

Jones (1994) examined lung cancer mortality among workers at an antimony smelter in north-eastern England that produced antimony metal and antimony alloys up to 1970. Production of antimony(III) oxide increased, beginning in the 1950s, and became exclusive after 1973. The smelter also produced arsenical antimony, and the ore [raw material] that was processed varied over time. Ores contained up to 0.5% of arsenic, and arsenic metal and arsenic oxide were additionally produced by the plant (for an unspecified period). Although the smelter began operations in the early part of the 20th century, records of individuals who left employment before 1961 were not available. A cohort of 1452 men employed at the smelter for at least 3 months was identified, including all active employees as of January 1961 and workers who joined after that date until the end of follow-up in 1992. Thirty-two employees could not be traced and were excluded from the analysis, yielding an analytical cohort of 1420. [The Working Group noted that some analyses were presented separately for the active employees in 1961 and those hired later; however, the number of workers in each group was not specified.] Smelter workers were exposed to a variety of agents, including lead, antimony and its oxides, arsenic and arsenic oxides, sulfur dioxide, and PAHs. Regional mortality rates were used to calculate expected deaths. The population was divided into four occupational groups: antimony workers, maintenance workers, zircon workers, and others (this category included office workers and management staff). Because permanent job transfers occurred, an antimony worker was defined as any person who worked in the antimony plant for at least 3 months regardless of present or last occupation.

Using regional referent rates (Tyne and Wear, UK), the standardized mortality ratio for lung cancer was elevated for antimony workers [1.5; 95% CI, 1.1–2.1] and for maintenance workers [1.9; 95% CI, 1.1–3.0]. No statistically significant excesses were found for zircon workers or the category of "other" workers. Among antimony workers, this excess was largely among those hired before 1961 ([SMR, 2.2; 95% CI, 1.5–3.0]) and those who died 21–30 years after first employment ([SMR, 2.4; 95% CI, 1.5–3.6]). Higher observed versus expected numbers of lung cancer deaths were additionally identified for maintenance workers hired before 1961 ([SMR, 2.3; 95% CI, 1.2–3.8]), but not after. [The Working Group noted that the workers actively employed in 1961 represent a survivor population

Table 2.1 Epidemiological studies on exposure to antimony and cancer of the lung and other parts of the respiratory tract

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jones (1994) North-eastern England 1961–1992 Cohort	1420 men working in an antimony-manufacturing plant, employed on 1 January 1961 or after, for ≥ 3 mo Comparisons were made between the worker population relative to the national (England and Wales) and local (Tyneside conurbation 1961–1973, Tyne and Wear 1974–1983) populations Exposure assessment method: based on company employment records; subcohort grouping by job type, calendar period of first employment, years of exposure, and years since first exposure	Lung, mortality	Occupational group (SMR):			Age, calendar year	*Exposure assessment critique*: Key strengths include: exposures assessed before the development of the outcome; duration of exposure, calendar period of first employment, and years since first exposure probably assessed with minimal error; and stratification in occupational groups with presumably similar exposures. Key limitations include: the potential for exposures to other IARC Group 1 carcinogens (e.g. arsenic); exposure metrics not specific to a particular contaminant; and time-dependent exposure metrics account for duration, but not magnitude, of exposure. *Other strengths*: comparisons with other types of workers in the plant. *Other limitations*: no individual antimony exposure estimates.
			Antimony workers	37	[1.5 (1.1–2.1)]		
			Maintenance workers	15	[1.9 (1.1–3.0)]		
			Zircon workers	5	[0.6 (0.2–1.3)]		
			Others (including office and management)	6	[1.0 (0.4–2.0)]		
		Lung, mortality	Antimony workers, hire year (SMR):				
			Hired before 1961	32	[2.2 (1.5–3.0)]		
			Hired after 1961	5	[0.5 (0.2–1.2)]		
		Lung, mortality	Antimony workers, years since first exposure (SMR):				
			< 1 yr	0	[0 (0–18.3)]		
			1–5 yr	0	[0 (0–3.7)]		
			6–10 yr	3	[1.4 (0.4–3.9)]		
			10–20 yr	7	[0.9 (0.4–1.8)]		
			21–30 yr	20	[2.4 (1.5–3.6)]		
			31–40 yr	6	[1.9 (0.8–4.0)]		
			41–50 yr	1	[1.1 (0.1–5.5)]		
			> 50 yr	0	[0 (0–18.3)]		
		Lung, mortality	Maintenance workers, hire year (SMR):				
			Hired before 1961	12	[2.3 (1.2–3.8)]		
			Hired after 1961	3	[1.1 (0.3–2.9)]		

Table 2.1 (continued)

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schnorr et al. (1995) Texas, USA Enrolment, 1937–1971/follow-up, 1989 Cohort	1014 men employed for ≥ 3 mo at an antimony smelter (91 White and 923 Spanish-surnamed) Exposure assessment method: comparisons of worker mortality rates with the general population (assumed to be unexposed): both national and Texas ethnicity-specific cancer rates; workers grouped into job categories based on company records; additional metric was duration of employment	Respiratory tract, mortality	Smelter employees (SMR, USA rates for White men):			Age, calendar time	*Exposure assessment critique*: A key strength was that exposures were assessed before the development of the outcome. Exposure was corroborated with area and personal air sampling. Key limitations include the potential for exposures to other IARC Group 1 carcinogens (e.g. arsenic and cadmium) and exposure metrics are not specific to a particular contaminant. *Other strengths*: area and personal air monitors established antimony concentrations exceeding OSHA standards; analysed duration of employment; standardization to ethnicity-specific state-wide rates. *Other limitations*: no individual antimony exposure estimates; potential confounding by other metals/metalloids, and other factors such as smoking. *Other comments*: 91.5% of study cohort was Spanish-surnamed; Spanish surnames identified using data from 1980 census.
			All	34	0.81 (0.56–1.13)[a]		
		Lung, mortality	Smelter employees (SMR, USA rates for White men):				
			All	30	[0.75 (0.52–1.06)][a]		
		Lung, mortality	Smelter employees (SMR, Texas, rates for White and Spanish-surnamed men):			Age, calendar time, race/ethnicity	
			All employees	28	[1.39 (0.94–1.96)][a]		
			Spanish-surnamed employees	25	[1.40 (0.93–2.04)][a]		
			White employees	3	[1.27 (0.32–3.46)][a]		
		Lung, mortality	Duration of employment (SMR, Texas rates for White and Spanish-surnamed men):				
			< 5 yr	11	[0.83 (0.43–1.44)][a]		
			5–10 yr	8	[2.24 (1.04–4.26)][a]		
			> 10 yr	9	[2.73 (1.33–5.01)][a]		
			Trend-test *P*-value, < 0.005				

Table 2.1 (continued)

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jones et al. (2007) Humberside, UK Enrolment, 1967–1995/follow-up, 2001 Cohort	1462 men employed for ≥ 12 mo at Capper Pass tin smelter Exposure assessment method: > 20 000 measurements were used to generate JEM with annual averages by process and non-process area for 1972–1991; three methods were applied to estimate exposures for earlier years by: (A) applying the mean of the 3 earliest years in which data were available; (B) applying a linear increasing trend from baseline values to values higher by 2-fold in the early 1940s; or (C) applying a linear increasing trend as in (B) to values higher by 2-fold in 1960 and subsequently declining to one half of the baseline in 1937); annual averages were linked to work histories to generate estimates of cumulative exposure under each scenario	Lung, mortality	Cumulative exposure (mg year m^{-3}), back-extrapolated using method A (ERR):			Age, calendar year	*Exposure assessment critique*: Key strengths include: exposures assessed before the development of the outcome; the creation of a JEM based on area and personal air sampling measurements for antimony and four other metals coupled to worker histories; and multiple methods for extrapolating exposures to earlier periods. Key limitations include: use of data from worst-case scenario sampling, which may have overestimated exposure; area air sampling measurements likely underestimate personal exposures; varying quality and quantity of the data over the 20 yr period; and no assessment for co-exposures in the statistical analyses. *Other strengths*: individual antimony exposure estimates. *Other limitations*: potential for confounding by other metals/metalloids, and other factors such as smoking.
			Unweighted	62	0.21 (−0.24 to 0.65)		
			Weighted	62	1.66 (0.56–3.77)		
			Trend-test *P*-value, 0.48 (unweighted), 0.004 (weighted)				
		Lung, mortality	Cumulative exposure (mg year m^{-3}), back-extrapolated using method B (ERR):				
			Unweighted	62	0.12 (−0.22 to 0.47)		
			Weighted	62	1.18 (0.28–3.08)		
			Trend-test *P*-value, 0.59 (unweighted), 0.013 (weighted)				
		Lung, mortality	Cumulative exposure (mg year m^{-3}), back-extrapolated using method C (ERR):				
			Unweighted	62	0.11 (−0.22 to 0.44)		
			Weighted	62	1.20 (0.35–2.09)		
			Trend-test *P*-value, 0.59 (unweighted), 0.016 (weighted)				

CI, confidence interval; ERR, excess relative risk; JEM, job-exposure matrix; mo, month; OSHA, Occupational Safety and Health Administration; SMR, standardized mortality ratio; US, United States; yr, year.

[a] The CIs for this study are 90%.

in which long-term employees may be over-represented and those who left employment before 1961 because of disability or death would not be included. The study relied on job classification as a measure of antimony exposure and thus does not include quantitative exposure estimates for antimony metal and antimony(III) oxide, or assess important co-exposures such as arsenic, an agent that is classified in IARC Group 1, *carcinogenic to humans*, with *sufficient* evidence for cancer of the lung. While no adjustment was made for cigarette smoking in the analysis, the elevated standardized mortality ratios were specific to antimony workers and maintenance workers but not to zircon workers or the category of "other" workers, which suggests that confounding by cigarette smoking was unlikely to explain the elevated standardized mortality ratios observed among antimony workers.] Reports from McCallum (1989) and Doll (1985) refer to data from antimony-process workers in the north of England that fitted the description of Jones (1994) but with scant information. [The Working Group did not consider the reports from Doll (1985) and McCallum (1989) in its evaluation because of the sparse description of the studies, probable overlap with Jones (1994), and, for McCallum (1989), the lack of quantitative risk estimates.]

An occupational cohort study was conducted at an antimony smelter in Texas, USA, that produced both antimony metal and antimony oxide from ore that probably contained primarily antimony(III) oxide or antimony(III) sulfide (see Sections 1.1 and 1.2; Schnorr et al., 1995). The study cohort included 91 White and 923 Spanish-surnamed men (n = 1014 workers) who worked a minimum of 3 months between 1 January 1937 and 1 July 1971. Spanish-surnamed members of the cohort were identified by matching the surnames of study participants to Spanish surnames on a computer tape from the 1980 census. Work histories, including start and end dates of employment but not job title or department, were obtained through 1975 from employment and payroll records. Vital status as of 31 December 1989 was obtained from the Social Security Administration, Internal Revenue Service, Veterans Administration, Health Care Finance Administration, National Death Index, and other state and local sources. Only 3.3% of Spanish-surnamed and 2.2% of White workers had unknown vital status as of 31 December 1989. Employment records were reviewed through 1975. Additionally, NIOSH conducted area sampling and personal air monitoring in 1975 and 1976, respectively. Using White men in the USA as the standard, the standardized mortality ratio for lung cancer was 0.75 ([95% CI, 0.52–1.06]). Using rates for Spanish-surnamed and White Texas populations as the standard, the standardized mortality ratios for lung cancer were 1.39 ([95% CI, 0.94–1.96]) overall, and 0.83 ([95% CI, 0.43–1.44]), 2.24 ([95% CI, 1.04–4.26]), and 2.73 ([95% CI, 1.33–5.01]) for < 5, 5–10, and > 10 years of employment, respectively (excluding 2 deaths occurring in the 1950s before the availability of state rates). Standardized mortality ratios did not differ markedly for Spanish-surnamed compared with White men, although the lung cancer mortality rates were lower for Spanish-surnamed men in the population than for White men. [The Working Group considered the ethnicity-specific mortality rates for men in Texas to be more representative of the study population than rates in the USA.]

The primary source of ore was from Mexico, and the ore was composed largely of antimony oxide and sulfide. The composition of antimony ore from Mexico measured in bulk samples collected in 1975 was 31% antimony, 0.054% arsenic, 0.46% sulfur, and 0.136% lead. On the basis of results of the NIOSH surveys reported by Schnorr et al. (1995), the geometric mean values of area air samples for antimony taken in 1975 and personal air samples in 1976 averaged 551 and 747 μg/m^3, respectively; on average, personal air samples exceeded the OSHA PEL of

500 μg/m³. The concurrently measured arsenic levels were 2 and 5 μg/m³, respectively, which were well below the OSHA standard at the time of 500 μg/m³. Schnorr et al. (1995) used an OSHA risk assessment model to estimate that an excess of 0.6 deaths from lung cancer would be expected for the 1014 workers exposed to arsenic for 6.8 years. [The Working Group noted that, although the observed trend towards increasing risk by duration of employment is compelling, it does not consider specific job tasks or estimated levels of exposure. The study lacked the ability to adjust for co-exposures including arsenic, an IARC Group 1 lung carcinogen. Air concentrations for arsenic exposure overall were orders of magnitude lower than those for antimony (with some exceedances based on the current OSHA PEL of 10 μg/m³), and plant processes were considered to be fairly consistent over time. Modelling studies have estimated exposure–response relations between relatively low levels of occupational exposure to arsenic in air and lung cancer (e.g. Hertz-Picciotto & Smith, 1993; Lubin et al., 2008); however, the lowest ranges of arsenic exposure for which study data were available in those studies exceeded the arsenic air levels reported in this study. On the basis of these data, the Working Group concluded that the low levels of arsenic present in the facility would be unlikely to fully explain the strong positive associations with duration of employment, although some role for arsenic cannot be ruled out. Tobacco smoking was a potential confounder. In earlier reports, smoking prevalence rates were lower in men with Spanish surnames than in other men, thus the inclusion of a Spanish-surnamed standard population reduced the likelihood of confounding, which would not be expected given the magnitudes of the exposures and unlikely association with tobacco smoking.]

Jones et al. (2007) added quantitative estimates of cumulative antimony exposure to the analysis of the cohort previously reported by Binks et al. (2005) of workers involved in the production of high-purity tin and antimony/lead alloy. The cohort included men who were employed for at least 12 months at a tin smelter in Humberside, UK, between 1 November 1967 and 28 July 1995, and followed until 31 December 2001 ($n = 1462$). Expected numbers of deaths were computed from national lung cancer mortality rates among men (England and Wales). Individual exposure estimates were derived from a JEM using data from area air and personal air sampling carried out between 1972 and 1991. Exposures were back-extrapolated to earlier years using three exposure models (scenarios A, B, and C). Scenario A used constant back-extrapolation and the mean levels for the earliest 3 years of sampling. Scenario B used a linearly increasing trend for back-extrapolation from baseline levels (in scenario A) to values in the 1940s that were higher by two-fold. Scenario C used levels of antimony that were greater by 2-fold than those at baseline in 1960, then back-extrapolated declining levels to one half of baseline by 1937. Estimated cumulative antimony exposure was unrelated to lung cancer mortality in the unweighted analysis of all three exposure models. Poisson regression models assessed exposures weighted for the assumption that exposures decreased with time since exposure and attained age; associations with lung cancer were detected in models that weighted cumulative exposure with excess relative risks of 1.66 (90% CI, 0.56–3.77; $P = 0.004$), 1.18 (90% CI, 0.28–3.08; $P = 0.013$), and 1.20 (90% CI, 0.35–2.09; $P = 0.016$) per mg year/m³ of cumulative exposure for scenarios A, B, and C, respectively, on the basis of smoothed weights. [The Working Group noted that the authors reported that "stepwise" weights produced similar results, but the data were not shown. The Working Group noted that while there were advantages to the JEM-based individual exposure estimation, the quantity and quality of exposure data varied over time. In particular, exposure to specific antimony compounds may have varied over time because

of differences in the composition of the feedstock processed at the smelter. Co-exposures to other metals or metalloids such as arsenic were not adjusted for in the analysis. Risk estimates for arsenic exposure appeared lower than those for antimony; however, it was not possible to fully distinguish the independent effects of arsenic. In addition, the analysis did not include adjustment for other potentially confounding factors such as tobacco smoking; but this was not considered an important confounder in this study by the Working Group, given the magnitude of the antimony exposure concentrations and that they were unlikely to be associated with tobacco smoking.]

2.2 Cancer of the stomach, colon, rectum, and other digestive organs

See Table 2.2.

A death certificate-based case–control study on stomach and colon cancer was conducted in an area of Sweden where numerous glassworks were located (Wingren & Axelson, 1993). Two occupational cohort studies on mortality of antimony-smelter workers in the UK and USA were conducted (Jones, 1994; Schnorr et al., 1995). Case–control studies on the association between residence near antimony-emitting industrial facilities and cancer of the stomach and colorectal cancer were carried out in the context of a population-based multicase–control study of common tumours in Spain (MCC-Spain) (García-Pérez et al., 2020, 2021).

Wingren & Axelson (1993) conducted a case–referent [case–control] study on deaths from stomach and colon cancer at age 45 years or older among male residents of seven parishes where many glassworks facilities were located. A total of 3523 deceased men were included in the analysis. Deaths from stomach and colon cancers (number not specified) were selected as cases, and referents [controls] included men who had died from causes other than cancer or cardiovascular disease. Levels of exposure to antimony among glassworkers were categorized as none, low, and high, on the basis of information about the volume of metal used (kg/year) and number of employees provided by each of the glassworks facilities, with the referent group defined as decedents who had not worked in glassworks. There was no apparent association between level of use of antimony and stomach cancer, although positive associations were found for use of other metals, including copper, nickel, and manganese. For colon cancer, the odds ratio (OR) for glassworkers in the "no antimony exposure" category was 1.4 (95% CI, 0.6–3.3), the low-exposure category was 1.8 (95% CI, 0.8–13.8), and the high-exposure category was 5.0 (95% CI, 2.6–9.6), compared with decedents who had not been glassworkers. A positive association with colon cancer was also found for lead exposure levels, which were positively correlated ($r = 0.76$) with antimony exposure levels. [The Working Group noted that the exposure assessment was unspecific on the basis of reported antimony use at each facility, and the analyses did not account for co-exposures to other metals, including inorganic lead, which is considered by IARC to have *limited* evidence for stomach cancer in humans. An earlier death certificate-based study of similar design (Wingren & Axelson, 1987) was considered uninformative, because the results were presented for glassworkers overall and without antimony-specific exposure assessment.]

In the study of antimony-smelter workers in north-eastern England, UK (Jones, 1994), described in Section 2.1, there were only 5 observed and 9.4 expected deaths from stomach cancer in the total population (SMR, [0.5]; 95% CI, [0.2–1.2]), and only 2 observed and 4.8 expected deaths from stomach cancer among workers assigned to the antimony department (SMR, [0.4]; 95% CI, [0.1–1.4]). Results for cancers of the colon, rectum, and other digestive organs

Table 2.2 Epidemiological studies on exposure to antimony and cancer of the stomach, colon, rectum, and other organs of the digestive tract

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wingren & Axelson (1993) South-east Sweden 1950–1982 Case–control	Cases: number of cases not reported; deaths of men from stomach and colon cancer aged ≥ 45 yr, residents of 7 parishes where glassworks provided information about metal use Controls: number of controls not reported; deaths of men from causes other than cancer or cardiovascular disease aged ≥ 45 yr, residents of 7 parishes where glassworks provided information about metal use Exposure assessment method: based on job type within glass industry (in the context of antimony(III) oxide), supplemented by information on metal consumption across job types; exposure to individual metals by type of production assessed via questionnaire received from 7 glassworks	Stomach, mortality	Exposure to antimony (OR):			Age at death (45–64, 65–74, or ≥ 75 yr)	*Exposure assessment critique*: This study used an improved metal-specific exposure assessment metric compared to its earlier counterpart. However, the exposure assessment undertaken was still qualitative in design, which did not permit proper quantification of numerous co-exposures to other metals.
			No glasswork employment	NR	1		
			None	NR	2.0 (1.3–3.1)		
			Low	NR	1.6 (0.9–2.6)		
			High	NR	0.8 (0.3–2.0)		
		Colon, mortality	Exposure to antimony (OR):				
			No glasswork employment	NR	1		
			None	NR	1.4 (0.6–3.3)		
			Low	NR	1.8 (0.8–13.8)		
			High	NR	5.0 (2.6–9.6)		

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jones (1994) North-east England 1961–1992 Cohort	1420 men employed at an antimony smelter for ≥ 3 mo and traced for mortality through 1992 Exposure assessment method: comparisons were made in the mortality experience between the worker population relative to the national (England and Wales) and local (Tyneside conurbation 1961–1973, Tyne and Wear 1974–1983) populations (presumed to be unexposed); subcohort grouping by job type, based on company records	Stomach, mortality	Occupational group (SMR): Antimony workers Maintenance workers Zircon workers Others (including office and management) Total	 2 1 2 0 5	 [0.4 (0.1–1.4)] [0.6 (0.0–2.9)] [1.1 (0.2–3.7)] [0 (0–3.1)] [0.5 (0.2–1.2)]	Age, calendar year	*Exposure assessment critique*: Key strengths include: exposures assessed before the development of the outcome; duration of exposure, calendar period of first employment, and years since first exposure were likely assessed with minimal error; and stratification in occupational groups with presumably similar exposures. Key limitations include: the potential for exposures to other IARC Group 1 carcinogens (e.g. arsenic); exposure metrics are not specific to a particular contaminant; and time-dependent exposure metrics account for duration, but not magnitude, of exposure. *Other strengths*: low loss to follow-up; major products were antimony metal, antimony alloys, and antimony(III) oxide.

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jones (1994) North-east England 1961–1992 Cohort (cont.)							*Other limitations*: very small sample size; potential exposure to arsenic, sulfur dioxide, lead, and polycyclic aromatic hydrocarbons; no quantitative exposure data available.
Schnorr et al. (1995) Texas, USA Enrolment, 1937–1971/follow-up, 1989 Cohort	1014 men employed ≥ 3 mo at an antimony smelter (91 White and 923 Spanish-surnamed) Exposure assessment method: records; comparisons in worker mortality rates between the national population (assumed to be unexposed) and Texas-specific ethnic cancer rates	Stomach, mortality	Smelter employees (SMR, USA rates for White men): All	10	1.49 (0.71–2.74)	Age, calendar time	*Exposure assessment critique*: A key strength was that exposures were assessed before the development of the outcome. Exposure was corroborated with area and personal air sampling. Key limitations include: (1) The potential for co-exposures to IARC Group 1 carcinogens (e.g. arsenic and cadmium); and (2) exposure metrics are not specific to a particular contaminant. *Other strengths*: two industrial hygiene studies conducted at the smelter estimated relative levels of exposure to antimony and arsenic.
		Stomach, mortality	Smelter employees (SMR, Texas rates for White and Spanish-surnamed men): All	7	1.24 (0.50–2.55)	Age, calendar time, race/ ethnicity	
		Liver, biliary tract, and gall bladder, mortality	Smelter employees (SMR, USA rates for White men): All	7	3.17 (1.27–6.52)	Age, calendar time	
		Liver, biliary tract, and gall bladder, mortality	Smelter employees (SMR, Texas rates for White and Spanish-surnamed men): All	6	1.58 (0.57–3.44)	Age, calendar time, race/ ethnicity	
		Colon and rectum, mortality	Smelter employees (SMR, USA rates for White men): All	2	0.12 (0.01–0.45)	Age, calendar time	

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schnorr et al. (1995) Texas, USA Enrolment, 1937–1971/follow-up, 1989 Cohort (cont.)							*Other limitations*: no individual exposure assessment; Spanish-surnamed rates were best available but may not have been fully representative of referent rates for the cohort. *Other comments*: rates for Spanish-surnamed men were only available for 1970–1974 and 1980–1984 and were interpolated for the other years (deaths from the 1950s were excluded)

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
García-Pérez et al. (2020) Spain 2008–2013 Case–control	Cases: 557 histologically confirmed cases of colorectal cancer diagnosed among residents of 11 provinces, aged 20–85 yr Controls: 2948 population-based controls selected from administrative records of primary health-care centres frequency-matched on sex, region, and age Exposure assessment method: a geospatial analysis using shortest distance from current residence to registered point sources of antimony pollution using 4 separate proxies of exposure	Colon and rectum, incidence	Residential proximity to industries releasing antimony (OR): Reference area (> 3.0 km) ≤ 1 km ≤ 1.5 km ≤ 2.0 km ≤ 2.5 km ≤ 3.0 km	 NR 11 46 76 97 105	 1 5.05 (2.10–12.19) 4.37 (2.69-7.10) 4.15 (2.61–6.60) 6.36 (4.05–9.98) 5.30 (3.45–8.15)	Province of residence (random effect), sex, age, BMI, family history of colorectal cancer, tobacco smoking, educational level, physical activity in leisure time, total energy intake, alcohol consumption, vegetable intake, red and processed meat intake	*Exposure assessment critique*: Strengths included: coupling residential proximity to industrial sources to an emissions inventory database; an assessment of calendar year of operation of facilities and sensitivity analysis accounted for potential errors in exposure assessment due to residential mobility. Limitations included: the indirect/proxy nature of this exposure assessment; exposure metrics are not specific to contaminants (except for strategy 4 classification); no assessment of potential for co-exposures; and use of pollutant emissions data for a single year. *Other strengths*: large case–control study; extensive information on covariates. *Other limitations*: method for adjustment for multiple comparisons referenced but not described.

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
García-Pérez et al. (2020) Spain 2008–2013 Case–control (cont.)		Colon and rectum, incidence	Residential proximity to industries releasing antimony, sensitivity analysis with long-term residents (OR): Reference area (> 3.0 km) ≤ 1 km ≤ 1.5 km ≤ 2.0 km ≤ 2.5 km ≤ 3.0 km	 NR 10 38 68 85 91	 1 5.99 (2.36–15.20) 3.97 (2.33–6.76) 4.46 (2.68–7.45) 6.57 (4.01–10.78) 5.17 (3.23-8.27)	Province of residence (random effect), sex, age, BMI, family history of colorectal cancer, tobacco smoking, educational level, physical activity in leisure time, total energy intake, alcohol consumption, vegetable intake, red and processed meat intake	
García-Pérez et al. (2021) Spain 2008–2013 Case–control	Cases: 137 histologically confirmed cases of stomach cancer diagnosed among residents of 9 provinces, aged 20–85 yr Controls: 2664 population-based controls selected from administrative records of primary health-care centres frequency-matched on sex, region, and age	Stomach, incidence	Residential proximity to industries releasing antimony (OR): Reference area (> 3.0 km) ≤ 1.5 km ≤ 2.0 km ≤ 2.5 km ≤ 3.0 km	 NR 8 9 12 14	 1 6.18 (2.29–16.63) 3.88 (1.43–10.57) 5.01 (1.97–12.71) 4.82 (1.94–12.01)	Province of residence (random effect), sex, age, family history of stomach cancer, tobacco smoking, educational level	*Exposure assessment critique*: Strengths included: coupling residential proximity to industrial sources to an emissions inventory database; an assessment of calendar year of operation of facilities and sensitivity analysis accounted for potential errors in exposure assessment due to residential mobility.

Table 2.2 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
García-Pérez et al. (2021) Spain 2008–2013 Case–control (cont.)	Exposure assessment method: a geospatial analysis using shortest distance from current residence to registered point sources of antimony pollution using 4 separate proxies of exposure	Stomach, incidence	Residential proximity to industries releasing antimony, sensitivity analysis with long-term residents (OR):			Province of residence (random effect), sex, age, family history of stomach cancer, tobacco smoking, educational level	Limitations include: the indirect/proxy nature of this exposure assessment; exposure metrics are not specific to contaminants (except for strategy 4 classification); no assessment of potential for co-exposures; and use of pollutant emissions data for a single year. *Other strengths*: large case–control study; extensive information on covariates. *Other limitations*: 43 pollutants analysed; method for adjustment for multiple comparisons referenced but not described; although ORs are significant, based on relatively small numbers of cases.
			Reference area (> 3.0 km)	NR	1		
			≤ 1.5 km	7	6.53 (2.24–19.07)		
			≤ 2.0 km	8	4.36 (1.52–12.54)		
			≤ 2.5 km	10	4.66 (1.71–12.68)		
			≤ 3.0 km	11	3.81 (1.43–10.18)		
		Stomach (non-cardia tumours), incidence	Residential proximity to industries releasing antimony (OR):				
			Reference area (> 3.0 km)	NR	1		
			≤ 1.5 km	5	6.10 (1.81–20.50)		
			≤ 2.0 km	6	4.70 (1.48–14.89)		
			≤ 2.5 km	9	7.44 (2.60–21.26)		
			≤ 3.0 km	10	6.16 (2.18–17.43)		
			Residential proximity to industries releasing antimony, sensitivity analysis with long-term residents (OR):				
		Stomach (non-cardia tumours), incidence	Reference area (> 3.0 km)	NR	1		
			≤ 1.5 km	5	8.18 (2.35–28.51)		
			≤ 2.0 km	6	6.49 (2.04–20.60)		
			≤ 2.5 km	8	7.85 (2.59–23.84)		
			≤ 3.0 km	8	5.10 (1.69–15.41)		

BMI, body mass index; CI, confidence interval; IARC, International Agency for Research on Cancer; mo, month; NR, not reported; OR, odds ratio; SMR, standardized mortality ratio; yr, year.

were not reported. [The Working Group noted that the workers actively employed in 1961 represent a survivor population in which long-term employees may be over-represented, and that those who left employment before 1961 because of disability or death would not be included. The observed and expected numbers of stomach cancer deaths were very small, and observed and expected numbers of deaths were not reported for other digestive organs. The exposure assessment was based on department assignment only and was not specific to a particular agent. It also did not account for co-exposures, including inorganic lead, which is considered by IARC to have *limited* evidence for stomach cancer in humans.]

In the study of antimony-smelter workers in Texas, USA, by Schnorr et al. (1995), standardized mortality ratios for stomach, liver, and gall bladder cancer, and cancers of the colon and rectum, were analysed using US White male referent rates and referent rates obtained from the Texas State Health Department for liver and biliary tract stomach cancer for Spanish-surnamed men and White men in Texas (see Section 2.1). The study found a significant excess in mortality from cancers of the liver, biliary tract, and gall bladder (SMR, 3.17; 95% CI, 1.27–6.52; 7 deaths) and a non-significant excess for stomach cancer (SMR, 1.49; 95% CI, 0.71–2.74) in analyses using US rates. When using the Texas ethnicity-specific rates as the comparison, the standardized mortality ratio attributable to cancers of the liver, biliary tract, and gall bladder was 1.58 (n = 6 deaths; 95% CI, 0.57–3.44) and for stomach cancer was 1.24 (n = 7 deaths; 95% CI, 0.50–2.55). There were only 2 deaths from cancers of the colon and rectum, with 16.19 expected based on US referent rates (expected numbers were not calculated based on Texas ethnicity-specific rates). [The Working Group noted that ethnicity-specific rates for Texas provide the more appropriate referent population because mortality patterns are known to be very different for Hispanic people and non-Hispanic people in the USA. Major limitations of the study included lack of job history or individual exposure assessment and relatively small population size, which limited statistical power for identifying potential excess risks associated with antimony exposure for these sites. Arsenic exposure is also a potential confounding exposure for liver cancer.]

An additional occupational cohort study was identified as potentially relevant for evaluating the carcinogenicity of antimony in relation to the digestive tract. Binks et al. (2005) studied workers employed at a tin smelter in north Humberside, UK, that processed a variety of tin ore concentrates and residues to produce high-purity tin as its main product, and lead, copper, cadmium, antimony, and silver as secondary products. Workers were potentially exposed to a variety of substances, including tin, lead, antimony, arsenic, cadmium, sulfur dioxide, natural-series radionuclides, and combustion products. [This study was judged to be uninformative, because no analyses were presented that could distinguish cancer risks associated with antimony from risks associated with other exposures. The cohort was updated with additional exposure information by Jones et al. (2007), but the results were reported only for lung cancer].

Case–control studies of cancer of the stomach and colorectal cancer were conducted in the context of a population-based multicase–control study of common tumours in Spain (MCC-Spain) to assess the possible associations with residential proximity to industrial installations, according to categories of industrial groups and specific pollutants released by the plants (García-Pérez et al., 2020, 2021). The MCC-Spain study included five types of tumour (breast, colorectum, leukaemia, prostate, and stomach) diagnosed among men and women aged 20–85 years recruited in 2008–2013 in 11 provinces of Spain. Population-based controls (n = 3440) for the entire MCC-Spain study were randomly selected from the administrative records of the primary health-care centres located within the hospital catchment areas and

were frequency-matched on the overall distribution of cases of each type of cancer by age (in 5-year age groups), province of residence, and sex. Exposure assessment for individual toxic substances was conducted by identifying industrial facilities that came into operation at least 10 years before the midpoint of the recruitment period in the study provinces. Toxic emissions to air and water by these facilities was determined from the European Pollutant Release and Transfer Register. To assess the relationship between residential proximity to industries releasing specific industrial pollutants and the cancer of interest, an exposure variable was calculated for each participant and each toxicant released by facilities within varying buffer sizes of their residence. Analyses were conducted to assess the change in risk of cancers of the colorectum and stomach with increasing proximity to industrial facilities releasing specific toxicants, and there was extensive control for person-level confounding exposures on the basis of interview data. Numerous toxicants were investigated, and only those with statistically significant odds ratios and numbers of cases and controls ≥ 10 were reported. [The Working Group noted that the proxy nature of this exposure assessment, which used geospatial data to calculate residential proximity to point sources of antimony pollution, probably resulted in non-differential exposure misclassification.]

A total of 557 cases and 2948 controls from 11 provinces were included in the case–control study of residential exposure to industrial emissions and colorectal cancer (García-Pérez et al., 2020). Among the toxicants studied, the highest odds ratios for stomach cancer were observed for individuals residing near industries releasing antimony – at ≤ 1 km (OR, 5.05; 95% CI, 2.10–12.19), ≤ 1.5 km (OR, 4.37; 95% CI, 2.69–7.10), ≤ 2 km (OR, 4.15; 95% CI, 2.61–6.60), ≤ 2.5 km (OR, 6.36; 95% CI, 4.05–9.98), and ≤ 3 km (OR, 5.30; 95% CI, 3.45–8.15) – compared with those residing > 3 km from industries releasing antimony. Similar results were obtained in the sensitivity analysis considering only long-term residents. [The Working Group noted that although there was extensive control for person-level confounding exposures, there was no control in the antimony analyses for confounding exposures to other toxicants or industrial types, some of which were highly associated with colorectal cancer. For example, positive associations were reported for residential proximity to the organic chemical industry at ≤ 1 km and for the inorganic chemical industry at ≤ 2 km; antimony was one of numerous toxicants associated with both industries. In addition, 43 pollutants were analysed, and the method for adjustment for multiple comparisons was referenced but not described. Confidence intervals for the risk estimates were wide, reflecting statistical imprecision.]

A total of 137 cases of stomach cancer and 2664 MCC-Spain study controls from 9 provinces were included in the case–control study on residential exposure to industrial emissions and stomach cancer (García-Pérez et al., 2021). Elevated odds ratios were observed for individuals residing near industries releasing antimony – at ≤ 1.5 km (OR, 6.18; 95% CI, 2.29–16.63), ≤ 2 km (OR, 3.88; 95% CI, 1.43–10.57), ≤ 2.5 km (OR, 5.01; 95% CI, 1.97–12.71), and ≤ 3 km (OR, 4.82; 95% CI, 1.94–12.01) – compared with those residing > 3 km from industries releasing antimony; similar results were obtained in the sensitivity analysis for stomach cancer considering only long-term residents and for non-cardia stomach cancer. There was no apparent trend towards higher risks associated with residing at shorter distances from the antimony source. [The Working Group noted that, as for the earlier study by García-Pérez et al. (2020), it is difficult to determine whether the observed increased risks of stomach cancer in this study are associated specifically with antimony exposure or result from uncontrolled confounding with other exposures to other pollutants or industries.

Confidence intervals for the risk estimates were wide, reflecting statistical imprecision.]

2.3 Cancer of the breast

See Table 2.3.

Studies on the potential association between antimony and breast cancer have used diverse exposure metrics and designs; some studies included subgroups of high-risk women, and others examined variation among breast cancer subtypes. Exposure metrics included antimony concentrations in plasma (Kotsopoulos et al., 2012), estimated antimony concentrations in ambient air (Kresovich et al., 2019; White et al., 2019), and antimony concentrations in toenails (Niehoff et al., 2021) and urine (Mérida-Ortega et al., 2022). One small case–control study was conducted in a cohort of women positive for *BRCA1* mutations (Kotsopoulos et al., 2012), and two studies (White et al., 2019; Niehoff et al., 2021) were conducted within a large prospective cohort of women whose sister had received a diagnosis of breast cancer (the Sister Study). One study compared antimony concentrations in women with ER/PR-negative versus ER/PR-positive breast cancers identified from a population-based case series [case–case comparison study] of incident cases of breast cancer (Kresovich et al., 2019). One population-based case–control study was conducted in an area of Mexico where metal exposures in the environment were considered to be high (Mérida-Ortega et al., 2022).

A case–control study within a registry cohort of *BRCA1*-mutation carriers, conducted in Poland, examined the relationship between antimony concentrations in plasma samples from 48 women who developed breast cancer and from 96 controls who did not (Kotsopoulos et al., 2012). The primary goal of the study was to determine whether dietary and environmental components (as assessed by measurement of 14 micronutrients and trace elements) influenced breast cancer risk in women with hereditary high risk. Blood samples were drawn from breast cancer cases shortly before or after diagnosis, but before chemotherapy, radiotherapy, or surgery. Two controls were selected for each case, matched on year of birth and oophorectomy status. Mean concentrations of antimony did not differ between cases (6.84 µg/L) and controls (6.75 µg/L). However, there appeared to be a positive association between plasma antimony concentrations (analysed by tertile) and breast cancer risk, with an estimated odds ratio of 1.71 (95% CI, 0.68–4.31) in the middle tertile and 2.43 (95% CI, 1.00–5.91) in the highest tertile (*P* for trend, 0.05). [The Working Group noted that the potential association between breast cancer and exogenous agents among women positive for *BRCA1* mutations is of interest, because the mechanisms of cancer may differ between women with high risk and women with average risk. Limitations of the study included very small sample size, the exposure assessment being conducted at only one point in time, and the potential for antimony concentrations to have been influenced by disease status.]

A case-series [case–case comparison] study compared estimated residential antimony levels in ambient air in 147 women with ER/PR-negative breast cancer and 549 women with ER/PR-positive (either or both receptors present) breast cancer (Kresovich et al., 2019). Metal exposure was based on the US EPA NATA level for census tract of residence in 2002, which was 3–6 years before diagnosis. In analyses by quintile of exposure, odds ratios were elevated in higher quintiles of antimony exposure for ER/PR-negative compared with ER/PR-positive women. Comparing the highest with the lowest quintiles, the odds ratio was 1.8 (95% CI, 0.9–3.7; *P* for trend, 0.05). [The Working Group noted that although the authors describe this as a case-series study, it might more accurately be described as a case–case comparison study. This design was of limited usefulness, because it does not directly

Table 2.3 Epidemiological studies on exposure to antimony and cancer of the breast

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kotsopoulos et al. (2012) Poland 2009–2011 Case–control	Cases: 48 cases selected from a prospective study of *BRCA1*-mutation carriers; blood drawn before or shortly after diagnosis Controls: 96 controls selected from a prospective study of *BRCA1*-mutation carriers, matched on year of birth (± 2 yr) and oophorectomy (yes/no) Exposure assessment method: quantitative measurements; plasma biomonitoring of total antimony and other trace elements and micronutrients was employed on a single occasion, which differed in timing, in cases and controls	Breast, incidence	Antimony levels (OR): ≤ 6.07 µg/L 6.08 to ≤ 7.11 µg/L > 7.11 µg/L Trend-test *P*-value, 0.05	 9 16 23	 1 1.71 (0.68–4.31) 2.43 (1.00–5.91)	Year of birth, oophorectomy status	*Exposure assessment critique*: Plasma micronutrients were examined within a population of *BRCA1*-mutation carriers to determine whether dietary and environmental exposures influence risk in high-risk women. *BRCA1* helps maintain genomic integrity through repair of DNA double-strand breaks. Limitations: the large proportion of cases included for whom exposure assessment was undertaken at a single time point post-diagnosis severely limits the quality of this exposure assessment. Furthermore, information on the source of antimony exposure was lacking. *Other limitations*: blood samples were drawn shortly before or after diagnosis, but before chemotherapy, radiotherapy, or surgery, thus, plasma levels may have been influenced by disease status.

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kresovich et al. (2019) Chicago 2005–2008 Case series [case–case comparison study]	Cases: 696; incident breast cancers among women (aged 30–79 yr) with a diagnosis of a first primary in situ or invasive breast cancer, self-identified as non-Latina White, non-Latina Black, or Latina living in the metropolitan Chicago area at time of diagnosis, enrolled in the Breast Cancer Care in Chicago study and evaluated for ER/PR status: ER/PR-negative if negative for both ER and PR (n = 147); ER/PR-positive otherwise (n = 549) Exposure assessment method: records-based; total ambient inhalation exposure to antimony was quantitatively estimated at the census tract-level using US EPA NATA data that account for mobile and stationary sources of exposure, but do not include indoor sources or other occupational exposures	Breast, incidence	Quintiles of residential airborne antimony in ER/PR-negative vs ER/PR-positive cases (OR): Quintile 1 (< 0.02 ng/m^3) Quintile 2 (0.02–0.03 ng/m^3) Quintile 3 (0.03–0.04 ng/m^3) Quintile 4 (0.04–0.06 ng/m^3) Quintile 5 (> 0.06 ng/m^3) Trend-test P-value, 0.05	 NR NR NR NR	 1 1.3 (0.7–2.5) 1.7 (0.8–3.3) 2.1 (1.1–4.1) 1.8 (0.9–3.7)	Age, race/ethnicity, education, BMI, income, census tract affluence and disadvantage, reproductive factors	*Exposure assessment critique*: Non-differential exposure misclassification likely. Timing of exposure measurement may be outside the relevant time window of exposure for cancer outcome under study. Census tract-level concentrations are broad proxies for personal exposures. The reliance on residential address at a single point in time may have introduced non-differential exposure misclassification. Strengths include consideration of co-exposure to other metals in ambient air analyses. *Other strengths*: high proportion of ER/PR-negative cases (21%) giving enough power to detect etiological heterogeneity. *Other limitations*: 11% of participants were excluded due to missing residential history and 20% lacked information on tumour ER/PR status.

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
White et al. (2019) USA and Puerto Rico Enrolment, 2003–2009/ follow-up, July 2015 Cohort	2587 breast cancer cases; prospective cohort study of 50 884 women (aged 35–74 yr) who had a sister with a diagnosis of breast cancer but no prior breast cancer at enrolment (Sister Study), followed through July 2015 Exposure assessment method: assessment of antimony exposure was made for a single year in time quantitatively based on address at enrolment before the development of the outcome; annual census tract estimates of metal concentrations in air (μg/m³) for antimony, along with arsenic, cadmium, cobalt, chromium, lead, manganese, mercury, nickel, and selenium from the US EPA 2005 NATA were linked to participants' geocoded residences at baseline and categorized into quintiles for analysis	Breast, incidence	Quintiles of residential airborne antimony concentration (HR):			Age, race (non-Hispanic White, other), education, annual household income, marital status, parity (continuous), census tract median income, geographical region	*Exposure assessment critique*: A key strength was that weighted quantile sum regression was used to assess metal mixtures. Key limitations include: non-differential exposure misclassification likely, as neither temporal trends in outdoor metal levels nor residential mobility was accounted for in the exposure assessment, and potential for within-census tract variability in outdoor air levels of metals also likely introduced error in the exposure assessment. *Other strengths*: large prospective cohort study; address ascertained at baseline; extensive covariate information. An independent validation study in California found good agreement between monitored data and certain air toxics in the 2005 NATA data release. *Other limitations*: for exposure analysis, only the exposure levels at the enrolment residence were considered.
			Quintile 1	489	1		
			Quintile 2	509	1.0 (0.91–1.2)		
			Quintile 3	551	1.1 (0.99–1.3)		
			Quintile 4	557	1.1 (1.0–1.3)		
			Quintile 5	462	0.95 (0.83–1.1)		
			Trend-test *P*-value, 0.9				
		Breast, incidence	Quintiles of residential airborne antimony concentration, premenopausal women (HR):				
			Quintile 1	101	1		
			Quintile 2	95	0.81 (0.61–1.1)		
			Quintile 3	113	0.86 (0.65–1.1)		
			Quintile 4	130	0.95 (0.72–1.2)		
			Quintile 5	95	0.69 (0.51–0.94)		
			Trend-test *P*-value, 0.1				
		Breast, incidence	Quintiles of residential airborne antimony concentration, postmenopausal women (HR):				
			Quintile 1	388	1		
			Quintile 2	414	1.1 (0.95–1.3)		
			Quintile 3	436	1.2 (1.0–1.4)		
			Quintile 4	425	1.2 (1.0–1.4)		
			Quintile 5	367	1.0 (0.88–1.2)		
			Trend-test *P*-value, 0.5				

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
White et al. (2019) USA and Puerto Rico Enrolment, 2003–2009/ follow-up, July 2015 Cohort (cont.)		Breast, ER-positive vs non-cases, incidence	Quintiles of residential airborne antimony concentration (HR):			Age, race (non-Hispanic White, other), education, annual household income, marital status, parity (continuous), census tract median income, geographical region	
			Quintile 1	291	1		
			Quintile 2	301	1.06 (0.90–1.25)		
			Quintile 3	320	1.15 (0.97–1.35)		
			Quintile 4	306	1.09 (0.93–1.29)		
			Quintile 5	269	0.97 (0.82–1.16)		
		Breast, ER-negative vs non-cases, incidence	Quintiles of residential airborne antimony concentration (HR):				
			Quintile 1	65	1		
			Quintile 2	36	0.53 (0.35–0.81)		
			Quintile 3	55	0.79 (0.54–1.16)		
			Quintile 4	69	1.08 (0.75–1.55)		
			Quintile 5	36	0.53 (0.34–0.83)		
		Breast, ER-positive vs ER-negative cases, incidence	Quintiles of residential airborne antimony concentration (HR):				
			Quintile 1	NR	1		
			Quintile 2	NR	1.99 (1.27–3.11)		
			Quintile 3	NR	1.45 (0.95–2.20)		
			Quintile 4	NR	1.01 (0.68–1.50)		
			Quintile 5	NR	1.83 (1.14–2.92)		

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Niehoff et al. (2021) USA and Puerto Rico 2003–2009 Cohort	50 884 women (aged 35–74 yr) who had a sister with a diagnosis of breast cancer but no prior breast cancer at enrolment (Sister Study); case–cohort study design evaluated 1495 incident breast cancers (all non-Hispanic Black women and a random sample of non-Hispanic White women) and 1605 women randomly sampled from the cohort, stratified by race/ethnicity Exposure assessment method: concentrations of 15 metals, including antimony, were measured in toenail cuttings collected at baseline and categorized into tertiles for analysis	Breast, incidence	Antimony levels (HR):			Age, education, race/ethnicity, BMI, smoking status, parity/ breastfeeding	*Exposure assessment critique*: Key strengths include: (1) exposures were assessed before the development of the outcome; and (2) analyses considered the metal mixture. Limitations were that non-differential exposure misclassification was likely, and that metals in toenails cuttings typically represent exposures 3–12 mo before sampling (Gutiérrez-González et al., 2019), and hence a single toenail specimen may not have represented average exposure during the follow-up period. *Other strengths*: cases and controls were drawn from a large, national prospective study population; the case–control study had a large sample size with extensive covariate information.
			Tertile 1 (< 9.8 ng/g)	504	1		
			Tertile 2 (9.8–19.0 ng/g)	519	1.04 (0.86–1.25)		
			Tertile 3 (> 19.0 ng/g)	472	0.93 (0.77–1.13)		
		Breast (ER-positive), incidence	Antimony levels (HR):				
			Tertile 1 (< 9.8 ng/g)	373	1		
			Tertile 2 (9.8–19.0 ng/g)	381	1.03 (0.84–1.27)		
			Tertile 3 (> 19.0 ng/g)	339	0.92 (0.74–1.13)		
		Breast (ER-negative), incidence	Antimony levels (HR):				
			Tertile 1 (< 9.8 ng/g)	64	1		
			Tertile 2 (9.8–19.0 ng/g)	66	1.05 (0.71–1.54)		
			Tertile 3 (> 19.0 ng/g)	56	0.79 (0.52–1.18)		
		Breast, incidence	Antimony levels, non-Hispanic White (HR):				
			Tertile 1 (< 9.8 ng/g)	433	1		
			Tertile 2 (9.8–19.0 ng/g)	424	1.05 (0.86–1.29)		
			Tertile 3 (> 19.0 ng/g)	395	0.96 (0.78–1.18)		

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Niehoff et al. (2021) USA and Puerto Rico 2003–2009 Cohort (cont.)		Breast, incidence	Antimony levels, non-Hispanic Black (HR):			Age, education, race/ethnicity, BMI, smoking status, parity/ breastfeeding	
			Tertile 1 (< 9.8 ng/g)	71	1		
			Tertile 2 (9.8–19.0 ng/g)	95	0.86 (0.57–1.29)		
			Tertile 3 (> 19.0 ng/g)	77	0.56 (0.37–0.84)		
Mérida-Ortega et al. (2022) Northern Mexico 2007–2011 Case–control	Cases: 452 histopathologically confirmed breast cancer cases from main public and academic hospitals, aged ≥ 18 yr, no personal history of other type of cancer, ≥ 1 yr residence in study area, creatinine concentration in normal range (20–300 mg/dL), and available information for urinary metal concentrations , matched by age to cases (± 5 yr)	Breast, incidence	Antimony quartile (µg/g creatinine):			Age, schooling, estrogenic index, alcohol consumption, BMI	*Exposure assessment critique*: A key limitation of this study is the reliance on a single spot urine sample. The use of a single sample may not reflect the relevant exposure window, particularly as the sample was collected after the outcome. A strength of this study was the consideration of co-exposure to other metals and trace elements. *Other strengths*: population-based case–control study design; area studied has natural contamination by metals in water and the largest non-ferrous metal-processing site worldwide; exposure to other metals accounted for in the statistical analysis.
			Quartile 1	NR	1		
			Quartile 2	NR	0.70 (0.47–1.05)		
			Quartile 3	NR	0.37 (0.24–0.57)		
			Quartile 4	NR	0.92 (0.63–1.35)		
			Trend-test *P*-value, 0.269				
		Breast, incidence	Mixture 1 (high loadings of chromium, nickel, antimony, aluminium, lead, and selenium), natural log-transformed (ln-µg/g creatinine) (OR):				
			Per unit increase, all women	444	1.15 (1.06–1.25)		
			Per unit increase, premenopausal women	178	1.13 (0.98–1.29)		
			Per unit increase, postmenopausal women	266	1.20 (1.08–1.33)		

Table 2.3 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mérida-Ortega et al. (2022) Northern Mexico 2007–2011 Case–control (cont.)	Controls: 439 women with ≥ 1 yr residence in study area with no personal history of cancer, creatinine concentration in normal range (20–300 mg/dL), and available information for urinary metal concentrations, matched by age to cases (± 5 yr) Exposure assessment method: this study assessed antimony exposure (all routes) in urine samples collected at a single point in time; in addition, exposure to other metals and trace elements was assessed						*Other limitations*: urine samples collected after diagnosis, leading to potential for reverse causation; spot urine sample may not reflect exposures during biologically relevant time period.

BMI, body mass index; *BRCA1*, BRCA1 DNA repair associated; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; mo, month; NATA, National Air Toxics Assessment; NR, not reported; OR, odds ratio; PR, progesterone receptor; US EPA, United States Environmental Protection Agency; vs, versus; yr, year.

estimate the risk of breast cancer associated with antimony exposure. It is included here because the results for antimony exposure in women with ER/PR-negative and ER/PR-positive breast cancer can be compared with the findings of White et al. (2019), described below. An additional limitation of this study was that the exposure assessment was conducted a relatively short time before diagnosis.]

One cohort study investigated the potential association between residential exposure to metallic air pollutants (including antimony) in ambient air and breast cancer risk (White et al., 2019). This study was conducted within a nationwide prospective cohort study of 50 884 breast cancer-free women who had a sister with breast cancer recruited in 2003–2009 (the Sister Study). The US EPA NATA, a database that provides nationwide modelled airborne-concentration information on hazardous air toxics at the census-tract level (US EPA, 2005), was linked to the geocoded baseline residence of each study participant at recruitment and categorized in quintiles. A total of 2587 cases of breast cancer (including both invasive breast cancer and ductal carcinoma in situ), diagnosed before 31 July 2015, were included in the study. In analyses by quintiles of antimony exposure in the overall sample, slightly elevated risks of breast cancer were observed for antimony in quintile 3 (hazard ratio, HR, 1.1; 95% CI, 0.99–1.3) and quintile 4 (HR, 1.1; 95% CI, 1.0–1.3) compared with quintile 1; however, no excess risk was observed in quintile 5. No significant trends were observed for all breast cancers, or premenopausal or postmenopausal breast cancer. However, in the analysis of premenopausal breast cancer, hazard ratios in quartiles 2–5 were all below 1 and the hazard ratio for quintile 5 was 0.69 (95% CI, 0.51–0.94). Results were similar in subgroup analyses by ER status, with some evidence for an inverse, non-monotonic association with antimony concentrations among women with ER-negative breast cancer. The upper bounds of the 95% confidence intervals were below 1 in both quintile 2 (HR, 0.53; 95% CI, 0.35–0.81) and quintile 5 (HR, 0.53; 95% CI, 0.34–0.83). An analysis that compared ER-positive versus ER-negative cases found significantly elevated hazard ratios for quintiles 2 and 5, largely driven by inverse associations with increasing antimony exposures in ER-negative cases. [The Working Group noted that the strengths of this study included the large population and prospective study design. However, the exposure assessment quality was limited, because antimony air levels were estimated at one point in time on the basis of residence at diagnosis and because of the potential for measurement error in the exposure assessment. The results of the analysis by ER subtype contrasted with the findings of the study by Kresovich et al. (2019), which reported positive associations with increasing quintiles of antimony exposure for women with ER/PR-negative versus ER/PR-positive breast cancer.]

A case–cohort study within the Sister Study cohort investigated the relationship between antimony levels in toenail cuttings and incident breast cancer (Niehoff et al., 2021). Toenail cuttings were collected from Sister Study participants at the time of enrolment, and concentrations of 15 metals in toenail samples were measured for 1495 cases diagnosed through September 2017 and a race-stratified random subcohort of 1605 women (including 107 women who received a diagnosis of breast cancer after enrolment and 1498 women who remained breast cancer-free through follow-up). There was no evidence of a positive association between antimony levels and breast cancer among all cases and controls combined (HR in tertile 2, 1.04; 95% CI, 0.86–1.25; and HR in tertile 3, 0.93; 95% CI, 0.77–1.13). Similar exposure–response patterns were observed in analyses stratified by ER status and race (tests for trend were not reported for these analyses). [The Working Group noted the strengths of the study with respect to design and sample size. The exposure assessment

from a single point in time was a limitation, and there was only a twofold difference in the cut point values used to define the lowest (< 9.8 ng/g) and highest (> 19.0 ng/g) exposure categories. Sample sizes were small for some subgroup analyses, resulting in wide confidence intervals, for ER-negative breast cancers and cancers among non-Hispanic Black women.]

A population-based case–control study in Mexico examined associations between certain metals or metalloids and incident breast cancer in a region that has naturally high levels of metals in water, and houses the world's fourth largest non-ferrous metal-processing facility (Mérida-Ortega et al., 2022). Women with histopathologically confirmed breast cancer (n = 499) were identified from public hospitals in several states in northern Mexico and were matched on age (± 5 years) to controls. [The Working Group noted that the authors did not mention how the case group was selected from the larger case pool of 1045 histopathologically confirmed cases.] Controls were identified from a national population-based survey. Interviews were conducted to obtain covariate information, and height and weight were measured. Metals were measured in first morning-void urine samples near the time of interview and before any treatment had begun for the women with breast cancer (on average, 2 months after diagnosis). After excluding cases and controls with exceptionally low or high creatinine concentrations, 452 cases and 439 controls remained in the analysis. Odds ratios were calculated for creatinine-adjusted metal concentrations, both individually in models and grouped together using principal component analysis to assess mixture patterns. [The Working Group noted the somewhat imprecise age-matching as a limitation, and the high response rate (> 90%) of both cases and controls, and good control for confounding factors – e.g. body mass index (BMI), endogenous estrogen exposure, and alcohol consumption – as strengths.]

Antimony concentrations in urine were higher (although not significantly) among controls than among cases. In exposure–response analyses, antimony alone was not associated with breast cancer: the odds ratio for the highest quartile was 0.92 (95% CI, 0.63–1.35). Antimony was correlated most strongly with chromium (r = 0.72), lead (r = 0.56), and nickel (r = 0.52), and these metals – together with aluminium and tin – loaded highly on the first principal component. A positive association was observed for the mixture defined by this principal component (OR, 1.15; 95% CI, 1.06–1.25), which was slightly more pronounced among postmenopausal women (OR, 1.20; 95% CI, 1.08–1.33). [The Working Group noted that, while none of the studied metals has been found by IARC to have *limited* or *sufficient* evidence for breast cancer in humans, the relatively high correlations between antimony and other carcinogenic metals make it difficult to ascribe the positive findings to any particular metal. It is notable that in the analyses for individual metals, only tin was positively associated with breast cancer.]

2.4 Cancer of the thyroid and other sites, including all cancers combined

See Table 2.4.

A total of two cohort studies were identified that examined mortality from all cancers combined using NHANES. An additional hospital-based case–control study of thyroid cancer was conducted in China. An occupational cohort study of tin-smelter workers (Binks et al., 2005), which examined mortality from all cancers as well as specific cancers, was considered uninformative because it lacked information specific to antimony.

Guo et al. (2016) published results from a mortality follow-up study of NHANES, a survey selected by a stratified, multistage probability

Table 2.4 Epidemiological studies on exposure to antimony and cancer of the thyroid and other sites, including all cancers combined

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guo et al. (2016) USA Enrolment, 1999–2010/ follow-up, 2011 Cohort	7781; aged ≥ 20 yr, full covariate and metal data available from the NHANES survey followed for mortality through 2011 (average follow-up, 6.04 yr); mean baseline age, 45.2 yr among those alive at the end of follow-up and 67.25 yr among those who died Exposure assessment method: quantitative measurements; exposure assessment relied on spot urine samples; measurements were made using standard methods of analysis	All cancers combined, mortality	Creatine-adjusted urine concentrations (μg/g creatinine) (HR): Quartile 1: ≤ 0.048 (reference) Quartile 2: > 0.048–0.075 Quartile 3: > 0.075–0.121 Quartile 4: > 0.121 Trend-test *P*-value, 0.487	 23 31 43 48	 1 0.90 (0.49–1.62) 0.85 (0.46–1.59) 1.08 (0.63–1.86)	Age, sex, race/ ethnicity, smoking, drinking, marital status, educational level, PIR, BMI, hypertension, diabetes, eGFR, urinary creatine, lead, cadmium	*Exposure assessment critique*: Key limitations include: use of urine samples because the half-life of antimony in urine is of the order of several days to a couple of weeks (Wang et al., 2019a; CDC, 2017); use of single spot antimony levels in urine samples subject to substantial intra-individual variability; no assessment of co-exposures in the analyses. General comments: RR estimates are also provided for self-reported history of cancer (exposure measures after the outcome). *Other strengths*: biomarker of antimony exposure; large sample size. *Other limitations*: potential for exposure misclassification as urine is a short-term biomarker; all cancers combined is a heterogeneous outcome; mortality does not reflect incidence of cancers with low mortality rates.

Table 2.4 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Duan et al. (2020) USA Enrolment, 1999–2014/ follow-up, 2015 Cohort	26 056 participants aged ≥ 20 yr, not pregnant; with full covariate, mortality, and metal data drawn from the NHANES 1999–2014 survey sample of 82 091 participants; followed for mortality through 2015 (mean follow-up, 7.4 yr); mean age at baseline, 45.9 yr Exposure assessment method: exposure to antimony through all routes was assessed quantitatively from a single urine sample; WQS estimates were made of the metal mixture (including urinary levels of barium, cadmium, caesium, molybdenum, lead, titanium, cobalt, tungsten, and uranium, and blood levels of mercury, lead, and cadmium)	All cancers combined, mortality	Urine concentrations (μg/L) (RR): Median, 0.07 (IQR, 0.04–0.12) Trend-test *P*-value, 0.044	560	1.31 (1.01–1.70)	Sex, age, age^2, ethnicity, urinary creatinine, education, PIR, cotinine category, BMI, physical activity, CVD, diabetes	*Exposure assessment critique*: Key strengths include: single urine samples were collected before the development of the outcomes. Key limitations include: urinary levels of antimony have relatively short half-lives and hence, reflect recent rather than long-term exposure; single spot antimony levels in urine samples are subject to substantial intra-individual variability (Wang et al., 2019a; CDC, 2017). Non-differential exposure misclassification likely. Co-presence and relative weights of other metals were examined (however, other possible carcinogenic exposures were not assessed). *Other strengths*: metals considered as single elements and as a mixture taking into account collinearity; participants. drawn from the general population of the USA, relatively large sample size.
		All cancers combined, mortality	Urine concentrations (μg/L) (RR): Per unit increase	560	1.20 (0.87–1.65)	Sex, age, age^2, ethnicity, urinary creatinine, education, PIR, cotinine category, BMI, physical activity, CVD, diabetes, 9 other urinary metals (barium, cadmium, cobalt, caesium, molybdenum, lead, titanium, tungsten, and uranium)	
		All cancers combined, mortality	Urine WQS mixture (μg/L) (RR): Per unit increase	560	1.60 (1.02–2.52)	Sex, age, age^2, ethnicity, urinary creatinine, education, PIR, cotinine category, BMI, physical activity, CVD, diabetes	

Table 2.4 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Duan et al. (2020) USA Enrolment, 1999–2014/ follow-up, 2015 Cohort (cont.)							*Other limitations*: the relatively short follow-up period yielded a small number of death outcomes; potential for exposure misclassification: concentrations in the urine may not reflect the actual exposure; most metals have a short half-life, which reflects recent exposure; "all cancers combined" is a heterogeneous outcome; mortality does not reflect incidence of cancers with low mortality rates.

Table 2.4 (continued)

Reference Location Enrolment/ follow-up period Study design	Population size, description Exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Liu et al. (2021) Shenzen, China 2017–2019 Case–control	Cases: 111 with diagnosis of thyroid tumour Controls: 111 healthy controls matched on age (± 2 yr) and sex without thyroid abnormalities Exposure assessment method: quantitative assessment based on multi-element urinary biomonitoring, including total antimony, was employed on a single occasion after study recruitment	Thyroid (papillary thyroid microcarcinoma/ carcinoma), incidence	Urinary concentrations (μg/L) (OR): Quartile 1 Quartile 2 Quartile 3 Quartile 4 Trend-test *P*-value, 0.939	 NR NR NR NR	 1 0.71 (0.44–1.15) 0.53 (0.26–1.10) 0.08 (0.01–0.56)	Age, sex, BMI, duration of residence in Shenzen, smoking, drinking, education, household income, household renovation status	*Exposure assessment critique*: Limitations: urine sampling/analysis undertaken at a single time point post-diagnosis severely limits the quality of this exposure assessment: potential for reverse causation. Furthermore, information on the source of antimony exposure was lacking, making the findings difficult to interpret. *Other strengths*: histopathological confirmation of thyroid cancer; biomarker of exposure. *Other limitations*: hospital-based, case–control design with limited description of control group and small sample size; potential for exposure misclassification as urine is a short-term biomarker and taken after the diagnosis.

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OR, odds ratio; PIR, poverty-to-income ratio; RR, relative risk; WQS, weighted quantile sum; yr, year.

algorithm of the non-institutionalized population every 2 years from 1999 to 2010. The study by Guo et al. (2016) included 7781 participants aged 20 years or older, with a mean age of 45.2 years at baseline among those who remained alive and 67.25 years among those who died during the follow-up period. Participants were among the one third of individuals (aged over 6 years) randomly selected for measurement of antimony and other elements by ICP-MS in spot urine samples. Participants with missing data regarding sociodemographic and lifestyle factors, health conditions (BMI or estimated glomerular filtration rate), or urinary creatinine, or with abnormal urinary antimony concentrations, were excluded. The follow-up period ended on 31 December 2011, with an average follow-up of 6.04 years. Using the National Death Index, Centers for Medicare and Medicaid, Social Security Administration, and death certificates, 145 cancer deaths were identified. In Cox proportional hazard models weighted for the sampling design, quartiles of urinary antimony concentrations were unrelated to mortality from all malignant neoplasms, including in models adjusted for a large and varied number of potential confounders. [The Working Group noted that there is intraperson variability in a single urine measurement and that it represents short-term exposure; mortality from all malignant neoplasms is a heterogeneous outcome and does not reflect incidence of cancers with low fatality rates.]

Duan et al. (2020) subsequently examined 26 056 participants from NHANES 1999–2014, with an average age of 45.9 years, for whom mortality data were obtained until 31 December 2015 from the National Center for Health Statistics. Those pregnant, aged less than 20 years at enrolment, or with missing data for metals, covariates, or mortality were excluded. A multi-element analysis was performed of urinary metals including antimony, barium, cadmium, cobalt, caesium, molybdenum, lead, titanium, tungsten, and uranium, and also whole-blood lead, mercury, and cadmium. Concentrations of these elements were examined in relation to mortality from all cancers combined together with outcomes (cardiovascular disease and all causes). With an average follow-up of 7.4 years, there were 560 deaths from all malignant neoplasms. In the single-element covariate-adjusted Poisson model, antimony was associated with an elevated relative risk of all-cancer mortality (relative risk, RR, 1.31; 95% CI, 1.01–1.70), although this was not statistically significant after adjustment for multiple comparisons (false discovery rate-adjusted *P*-value, 0.168) or after adjustment for the other urinary metals listed above (RR, 1.20; 95% CI, 0.87–1.65). Using a mixtures approach (WQS regression) of all the urinary metals analysed, the relative risk for the mixture was 1.60 (95% CI, 1.02–2.52) with a weight of 13% for antimony. [The Working Group noted that there is intraperson variability in a single urine measurement and that it represents short-term exposure; all-cancer mortality is a heterogeneous outcome and not representative of the incidence of non-fatal malignancies.]

Liu et al. (2021) published results from a case–control study of 111 patients with thyroid cancer from Peking University Shenzhen Hospital and Shenzhen People's Hospital in Shenzhen, China, enrolled from September 2017 to September 2019. Cases included patients with histologically diagnosed papillary thyroid microcarcinoma or carcinoma. Controls were matched 1:1 (on age ± 2 years and sex) and enrolled from community health centres in the area. Concentrations of 12 elements – including antimony, chromium, manganese, cobalt, nickel, arsenic, selenium, molybdenum, cadmium, mercury, thallium, and lead – were measured in urine samples after 8 hours of fasting. In conditional logistic regression models adjusted for age, sex, BMI, duration of residence in Shenzhen, smoking, drinking, education level, household income, and house renovation status, no association was observed

across quartiles of urinary antimony concentrations (quartile 2: OR, 0.71; 95% CI, 0.44–1.15; quartile 3: OR, 0.53; 95% CI, 0.26–1.10; quartile 4: OR, 0.08; 95% CI, 0.01–0.56; as compared with quartile 1, *P* for trend, 0.939) in the single-element model. [This study also included a case group of nodular goitre confirmed via B-ultrasound and tested for associations with thyroid function tests. Multi-element models were performed only for the combined group of thyroid cancer and nodular goitre. The Working Group was unable to assess whether hospitalized cases were representative of the population of the area and from which controls were drawn, and no response rates were provided. Measurement of urinary antimony was carried out after diagnosis; it is a relatively short-term measure and there is intraperson variability in a single measurement.]

2.5 Evidence synthesis for cancer in humans

The epidemiological evidence base for the evaluation of the carcinogenicity of trivalent antimony consists of both occupational and population-based studies. The occupational studies include one death certificate-based study of workers exposed to antimony in glassworks, two occupational cohort studies in antimony-smelter workers, and one in tin-smelter workers. There were two retrospective case–control studies using residential distance from an industrial emission source as the exposure metric, one for stomach cancer and one for colorectal cancer, and a prospective cohort study on breast cancer examining risk in relation to baseline residential air pollution levels. Three studies on breast cancer in women used single time-point toenail-cutting, plasma, or urine samples to estimate individual exposure to antimony. Two general-population studies examining total cancer mortality in relation to a one-time urine antimony concentration, one case–case study of breast cancer, and one case–control study on thyroid cancer, were reviewed but not considered informative for this evaluation. No studies were identified that specifically evaluated cancer risk associated with pentavalent antimony in humans. It was unclear whether this form of antimony was present in any of the occupational or other studies considered in this evaluation.

2.5.1 Quality of exposure assessment for antimony and co-exposures

Quality of the exposure assessment was a major consideration in the evaluation of the studies by the Working Group. Detailed reports on the strengths and limitations of exposure evaluations in cohort and case–control studies are provided in Section 1.6.1.

The quality of exposure assessment methods varied among the occupational cohort studies, but each was found to have limitations with respect to defining antimony exposure and addressing co-exposure to arsenic and other lung carcinogens. Among the lung carcinogens of concern in these studies (see Table 1.12 and Section 1.6.1), arsenic was the most ubiquitous and of primary concern for interpreting the results. Wingren & Axelson (1993) classified decedents as glassworkers or not on the basis of occupations listed on death certificates, and estimated intensity of exposure to antimony and other metals, including arsenic, on the basis of qualitative use estimates from individual glassworks facilities. The study of antimony-smelter workers by Jones (1994) had no quantitative data on antimony, arsenic, or other co-exposures; co-exposure to arsenic is of particular concern in this facility where arsenical antimony is also manufactured. This study did report job history data, which were used to stratify exposures by four department assignments reflecting probable exposure to antimony. The study of antimony-smelter workers by Schnorr

et al. (1995) used duration of total employment at the smelter as the metric in exposure–response analyses but had no information on job titles. A strength of this study was the availability of antimony and arsenic air concentrations from industrial hygiene surveys conducted in 1975–1976. Although there were no quantitative data from earlier decades when members of the study cohort were employed, processes and materials were considered to be fairly consistent over time. Among the occupational cohort studies, the study of tin-smelter workers by Jones et al. (2007) had the most detailed and highest-quality exposure assessment. Individual-level exposure estimates were derived from a JEM using air sampling and personal monitoring antimony measurements. None of the occupational cohort studies had information on smoking history, a potential confounder in analyses of lung cancer risk. Although all the occupational studies had limitations in the quality of exposure assessment, they were considered particularly important in the evaluation because occupational exposures are generally orders of magnitude higher than population exposures, and even the crudest exposure metrics, such as duration of employment, reflect biologically relevant time periods. The wide range of potential exposures across jobs and individuals may also allow for meaningful exposure–response analyses.

Two case–control studies used geospatial data to calculate residential proximity to point sources of antimony pollution (García-Pérez et al., 2020, 2021). The proxy nature of this exposure assessment probably resulted in non-differential exposure misclassification. Exposure metrics were similarly developed for residence near specific types of industrial facility and residence near facilities emitting certain categories of industrial pollutants, including any agents categorized in IARC Group 1 (*carcinogenic to humans*), 2A (*probably carcinogenic to humans*), or 2B (*possibly carcinogenic to humans*). Analyses of associations with antimony did not control for these other exposure metrics. In a prospective study, White et al. (2019) linked modelled census tract-level estimates of outdoor air levels of antimony for a single year to each woman's address at enrolment, which may have resulted in misclassification by not accounting for temporal trends and variations in outdoor air levels of metals within census tracts. One study, the prospective Sister Study cohort (Niehoff et al., 2021), used antimony concentrations in toenail cuttings as a biological marker of exposure. In this study, toenail cuttings were obtained at baseline, thus enabling assessment of exposure before the onset of disease. Toenail cuttings may reflect more long-term concentrations than urine or blood for substances like antimony that are excreted in a few days to weeks and have relatively short half-lives in the blood. However, one-time measurement of toenail antimony may not represent cumulative exposures to antimony during biologically relevant time periods of exposure, although levels appear to be moderately correlated within individuals over a period of several years (see Section 1.6.1). A strength of the exposure assessment in the general-population studies described here is the much more extensive information on individual-level covariates and quantitative estimates of exposure to other environmental contaminants. Although not a reflection of low-quality assessment, the small range of exposures in the general-population studies included may limit the informativeness of exposure–response analyses.

2.5.2 Lung cancer

Of the cancer sites for which data in humans were available, the most evidence was available for lung cancer. All three occupational cohort studies found that lung cancer mortality was elevated compared with the general population, and one also found positive associations with antimony exposure (Jones, 1994; Schnorr et al., 1995; Binks et al., 2005; Jones et al., 2007). Two

studies were of antimony-smelter workers. One defined antimony exposure by job classification and found significantly elevated standardized mortality ratios in analyses of subgroups with early periods of employment and latency of 21–30 years (Jones, 1994). The second observed elevated standardized mortality ratios for lung cancer using ethnicity-specific referent rates, with an increasing trend by duration of exposure (Schnorr et al., 1995). A study of tin-smelter workers that used a JEM to estimate individual exposure reported trends of increasing risk with increasing cumulative antimony exposures weighted by time since exposure and attained age. The Working Group viewed the consistent results among these studies as important in evaluating carcinogenicity. A major concern was lack of ability to adjust for co-exposure to recognized lung carcinogens (e.g. those classified by IARC in Group 1), especially arsenic, which was present in all three studies. Tin-smelter workers in the study by Jones et al. (2007) had a wide range of exposures to other metals. The study by Schnorr et al. (1995) was viewed by the Working Group as having the strongest evidence for an association between lung cancer and antimony exposure, because antimony levels measured in 1975 and 1976 were orders of magnitude greater than arsenic levels, and arsenic levels were generally well below the lowest ranges of exposures at which elevated antimony has been associated with lung cancer (Hertz-Picciotto & Smith, 1993; Lubin et al., 2008). There is some question as to whether the levels of arsenic measured in 1975 and 1976 can be extrapolated to reflect earlier exposures. It may be reasonable to make inferences about historical relative and absolute levels of antimony and arsenic exposure in this facility from more recent data because the sources of the ore and processes were consistent over time. Jones (1994) lacked individual exposure estimates for antimony workers, and practices and materials changed over time. It was possible to compare risk with other workers in the plant, thus minimizing concerns about confounding by other factors such as tobacco smoking, which is not typically a concern in occupational studies of high exposures and where smoking is unlikely to be strongly associated with the exposures. However, the concern about arsenic remained because the ore contained higher levels of arsenic and because of the production of arsenical antimony at the smelter. Jones et al. (2007) estimated risks associated with other co-exposures such as arsenic but did not adjust for these in their analysis. Risk estimates for arsenic were lower than for antimony and imprecise for other elements, which strengthened the evidence for antimony. Thus, although positive associations were observed between antimony exposure and lung cancer mortality in all three occupational studies of smelter workers, the possibility that findings were attributable to confounding by co-exposure to arsenic or to other known lung carcinogens could not be reasonably excluded.

2.5.3 Other cancer sites

Few studies were available for other cancer types. Elevated standardized mortality ratios for some digestive tract cancers were reported in the study by Schnorr et al. (1995), but risk estimates were imprecise. In population-based case–control studies of colorectal cancer (García-Pérez et al., 2020) and stomach cancer (García-Pérez et al., 2021), high odds ratios were observed in all exposure quartiles on the basis of distance of residence from antimony emission sites. However, lack of exposure gradients with decreasing distance from an emission source, misclassification of individual exposure based on a very crude exposure metric, and lack of control for confounding by broader categories of exposure, such as industry type, precluded a causal interpretation.

Three studies on breast cancer used biomarkers as the exposure metric in populations that were not selected for occupational

exposure (Kotsopoulos et al., 2012; Niehoff et al., 2021; Mérida-Ortega et al., 2022), and two studies used area-based estimates of antimony levels in air (Kresovich et al., 2019; White et al., 2019). Collectively, these studies found little evidence for increased risk of breast cancer associated with antimony exposure, and all were found to have limitations in exposure assessment. Two of these studies were considered particularly relevant by the Working Group, because they were conducted in a very large and well-characterized prospective study (the Sister Study) (White et al., 2019; Niehoff et al., 2021). However, in both studies, the ability to detect a positive association was limited by use of a one-time exposure measure and the relatively small range of antimony exposure in the population.

Two general-population studies examined total cancer mortality, a heterogeneous outcome, in relation to a one-time urine antimony concentration (Guo et al., 2016; Duan et al., 2020). One study found no association (Guo et al., 2016), and another found elevated risk associated with urinary antimony in a mixture model, which was not statistically significant after adjusting for multiple comparisons. One case–control study on thyroid cancer measured urine levels after diagnosis (Liu et al., 2021). Thus, studies on cancer of the thyroid and other sites were minimally informative, too few in number, and did not provide consistent evidence for this evaluation.

3. Cancer in Experimental Animals

No data on pentavalent antimony were available to the Working Group. The available data concerned trivalent antimony only.

See Table 3.1.

3.1 Mouse

Antimony(III) oxide

Inhalation

In a well-conducted study that complied with Good Laboratory Practice (GLP), groups of 50 male and 50 female B6C3F$_1$/N mice (age, 6 weeks) were exposed by inhalation (whole-body) to aerosols of antimony(III) oxide (purity, > 99.9%; mass median aerodynamic diameter, 0.9–1.5 µm; geometric standard deviation, 1.7–2.2) at a concentration of 0, 3, 10, or 30 mg/m^3 for the control group and at the lowest, intermediate, and highest concentration, respectively, for 6 hours plus T_{90} (12 minutes; the theoretical value for the time to achieve 90% of the target concentration after the beginning of aerosol generation) per day, 5 days per week, for up to 105 weeks (NTP, 2017). Survival of males and females at the intermediate and highest concentration was less than that of controls, primarily because of bronchioloalveolar carcinomas and lung inflammation in males, and malignant lymphoma and lung inflammation in females. At study termination, survival was 38/50, 30/50, 27/50, and 17/50 in males, and 36/50, 31/50, 26/50, and 15/50 in females, for the control group and at the lowest, intermediate, and highest concentration, respectively. At the highest concentration, antimony(III) oxide reduced body weights by between 10% and 25% in males (starting from week 73) and by 10% in females (after week 85) compared with controls. Lung burden was assessed at multiple time points in female B6C3F$_1$/N mice. On the basis of measured lung burden and estimation of clearance half-lives, lung overload occurred at 10 and 30 mg/m^3. Lung overload did not occur at 3 mg/m^3. All mice underwent complete necropsy with histopathological evaluation, except one male at the lowest concentration and one female in the control group.

Table 3.1 Studies of carcinogenicity in mice and rats exposed to antimony(III) oxide

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (M) 6 wk 105 wk NTP (2017)	Inhalation (whole-body exposure) Antimony(III) oxide, > 99.9% Air 0, 3, 10, 30 mg/m^3 6 h + T_{90} (12 min) per day, 5 days/wk for 105 wk 50, 50, 50, 50 38, 30, 27, 17	*Lung* Bronchioloalveolar carcinoma (includes multiple) 4/50 (8%), 18/50 (36%)*, 20/50 (40%)*, 27/50 (54%)* Bronchioloalveolar adenoma or carcinoma (combined) 13/50 (26%), 29/50 (58%)*, 28/50 (56%)*, 34/50 (68%)* Bronchioloalveolar adenoma (includes multiple) 10/50 (20%), 14/50 (28%), 9/50 (18%), 14/50 (28%) *Skin* Fibrous histiocytoma 0/50, 1/50 (2%), 1/50 (2%), 4/50 (8%)* Fibrosarcoma 0/50 (0%), 0/50 (0%), 2/50 (4%), 0/50 (0%) Fibrous histiocytoma or fibrosarcoma (combined) 0/50, 1/50 (2%), 3/50 (6%), 4/50 (8%)*	$P < 0.001$, poly-3 trend test [Cochran–Armitage trend test] *$P < 0.001$, poly-3 test $P < 0.001$, poly-3 trend test [Cochran–Armitage trend test] *$P < 0.001$, poly-3 test NS $P = 0.012$, poly-3 trend test *$P = 0.039$, poly-3 test NS $P = 0.023$, poly-3 trend test *$P = 0.039$, poly-3 test	Principal strengths: GLP study; males and females used; adequate duration of exposure and observation; multiple doses used; and adequate number of animals per group. Other comments: MMAD, 0.9–1.5 µm; GSD, 1.7–2.2. Historical controls: Bronchioloalveolar adenoma: inhalation studies 35/250 (14.0% ± 3.7%), range, 10–20%; all routes 83/550 (15.1% ± 5.9%), range, 8–26%. Bronchioloalveolar carcinoma: inhalation studies 42/250 (16.8% ± 5.4%), range, 8–22%; all routes 75/550 (13.6% ± 6.4%), range, 4–22%. Bronchioloalveolar adenoma or carcinoma (combined): inhalation studies 69/250 (27.6% ± 2.6%), range, 26–32%; all routes 147/550 (26.7% ± 6.5%), range, 16–38%. Skin, fibrous histiocytoma and fibrosarcoma: inhalation studies 1/250 (0.4% ± 0.9%), range, 0–2%; all routes 2/550 (0.4% ± 0.8%), range, 0–2%. Skin, fibrous histiocytoma or fibrosarcoma (combined): inhalation studies 2/250 (0.8% ± 1.1%), range, 0–2%; all routes 5/550 (0.9% ± 1.0%), range, 0–2% (includes one sarcoma).

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 6 wk 105 wk NTP (2017)	Inhalation (whole-body exposure) Antimony(III) oxide, > 99.9% Air 0, 3, 10, 30 mg/m^3 6 h + T_{90} (12 min) per day, 5 days/wk for 105 wk 50, 50, 50, 50 36, 31, 26, 15	*Lung* Bronchioloalveolar adenoma (includes multiple) 1/50 (2%), 10/50 (20%)*, 19/50 (38%)**, 8/50 (16%)*	[$P < 0.001$, Cochran–Armitage trend test] *$P < 0.01$, poly-3 test **$P \leq 0.001$, poly-3 test	Principal strengths: GLP study; males and females used; adequate duration of exposure and observation; multiple doses used; and adequate number of animals per group. Other comments: MMAD, 0.9–1.5 µm; GSD, 1.7–2.2. Historical controls: Bronchioloalveolar adenoma: inhalation studies 12/249 (4.8% ± 2.7%), range, 2–8%; all routes, 27/549 (4.9% ± 3.5%), range, 0–10%. Bronchioloalveolar carcinoma: inhalation studies 17/249 (6.8% ± 3.7%), range, 2–10%; all routes 24/549 (4.4% ± 3.5%), range, 0–10%. Bronchioloalveolar adenoma or carcinoma (combined): inhalation studies 28/249 (11.3% ± 5.5%), range, 6–18%; all routes 50/549 (9.1% ± 5.2%), range, 2–18%. All organs, malignant lymphoma (all organs): inhalation studies 63/250 (25.2% ± 8.4%), range, 14–36%; all routes 109/550 (19.8% ± 7.9%), range, 12–36%. Skin, squamous cell carcinoma of skin: inhalation studies 0/250; all routes, 0/550.
		Bronchioloalveolar carcinoma (includes multiple) 2/50 (4%), 14/50 (28%)**, 11/50 (22%)*, 11/50 (22%)*	[$P = 0.016$, Cochran–Armitage trend test] **$P < 0.001$, poly-3 test *$P \leq 0.003$, poly-3 test	
		Bronchioloalveolar adenoma or carcinoma (combined) 3/50 (6%), 22/50 (44%)*, 27/50 (54%)*, 18/50 (36%)*	$P = 0.019$, poly-3 trend test *$P < 0.001$, poly-3 test	
		All organs Malignant lymphoma 7/50 (14%), 17/50 (34%)*, 20/50 (40%)**, 27/50 (54%)**	$P < 0.001$, poly-3 trend test *$P = 0.013$, poly-3 test **$P < 0.001$, poly-3 test	
		Skin Squamous cell carcinoma 0/50, 0/50, 0/50, 2/50	NS	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Wistar Han[Crl:WI(Han)] (M) 6 wk 105 wk NTP (2017)	Inhalation (whole-body exposure) Antimony(III) oxide, > 99.9% Air 0, 3, 10, 30 mg/m^3 6 h + T_{90} (12 min) per day, 5 days/wk for 105 wk 50, 50, 50, 50 30, 30, 28, 18	*Lung* Bronchioloalveolar adenoma (includes multiple) 3/50 (6%), 4/50 (8%), 6/50 (12%), 8/50 (16%) Bronchioloalveolar carcinoma 0/50, 0/50, 2/50, 0/50 Bronchioloalveolar adenoma or carcinoma (combined) 3/50 (6%), 4/50 (8%), 8/50 (16%), 8/50 (16%) *Adrenal medulla* Benign pheochromocytoma 1/49 (2%), 0/50 (0%), 2/49 (4%), 7/50 (14%)*	NS NS NS $P < 0.001$, poly-3 trend test *$P = 0.030$, poly-3 test	Principal strengths: GLP study; males and females used; adequate duration of exposure and observation; multiple doses used; and adequate number of animals per group. Other comments: MMAD, 0.9–1.5 µm; GSD, 1.7–2.2. Historical controls: Bronchioloalveolar adenoma and bronchioloalveolar adenoma or carcinoma (combined): inhalation studies 4/150 (2.7% ± 3.1%), range, 0–6%; all routes 4/299 (1.3% ± 2.4%), range, 0–6%. Bronchioloalveolar carcinoma: inhalation studies 0/150; all routes 0/299. Adrenal medulla, benign pheochromocytoma: inhalation studies 5/149 (3.4% ± 4.2%), range, 0–8%; all routes 6/297 (2.0% ± 3.1%), range 0–8%.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Wistar Han[Crl:WI(Han)] (F) 6 wk 105 wk NTP (2017)	Inhalation (whole-body exposure) Antimony(III) oxide, > 99.9% Air 0, 3, 10, 30 mg/m^3 6 h + T_{90} (12 min) per day, 5 days/wk for 105 wk 50, 50, 50, 50 39, 38, 28, 20	*Lung* Bronchioloalveolar adenoma (includes multiple) 0/50 (0%), 2/50 (4%), 6/50 (12%)*, 5/50 (10%)* Cystic keratinizing epithelioma or squamous cell carcinoma (combined) 0/50, 0/50, 0/50, 3/50 (6%) Cystic keratinizing epithelioma 0/50, 0/50, 0/50, 2/50 Squamous cell carcinoma 0/50, 0/50, 0/50, 1/50 *Adrenal medulla* Benign pheochromocytoma 0/49, 2/49 (4%), 2/49 (4%), 6/50 (12%)* Benign or malignant pheochromocytoma (combined) 0/49, 2/49 (4%), 2/49 (4%), 7/50 (14%)*	$P = 0.029$, poly-3 trend test *$P \leq 0.021$, poly-3 test NS NS $P = 0.004$, poly-3 trend test *$P = 0.009$, poly-3 test $P < 0.001$, poly-3 trend test *$P = 0.004$, poly-3 test	Principal strengths: GLP study; males and females used; adequate duration of exposure and observation; multiple doses used; and adequate number of animals per group. Other comments: MMAD, 0.9–1.5 µm; GSD, 1.7–2.2. Historical controls: Bronchioloalveolar adenoma, cystic keratinizing epithelioma, or squamous cell carcinoma (combined) of the lung: inhalation studies 0/150; all routes 0/300. Adrenal medulla, benign pheochromocytoma: inhalation studies 1/148 (0.7% ± 1.2%), range, 0–2%; all routes 5/297 (1.7% ± 1.5%), range, 0–4%. Adrenal medulla, benign or malignant (combined) pheochromocytoma: inhalation studies 2/148 (1.4% ± 2.4%), range, 0–4%; all routes 7/297 (2.4% ± 2.0%), range, 0–4%.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Wistar-derived albino (M) 8 mo 71–73 wk Groth et al. (1986)	Inhalation (whole-body exposure) Antimony(III) oxide, 80% antimony (contaminants including: titanium, < 3%; tin, 0.2%; lead, 0.2%; cerium, 0.014%; arsenic, 0.004%) Air 0, 45.0–46.0 mg/m^3 (TWA) 7 h/day, 5 days/wk, for 52 wk 75, 75 22, 22	*Thyroid gland* Total tumours 12/84, 15/83 *Pituitary gland* Total tumours 14/59, 15/62	NS NS	Principal strengths: high number of animals per group; males and females used; adequate duration of exposure and observation. Principal limitations: statistical test NR, only one dose tested; number of deaths and number killed not clearly separated; tumour status not always accurately stated. Other comments: survival data were given for animals (75 male and 75 females per group) designated for the core cohort scheduled for removal 20 wk after the final exposure; tumour data were presented for all study animals, which includes the core group and 15 interim removals (5 males and 5 females each at 6, 9, and 12 mo).

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Wistar-derived albino (F) 8 mo 71–73 wk Groth et al. (1986)	Inhalation (whole-body exposure) Antimony(III) oxide, 80% antimony (contaminants including: titanium, < 3%; tin, 0.2%; lead, 0.2%; arsenic, 0.004%) Air 0, 45.0–46.0 mg/m^3 (TWA) 7 h/day, 5 days/wk for 52 wk 75, 75 39, 31	*Lung* Total tumours 0/89, 19/89* Squamous cell carcinoma 0/89, 9/89* Scirrhous adenocarcinoma 0/89, 5/89* Bronchioloalveolar adenoma or carcinoma (combined) 0/89, 11/89* Total tumours (animals examined in weeks 41–72) 0/69, 19/70* *Thyroid gland* Total tumours 5/86, 6/88 *Pituitary gland* Total tumours 46/81, 50/77	 *$P \leq 0.001$, test NR [$P < 0.0001$, Fisher exact test] *[$P = 0.0016$, Fisher exact test] *[$P = 0.0295$, Fisher exact test] *[$P = 0.0004$, Fisher exact test] *$P \leq 0.001$, test NR [$P < 0.0001$, Fisher exact test] NS NS	Principal strengths: high number of animals per group; males and females used; adequate duration of exposure and observation. Principal limitations: statistical test NR; only one dose used; number of deaths and number killed not clearly separated; tumour status not always accurately stated. Other comments: survival data were given for animals (75 males and 75 females per group) designated for the core cohort scheduled for removal 20 wk after the final exposure; tumour data were presented for all study animals, which includes the core group and 15 interim removals (5 males and 5 females each at 6, 9, and 12 mo); the lung tumour types included squamous cell carcinoma, bronchioloalveolar adenoma, bronchioloalveolar carcinoma, and scirrhous adenocarcinoma.
Full carcinogenicity Rat, F344 (CDF F344 Crl BR) (M) 8 wk 24 mo Newton et al. (1994)	Inhalation (whole-body exposure) Antimony(III) oxide, 99.68 ± 0.10% Air 0, 0.06, 0.51, 4.50 mg/m^3 6 h/day, 5 days/wk for 52 wk 52, 52, 53, 52 [56–58%], [56–58%], [58%], [56%]	*Lung* Pulmonary carcinoma 1/52, 0/52, 0/53, 1/52	 [NS]	Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; adequate number of animals per group. Other comments: sections of the heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes, from all animals, were examined histologically; exact number of surviving animals NR.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344 (CDF F344 Crl BR) (F) 8 wk 24 mo Newton et al. (1994)	Inhalation (whole-body exposure) Antimony(III) oxide, 99.68 ± 0.10% Air 0, 0.06, 0.51, 4.50 mg/m^3 6 h/day, 5 days/wk for 52 wk 49, 52, 54, 50 [48%], [40%], [66%], [60%]	*Lung* Pulmonary carcinoma 0/49, 0/52, 1/54, 0/50	[NS]	Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; adequate number of animals per group. Other comments: sections of the heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes, from all animals, were examined histologically; exact number of surviving animals, NR.
Full carcinogenicity Rat, F344 (CDF) (F) 19 wk 25–28 mo (12–15 mo observation period post-exposure) Watt (1983)	Inhalation (whole-body exposure) Antimony(III) oxide, 99.4% (major impurities, 0.02% arsenic, 0.2% lead) Air 0, 1.6, 4.2 mg/m^3 6 h/day, 5 days/wk for 13 mo 42, 44, 45 NR, NR, NR	*Lung* All tumours 1/13, 1/17, 14/18* Scirrhous adenocarcinoma 0/13, 0/17, 9/18* Squamous cell carcinoma 0/13, 0/17, 2/18 Bronchioloalveolar adenoma 0/13, 1/17, 3/18	[$P < 0.001$, Cochran–Armitage trend test] *$P < 0.01$, test NR [$P < 0.0001$, Fisher exact test] [$P < 0.001$, Cochran–Armitage trend test] *$P < 0.01$, test NR [$P < 0.003$, Fisher exact test] NS NS	Principal limitations: the use of one sex only; two rats per inhalation cage; rats treated in the same room as miniature swine; statistical test NR; and number of rats intentionally killed or number of early deaths in the groups NR. Other comments: number at start is the effective number of animals; data reported for the animals killed 12–15 mo after the end of exposure.

F, female; GLP, Good Laboratory Practice; GSD, geometric standard deviation; M, male; min, minute; MMAD, mass median aerodynamic diameter; mo, month; NR, not reported; NS, not significant; T_{90}, the theoretical value for the time to achieve 90% of the target concentration after the beginning of aerosol generation; TWA, time-weighted average; wk, week.

In male mice, there was a significant positive trend in the incidence of bronchioloalveolar carcinoma and of bronchioloalveolar adenoma or carcinoma (combined) ($P < 0.001$, poly-3 test [$P < 0.001$, Cochran–Armitage test]). The incidence of bronchioloalveolar carcinoma (control, 4/50; lowest concentration, 18/50; intermediate concentration, 20/50; and highest concentration, 27/50), and of bronchioloalveolar adenoma or carcinoma (combined) (control, 13/50; lowest concentration, 29/50; intermediate concentration, 28/50; and highest concentration, 34/50), was significantly increased in all treated groups ($P < 0.001$, poly-3 test). The incidence of bronchioloalveolar adenoma at the lowest and the highest concentration – both 14/50 (28%) – exceeded the upper bound of the range observed in historical controls from this laboratory: inhalation, 35/250 (14.0% ± 3.7%); range, 10–20%; and all routes, 83/550 (15.1% ± 5.9%); range 8–26%. There was a significant positive trend in the incidence of fibrous histiocytoma of the skin ($P = 0.012$, poly-3 test). The incidence of fibrous histiocytoma of the skin – control, 0/50; lowest concentration, 1/50 (2%); intermediate concentration, 1/50 (2%); and highest concentration, 4/50 (8%) – was significantly increased ($P = 0.039$, poly-3 test) at the highest concentration, and exceeded the upper bound of the range observed in historical controls from this laboratory: inhalation, 1/250 (0.4% ± 0.9%); range, 0–2%; and all routes, 2/550 (0.4% ± 0.8%); range 0–2%. There was a significant positive trend in the incidence of fibrous histiocytoma or fibrosarcoma (combined) of the skin ($P = 0.023$, poly-3 test). The incidence of fibrous histiocytoma or fibrosarcoma (combined) of the skin was significantly increased ($P = 0.039$, poly-3 test) at the highest concentration compared with controls – control, 0/50; lowest concentration, 1/50 (2%); intermediate concentration, 3/50 (6%); and highest concentration, 4/50 (8%) – and exceeded the upper bound of the range (at the intermediate and highest concentration) observed in historical controls from this laboratory: inhalation, 2/250 (0.8% ± 1.1%); range, 0–2%; and all routes, 5/550 (included one sarcoma) (0.9% ± 1.0%); range, 0–2%. The incidence of fibrosarcoma of the skin at the intermediate concentration – 2/50 (4%) – exceeded the upper bound of the range observed in historical controls from this laboratory: inhalation, 1/250 (0.4% ± 0.9%); range, 0–2%; and all routes, 2/550 (0.4% ± 0.8%); range, 0–2%.

In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma (includes multiple) [$P < 0.001$, Cochran–Armitage test], of bronchioloalveolar carcinoma (includes multiple) [$P = 0.016$, Cochran–Armitage test], and of bronchioloalveolar adenoma or carcinoma (combined) ($P = 0.019$, poly-3 test). The incidence of bronchioloalveolar adenoma (control, 1/50; lowest concentration, 10/50; intermediate concentration, 19/50; and highest concentration, 8/50), of bronchioloalveolar carcinoma (control, 2/50; lowest concentration, 14/50; intermediate concentration, 11/50; and highest concentration, 11/50), and of bronchioloalveolar adenoma or carcinoma (combined) (control, 3/50; lowest concentration, 22/50; intermediate concentration, 27/50; and highest concentration, 18/50), was significantly increased in all exposed groups of females ($P < 0.01$, poly-3 test). There was a significant positive trend in the incidence of malignant lymphoma ($P < 0.001$, poly-3 test). The incidence of malignant lymphoma was significantly increased ($P \leq 0.013$, poly-3 test) in all treated groups – control, 7/50 (14%); lowest concentration, 17/50 (34%); intermediate concentration, 20/50 (40%); highest concentration, 27/50 (54%) – exceeding the upper bound of the range (at the intermediate and high concentration) in historical controls from this laboratory: inhalation, 63/250 (25.2% ± 8.4%); range, 14–36%; and all routes, 109/550 (19.8% ± 7.9%); range, 12–36%. The incidence of squamous cell carcinoma of the skin at the highest concentration – 2/50 (4%) – exceeded the incidence in historical controls

from this laboratory (inhalation, 0/250; and all routes, 0/550).

Regarding non-neoplastic lesions of the lung, there was a significant increase in the incidence of hyperplasia of the alveolar epithelium and of bronchiolar epithelium in all exposed groups of males and females (NTP, 2017). [The Working Group noted that this was a well-conducted GLP study using an adequate number of mice per group, both sexes, multiple concentration groups, and an adequate duration of exposure and observation.]

3.2 Rat

3.2.1 Antimony(III) oxide

Inhalation

In a well-conducted study that complied with GLP, groups of 50 male and 50 female Wistar Han [Crl:WI(Han)] rats (age, 6 weeks) were exposed by inhalation (whole-body) to aerosols of antimony(III) oxide (purity > 99.9%; mass median aerodynamic diameter, 0.9–1.5 µm; geometric standard deviation, 1.7–2.2) at a concentration of 0, 3, 10, or 30 mg/m^3 for the control group and at the lowest, intermediate, and highest concentration, respectively, for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks or less (NTP, 2017). Survival of females at the intermediate and highest concentration was less than that of controls, primarily because of lung proteinosis. In males, the negative trend in survival was primarily attributed to lung inflammation and proteinosis. At study termination, survival was 30/50, 30/50, 28/50, and 18/50 in males, and 39/50, 38/50, 28/50, and 20/50 in females, for the control group and at the lowest, intermediate, and highest concentration, respectively. Body weight of males at the highest concentration was less (10% or more) than that of controls after week 69 until the end of the study. Body weight of females at the lowest, intermediate, and highest concentration was 10% or less than that of controls by weeks 99, 81, and 65, respectively; and females at the intermediate and highest concentration continued to lose body weight (20% and 28% less than controls, respectively) until the end of the study. Lung burden was assessed at multiple time points for female rats. On the basis of measured lung burden and estimation of clearance half-lives, lung overload occurred at 10 and 30 mg/m^3. Lung overload did not occur at 3 mg/m^3. All rats underwent complete necropsy with histopathological evaluation (NTP, 2017).

In male rats, there was no significant increase in the incidence of lung tumours in treated rats compared with controls. The incidence of bronchioloalveolar adenoma (includes multiple) – 3/50 (6%), 4/50 (8%), 6/50 (12%), and 8/50 (16%) – and bronchioloalveolar adenoma or carcinoma (combined) – 3/50 (6%), 4/50 (8%), 8/50 (16%), and 8/50 (16%) – for the control group and at the lowest, intermediate, and highest concentration, respectively, exceeded the upper bound of the range observed in historical controls for bronchioloalveolar adenoma and brochioloalveolar adenoma or carcinoma (combined) from this laboratory: inhalation, 4/150 (2.7% ± 3.1%); range, 0–6%; and all routes, 4/299 (1.3% ± 2.4%); range, 0–6%. The incidence of bronchioloalveolar carcinoma at the intermediate concentration – 2/50 (4%) – exceeded the incidence observed in historical controls from this laboratory: inhalation, 0/150; all routes, 0/299. There was a significant positive trend in the incidence of benign pheochromocytoma of the adrenal medulla in males ($P < 0.001$, poly-3 test), with the incidence – control, 1/49 (2%); lowest concentration, 0/50; intermediate concentration, 2/49 (4%); and highest concentration, 7/50 (14%) – being significantly increased ($P = 0.030$, poly-3 test) at the highest concentration, and exceeding the upper bound of the range observed in historical controls from this laboratory – inhalation, 5/149 (3.4% ± 4.2%); range, 0–8%; and all routes, 6/297 (2.0% ± 3.1%); range, 0–8%.

In female rats, there was a significant positive trend in the incidence of bronchioloalveolar adenoma (includes multiple) (P = 0.029, poly-3 test). The incidence of bronchioloalveolar adenoma – control, 0/50; lowest concentration, 2/50 (4%); intermediate concentration, 6/50 (12%); and highest concentration, 5/50 (10%) – was significantly increased in groups at the intermediate and highest concentration ($P \leq 0.021$, poly-3 test), exceeding the incidence in historical controls from this laboratory: inhalation, 0/150; all routes, 0/300. In females at the highest concentration there was also one squamous cell carcinoma (incidence, 1/50) and two cystic keratinizing epitheliomas of the lung (incidence, 2/50). There was a significant positive trend in the incidence of cystic keratinizing epithelioma or squamous cell carcinoma (combined) ($P = 0.006$, poly-3 trend test), and incidence exceeded that in historical controls from this laboratory: inhalation, 0/150; all routes, 0/300. There was a significant positive trend in the incidence of benign pheochromocytoma of the adrenal medulla and of benign or malignant pheochromocytoma (combined) of the adrenal medulla in female rats ($P = 0.004$ and $P < 0.001$, respectively; poly-3 test). [The Working Group indicated that the differential diagnosis of malignant pheochromocytoma is difficult to assess based only on histomorphology (see Patterson et al., 1995; Thompson, 2002).] The incidence of benign pheochromocytoma of the adrenal medulla – 0/49, 2/48 (4%), 2/49 (4%), and 6/50 (12%) – and of benign or malignant pheochromocytoma (combined) – 0/49, 2/49 (4%), 2/49 (4%), and 7/50 (14%) – for the control group and at the lowest, intermediate, and highest concentration, respectively, was significantly increased at the highest concentration (P = 0.009 and P = 0.004, respectively; poly-3 test). This exceeded the upper bound of the range observed in historical controls from this laboratory: for benign pheochromocytoma of the adrenal medulla, inhalation, 1/148 (0.7% ± 1.2%); range, 0–2%; and all routes, 5/297 (1.7% ± 1.5%); and for benign or malignant pheochromocytoma (combined), inhalation, 2/148 (1.4% ± 2.4%); range, 0–4%; and all routes, 7/297 (2.4% ± 2.0%); range, 0–4% (NTP, 2017).

Regarding non-neoplastic lesions, there was a significant increase in the incidence of alveolar epithelial hyperplasia of the lung, bronchiolar epithelial hyperplasia of the lung, respiratory epithelium hyperplasia of the nasal cavity, and medullary hyperplasia of the adrenal gland in exposed males and females (NTP, 2017). [The Working Group noted that this was a well-conducted GLP study using an adequate number of rats per group, both sexes, multiple concentration groups, and an adequate duration of exposure and observation.]

In another study, groups of 90 male and 90 female Wistar rats (age, 8 months) were exposed by inhalation (whole-body) to antimony(III) oxide (80% antimony; with contaminants including: titanium, < 3%; tin, 0.2%; lead, 0.2%; cerium, 0.014%; and arsenic, 0.004%) at a concentration of 0 (control) or 45.0–46.0 mg/m^3 (TWA) for 7 hours per day, 5 days per week, for 52 weeks (exposures did not occur on a few days, because of holidays or mechanical breakdowns) (Groth et al., 1986). Groups of 5 males and 5 females were killed at 6, 9, and 12 months after initiation of the exposure. The remaining rats were killed 18–20 weeks after exposure ended. There was no difference in survival between groups of treated male or female rats and their respective controls. Mean body weights were consistently decreased in treated males after 26 weeks of exposure. A total of 22 control males, 22 treated males, 39 control females, and 31 treated females were killed at the end of the study (at 71–73 weeks). The total numbers of rats killed between weeks 0 and 73 were 84 control males, 83 treated males, 86 control females, and 88 treated females.

In female rats, the first lung tumours were seen in 2 out of 5 treated rats (one adenoma and one squamous cell carcinoma) killed at 53 weeks.

A total of 19/70 (27%; $P \leq 0.001$ [statistical test not reported] [$P < 0.0001$, Fisher exact test]) treated females examined between weeks 41 and 72 developed lung tumours, compared with 0/69 controls. The incidence of lung tumours in treated females was: squamous cell carcinoma, 9/89 [$P = 0.0016$, Fisher exact test]; scirrhous carcinoma [scirrhous adenocarcinoma], 5/89 [$P = 0.0295$, Fisher exact test]; and bronchioloalveolar adenoma or carcinoma (combined) [incidence of adenoma and incidence of carcinoma was unspecified], 11/89 [$P = 0.0004$, Fisher exact test], compared with 0/89 controls.

No lung tumours were observed in treated males or in any male or female controls. The incidence of tumours in tissues or organs other than the lung was not significantly different in treated and control rats of either sex (Groth et al., 1986). [The Working Group noted that statistical tests were used but analyses were undefined, only one concentration was tested, the number of deaths and number killed were not clearly separated, and tumour status was not always accurately stated. The control groups of males and females were the same as in the study on antimony ore concentrate by the same authors (see below).]

In another study, groups of approximately 50 male and 50 female Fischer 344 (CDF F344 Crl BR) rats (age, 8 weeks) were exposed by inhalation (whole-body) to antimony(III) oxide dust (purity, 99.68% ± 0.10%; mass median aerodynamic diameter, mean ± SD, 3.76 ± 0.84 μm; geometric standard deviation, 1.79 ± 0.32) at a concentration of 0, 0.06, 0.51, or 4.50 mg/m^3 for the control group and at the lowest, intermediate, and highest concentration, respectively, for 6 hours per day, 5 days per week, for 52 weeks, followed by a 12-month observation period (Newton et al., 1994). There were about 50 rats per group (males: 52, 52, 53, and 52; and females: 49, 52, 54, and 50; for the control group and at the lowest, intermediate, and highest concentration, respectively). Numerical values for survival were not reported, but survival [read from figures] was 56–58%, 56–58%, 58%, and 56% for males, and 48%, 40%, 66%, and 60% for females in the control group and at the lowest, intermediate, and highest concentration, respectively. Body weights of females and males were unaffected by exposure. All survivors were killed at 24 months (12 months post-exposure) and complete gross examinations were performed.

Three lung carcinomas were reported, two in males (one in the controls and one in the group at the highest concentration) and one in females (at the intermediate concentration). These tumours were assessed as comparable in incidence in all groups and were within the range reported for historical controls. No other primary neoplasms were seen in the lungs of treated rats. Microscopic changes in the lungs after treatment were limited to interstitial inflammation, increased alveolar macrophages, perivascular lymphoid aggregates, fibrosis, and foreign material (Newton et al., 1994). [The Working Group noted that this study used an adequate number of rats per group, both sexes, multiple concentrations, and an adequate duration of exposure and observation, but the numbers of rats at study termination was not reported.]

In another study reported in a doctoral dissertation, groups of female Fischer 344 (CDF) rats (age, 19 weeks) were exposed by inhalation (whole-body) to antimony(III) oxide dust (purity, 99.4%; arsenic, 0.02%; lead, 0.2%) at a concentration of 0, 1.6, or 4.2 mg/m^3 (as antimony), for the control group and at the lower and higher concentration, respectively, for 6 hours per day, 5 days per week, for 13 months or less, followed by a 12–15-month observation period without exposure (Watt, 1983). Group sizes were 42, 44, and 45 for the control group and at the lower and higher concentration, respectively. Mean body weight in treated groups at start of the study was slightly higher than that of controls but, after exposure and towards the end of the study, it was similar to that of controls. Small groups of rats [number of rats per group not reported]

were either killed or died [not clearly specified], and histopathology was assessed after 3, 6, 9, or 12 months of exposure. Groups of rats [number of rats per group not reported] were also killed 2 months after the end of exposure and at the end of the 12-month post-exposure period. However, the largest groups were killed at 12–15 months after the end of treatment.

In the rats killed 12–15 months after the end of exposure, there was a significant positive trend in the incidence of lung tumours [$P < 0.001$, Cochran–Armitage test]. The incidence of lung tumours (control group, 1/13; lower concentration, 1/17; and higher concentration, 14/18) was significantly increased at the higher concentration ($P < 0.01$ [statistical test not reported; $P < 0.0001$, Fisher exact test]). There was a significant positive trend in the incidence of scirrhous carcinoma [scirrhous adenocarcinoma] of the lung [$P < 0.001$, Cochran–Armitage test]. The incidence of scirrhous carcinoma (control group, 0/13; lower concentration, 0/17; and higher concentration, 9/18) was significantly increased in rats at the higher concentration ($P < 0.01$ [statistical test not reported; $P < 0.003$, Fisher exact test]). The incidence of scirrhous carcinoma was also increased in rats at the higher concentration that died or were killed between 2 months after the end of exposure and at the end of the 12-month post-exposure period (control, 0/6; higher concentration, 5/7) ($P < 0.05$ [test not reported; $P < 0.02$, Fisher exact test]) (Watt, 1983). [The Working Group noted that only female rats were used, there were 2 rats per inhalation cage, rats were treated in the same room as miniature swine, the statistical analyses used were not specified, and the numbers of rats intentionally killed and numbers of early deaths were not reported.]

3.2.2 Antimony ore concentrate

Inhalation

Groups of 90 male and 90 female Wistar rats (age, 8 months) were exposed by inhalation (whole-body) to antimony ore concentrate (antimony, 46%; titanium, < 4%; aluminium, 0.5%; tin, 0.2%; lead, 0.3%; iron, 0.3%; arsenic, 0.08%) [the Working Group noted that the antimony ore was principally antimony(III) sulfide; however, the amount of antimony(III) sulfide contained in the test agent was not reported] at a concentration of 0 (control) or 36.0–40.1 mg/m^3 (TWA) for 7 hours per day, 5 days per week, for 52 weeks (Groth et al., 1986). Groups of 5 males and 5 females were killed at 6, 9, and 12 months after initiation of the exposure. The remaining rats were killed between 18 and 20 weeks after the end of exposure. There was no difference in survival between the groups treated with antimony ore concentrate and the control groups for either sex. Body weights were reduced from week 26 onwards in females treated with the ore concentrate. [The Working Group noted that only one concentration was tested, statistical tests were used but analyses undefined, the numbers of deaths and numbers killed were not clearly separated, and tumour status was not always accurately stated. The control groups of males and females were the same as those used in the study on antimony(III) oxide by the same authors (see above). In addition, the Working Group noted that the test article characterization did not specify the amount of antimony forms (e.g. antimony(III) sulfide) within the ore concentrate; therefore, the Working Group considered that the study was inadequate for the evaluation of the carcinogenicity of trivalent antimony in experimental animals.]

3.3 Evidence synthesis for cancer in experimental animals

3.3.1 Pentavalent antimony

No data on pentavalent antimony were available to the Working Group.

3.3.2 Trivalent antimony

(a) Antimony(III) oxide

The carcinogenicity of antimony(III) oxide has been assessed in one well-conducted study that complied with GLP in male and female mice exposed by inhalation (whole-body), in one well-conducted study that complied with GLP in male and female rats exposed by inhalation (whole-body) (NTP, 2017), and in three additional studies: two in male and female rats (Groth et al., 1986; Newton et al., 1994) and one in female rats (Watt, 1983) exposed by inhalation (whole-body).

In a well-conducted study that complied with GLP in male and female B6C3F$_1$/N mice exposed to antimony(III) oxide by inhalation (whole-body), there was a significant increase, with a significant positive trend, in the incidence of bronchioloalveolar carcinoma, and bronchioloalveolar adenoma or carcinoma (combined), in males and females; of fibrous histiocytoma of the skin, and fibrous histiocytoma or fibrosarcoma (combined) of the skin, in males; and of bronchioloalveolar adenoma, and malignant lymphoma (all organs), in females (NTP, 2017).

In a well-conducted study that complied with GLP in male and female Wistar rats exposed to antimony(III) oxide by inhalation (whole-body), there was a significant increase, with a significant positive trend, in the incidence of bronchioloalveolar adenoma, benign pheochromocytoma of the adrenal medulla, and benign or malignant pheochromocytoma (combined) of the adrenal medulla in females, and of benign pheochromocytoma of the adrenal medulla in males. There was also a significant positive trend in the incidence of cystic keratinizing epithelioma or squamous cell carcinoma (combined) of the lung in females (NTP, 2017).

In a study in male and female Wistar rats exposed to antimony(III) oxide by inhalation (whole-body), there was a significant increase in the incidence of squamous cell carcinoma, scirrhous adenocarcinoma, and bronchioloalveolar adenoma or carcinoma (combined) of the lung in exposed females (Groth et al., 1986).

In a study in female Fischer 344 (CDF) rats exposed to antimony(III) oxide by inhalation (whole-body), there was a significant increase in the incidence of lung tumours and of scirrhous adenocarcinoma of the lung (Watt, 1983).

In a study in male and female Fischer 344 (CDF) rats exposed to antimony(III) oxide by inhalation (whole-body), there was no significant increase in the incidence of tumours (Newton et al., 1994).

(b) Antimony ore concentrate

A study in male and female Wistar rats exposed to antimony ore concentrate by inhalation (whole-body exposure) was considered inadequate for the evaluation of the carcinogenicity of trivalent antimony in experimental animals (Groth et al., 1986).

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Absorption and distribution

(a) Humans

(i) Inhalation

Trivalent antimony

A study by Wu & Chen (2017) reported on the absorption and distribution of antimony in 91 male workers from various manufacturing plants who were exposed to antimony(III) oxide or sodium antimonite in Taiwan, China, with 42 male administrators as a control group. Antimony distributed to blood, hair, and urine. The levels were higher in workers than in the control group and were correlated with antimony concentrations in the air of work sites (see also Sections 1.4.2 and 1.6.2). (Wu & Chen, 2017). Kentner et al. (1995) examined the levels of antimony in blood and urine samples from workers involved in lead battery production. Among 7 workers from the casting area exposed to antimony(III) oxide and 14 workers from the formation area exposed to both stibine and antimony(III) oxide (all men), the median levels of antimony in personal air samples were 4.5 and 12.4 μg/m^3, respectively. Both antimony compounds exhibited similar pulmonary absorption and renal elimination. The median blood and urinary antimony concentrations were 2.6 μg/L and 3.9 μg/g creatinine, and 10.1 μg/L and 15.2 μg/g creatinine, for the formation workers and casters, respectively (Kentner et al., 1995). Measurements of antimony in blood were 5–10 times as high in a group of port workers exposed to trivalent antimony from heavyweight vehicular traffic as in workers in two control groups. [The Working Group noted that exposure levels were not provided.] More than 60% antimony was found in the erythrocyte fractions of blood samples in all three groups (Quiroz et al., 2009).

In a group of seven workers accidentally exposed to radioactive antimony (^{125}Sb) oxide aerosols, antimony was found to be mainly accumulated in the lungs (Garg et al., 2003).

Metallic antimony

Gerhardsson et al. (1982) reported tissue concentrations of antimony in the lung, liver, and kidney from a group of 40 deceased smelter workers in Sweden compared with a control group of 11 deceased people without occupational exposure. The median value of antimony in lung tissue from smelter workers was 315 μg/kg, 12 times that in controls. For lung tissue, there was no trend towards decreased antimony concentrations with time after cessation of exposure, indicating long-term retention. Antimony concentrations in the liver and kidney of workers did not differ significantly from those of controls (Gerhardsson et al., 1982). The distributions and concentrations of 27 trace elements, including antimony, in human lung and lymph nodes were investigated in eight deceased individuals who were assumed to have been exposed to airborne dust. [The Working Group noted that exposure information was not provided.] While some elements were homogeneously distributed over a lung pair and showed few differences in interindividual concentrations, antimony and a few other elements were not homogeneously distributed. The content of antimony in hilar lymph nodes (60–479 ng/g wet tissue) was higher than that in lung (3.5–48.2 ng/g wet tissue). The non-homogeneity and the concentration increased with age, suggesting the accumulation of atmospheric contaminants (Vanoeteren et al., 1986a, b, c).

(ii) Other exposure routes

Trivalent antimony

Accidental ingestion of antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$; 0.85–2.5 g) was reported for four patients; in three patients, the blood antimony levels increased during the first 12 hours; in one patient, the peak level was reached on admission. Antimony content was measured in one deceased individual, and high concentrations were found in the liver, gall bladder, and gastrointestinal tract. The estimated total body pool of antimony was 15–20 mg, which was a very small portion of the ingested dose (Lauwers et al., 1990). In one woman who intentionally ingested an unknown quantity of antimony(III) sulfide, concentrations of antimony in blood and urine remained elevated (blood, > 0.1 µg/100 mL; urine, > 1 µg/g creatinine) 1 week after ingestion, whereas antimony was undetectable in the bile and gastric fluid 100 hours after ingestion (Bailly et al., 1991).

Pentavalent antimony

In five healthy adult volunteers, after a single intramuscular injection of antimony(V) (as the drug Ulamina) at a dose of 5 mg/kg bw, the mean plasma concentration of total antimony [antimony(III) plus antimony(V)] after 15 minutes was 0.59 µg/mL, the C_{max} was 1.1 µg/mL, and the T_{max} was 1.3 hours (Vásquez et al., 2006).

Metallic antimony

A study aiming to establish a reference level for antimony in Irish infants showed the presence of low concentrations of antimony in the serum (0.09–0.25 µg/L) and urine (median, 0.42 ng/mg creatinine; upper 95% centile, 2.6 ng/mg creatinine) of 100 healthy infants (Cullen et al., 1998). Another study obtained a reference profile of 60 elements in 68 healthy Chinese men with death recorded as due to accidents but without obvious antimony exposure history. The lung showed the highest antimony concentration, followed by the liver, thyroid, and stomach (Zhu et al., 2010).

(b) Experimental systems

(i) Inhalation

Trivalent antimony

Both Newton et al. (1994) and the National Toxicology Program (NTP) (NTP, 2017) conducted studies of subchronic and chronic toxicity after inhalation of trivalent antimony.

In the study by Newton et al. (1994), groups of 50 male and 50 female Fischer 344 rats were exposed to antimony(III) oxide by inhalation (whole-body) at a concentration of 0 (control), 0.25, 1.08, 4.92, or 23.46 mg/m^3 for 6 hours per day, 5 days per week for 13 weeks, followed by a 27-week recovery period. In the lung, there was an initial rapid accumulation phase, followed by a second slower accumulation phase after 2–4 weeks. No steady-state level of antimony was reached. In the study of chronic toxicity, groups of 65 male and 65 female rats were exposed to antimony(III) oxide at a concentration of 0 (control), 0.06, 0.51, or 4.50 mg/m^3 for 12 months, followed by a 12-month recovery period. Elevated antimony concentrations were detected in erythrocytes, but not in the plasma. Antimony was present in the faeces. Lung burdens increased with increasing exposure concentration, and steady-state levels were reached 6 months after exposure. Pulmonary clearance of antimony was dependent on lung burden. For example, after the 12-month treatment, antimony lung burdens in male rats were 11.5, 132.0, and 1420 µg/g in the 0.06, 0.51, and 4.50 mg/m^3 exposure groups, respectively, and decreased to 0.4, 8.1, and 554 µg/g, respectively, after the 12-month recovery period. Similar trends were observed in female rats. The half-lives ranged from 2 to 10 months for the groups at 0.06, 0.51, and 4.50 mg/m^3 (Newton et al., 1994).

In a study conducted by the NTP (2017), groups of 5 female Wistar Han rats and groups of

5 female B6C3F$_1$/N mice were exposed by inhalation (whole-body) to antimony(III) oxide at a concentration of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3, for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 2 weeks, followed by a 4-week recovery period. Total antimony lung burdens and blood antimony concentrations increased with increasing exposure concentration in rats and mice. Kinetic parameters were determined using lung burden data obtained at the end of the 2-week exposure and 4-week post-exposure periods. Clearance half-lives in the lung ranged from 73 to 122 days in rats and 47 to 62 days in mice. The shortest half-life was for the lowest exposure concentration, but no clear concentration–response trend was observed. Deposition rates were approximately proportional or slightly less than proportional to exposure concentrations. Deposition rates increased 15-fold in rats and 13-fold in mice when exposure concentration increased 16-fold. Steady-state lung burdens in rats and mice were not reached during the post-exposure period. Steady-state lung burdens were expected to be reached after about five clearance half-lives. The expected half-lives were estimated to be 365–610 days in rats and 235–310 days in mice. Kinetic analysis of blood antimony concentration in mice indicated that the elimination half-life was between 22 and 32 days, and the concentration–response trend proportional to exposure was similar to that observed in the lung. In rats, blood antimony concentrations increased during the recovery period, indicating that antimony entered the bloodstream. In rats, blood concentration was 0.8% of lung concentration at the end of the 30 mg/m^3 exposure, and 2% of lung concentration at 4 weeks post-exposure. In mice, blood concentration was 0.005% of lung concentration at the end of the 30 mg/m^3 exposure, and 0.005% of lung concentration at 4 weeks post-exposure.

In the long-term study of chronic toxicity performed by the NTP (2017), groups of 5 female Wistar Han [Crl:WI(Han)] rats and groups of 5 female B6C3F$_1$/N mice were exposed by inhalation (whole-body) to antimony(III) oxide at a concentration of 0 (control), 3, 10, or 30 mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 79 weeks. Total antimony(III) oxide lung burdens and blood antimony concentrations increased with increasing exposure concentration in both rats and mice. Antimony(III) oxide particles were found in the lungs, nose, larynx, trachea, and bronchial, mediastinal, and mandibular lymph nodes of exposed mice. Lung burdens in rats at 3 or 10 mg/m^3 reached steady state; however, lung burdens in rats at 30 mg/m^3 and in all groups of treated mice increased steadily over time and did not reach steady state. In rats, lung deposition rates were proportional to exposure concentration and were indicative of deposition efficiencies that increased from approximately 3% to 5% of the inhaled antimony(III) oxide. The lung clearance half-lives in rats were 136, 203, and 262 days for the groups at 3, 10, and 30 mg/m^3, respectively. The reduced pulmonary clearance at higher concentrations (10 and 30 mg/m^3) was probably associated with lung overload. In rats, two thirds of the antimony dose to the lung was cleared over the course of the study in the group exposed to 3 mg/m^3. Only half of the antimony(III) oxide dose to the lung was cleared over the course of the study in the groups exposed to 10 and 30 mg/m^3. In rats and mice, blood antimony concentrations increased with exposure concentration. While blood concentrations increased with exposure duration in rats, they did not consistently increase over time in mice. The rate of clearance from the blood increased as exposure concentrations (and lung burdens) increased (NTP, 2017).

Pentavalent antimony

In an inhalation study in Syrian hamsters, both trivalent and pentavalent antimony accumulated in erythrocytes (Felicetti et al., 1974). However, an in vitro study showed that trivalent and pentavalent antimony had a notable affinity

for erythrocytes, but did not bind to haemoglobin (Hb) (Wu et al., 2018).

(ii) Oral administration and intraperitoneal injection

Trivalent antimony

Field voles (bred in the laboratory) were given feed containing antimony(III) oxide at a concentration of 500 or 6700 mg/kg diet. Antimony was detected in all three tissues examined, i.e. liver, lung, and kidney. The highest antimony concentration was in the liver (Ainsworth et al., 1991). Groups of 15 male and 15 female rats were given drinking-water containing antimony(III) potassium tartrate at a concentration of 0 (control), 0.5, 5, 50, or 500 ppm for 13 weeks. Ten additional rats were included in the control groups and groups at 500 ppm for a further 4-week recovery period after the 13-week exposure period. Tissue antimony concentrations were dose-related and followed the order: erythrocytes > spleen/liver > kidney > brain/fat > serum. After the 4-week recovery period, antimony concentrations in all tissues (except in the spleen) decreased in the group at 500 ppm (Poon et al., 1998). In a study by Hiraoka (1986), antimony was detected in the liver, spleen, lung, kidney, hair, bone, and blood of rats given feed containing 1.0% (w/w) antimony(III) oxide for 12 weeks. After exposure, the highest concentration was detected in the blood followed by the spleen. After a 12-week recovery period, 52% of antimony detected after the exposure period remained in the blood and 76% remained in the spleen, indicating slow excretion from the body (Hiraoka, 1986).

Fischer 344/N rats or B6C3F$_1$ mice were treated with antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$) in the drinking-water for 14 days, or as 12 intraperitoneal injections over 16 days, or as intraperitoneal injections every other day for 90 days (Dieter et al., 1991; NTP, 1992). In the 14-day drinking-water study, rats were exposed to antimony(III) potassium tartrate at a dose of 0 (control), 16, 28, 59, 94, or 168 mg/kg bw once per day. In rats, antimony was detected in the blood, kidney, heart, spleen, and liver, but without a clear dose–response relationship. Concentrations of antimony in the blood were about three times as high as those in other tissues examined. In the 16-day intraperitoneal injection study, rats were treated with antimony(III) potassium tartrate at a dose of 0 (control), 1.5, 3, 6, 11, or 22 mg/kg bw, and mice at doses of 0, 6, 13, 25, 50, or 100 mg/kg bw. Antimony was detected at dose-dependent concentrations in the blood, kidney, heart, spleen, and liver of rats. In mice, antimony was detected in the liver and spleen, but not in the blood, heart, or kidney. In the 90-day intraperitoneal injection study, rats and mice were exposed to antimony(III) potassium tartrate at a dose of 0, 1.5, 3, 6, 12, or 24 mg/kg bw, 3 times per week for 90 days. Dose-dependent accumulation of antimony was found in the blood, liver, kidney, spleen, and heart of rats, with the highest tissue concentration being detected in the spleen. Antimony was also detected in the liver and spleen of mice. Blood antimony concentrations in exposed rats in the 14-day drinking-water study (15–20 μg/g) were about twice those in exposed rats of the 16-day intraperitoneal injection study (4–12 μg/g). Since the rats in the 14-day study were given drinking-water that contained antimony at doses that were approximately 10-fold those administered to rats in the 16-day intraperitoneal injection study, absorption of the compound appeared to be lower when administered in drinking-water than when administered intraperitoneally, suggesting that antimony(III) potassium tartrate has poor absorption when given orally or low bioavailability via the gastrointestinal tract (Dieter et al., 1991; NTP, 1992).

Pentavalent antimony

Borborema et al. (2013) reported that in BALB/c mice treated with a single dose of radioactive pentavalent antimony by intraperitoneal injection, the uptake rate of radioactive antimony

was 0.02–1.6% after 72 hours. The blood profile indicated that antimony was rapidly absorbed and distributed, and slowly eliminated. Higher uptake of antimony was detected in the liver, and elimination occurred primarily through biliary excretion after liver processing, with a small proportion being excreted by the kidneys. Antimony did not accumulate in the brain, lungs, heart, or uterus.

Fernandes et al. (2013) reported that in Swiss and BALB/c mice treated with a pentavalent antimonial (a drug to treat leishmaniasis) at a dose of 200 mg/kg bw by gavage, there was rapid absorption, with a serum C_{max} of 2.9 mg/L and T_{max} of 1.3 hours, and liver accumulation. Ribeiro et al. (2010) reported that when three beagle dogs were treated with a single dose of the anti-leishmanial meglumine antimoniate(V) at a dose of 100 mg/kg bw (as antimony) by nasogastric intubation, the C_{max} of serum antimony was 7.5 mg/L, T_{max} was 0.9 hours, and mean residence time was 2.6 hours. Antimony was not detected in erythrocytes and was present exclusively in the serum.

(iii) Other exposure routes

Trivalent antimony

Syrian golden hamsters were treated with antimony(III) oxide particles (suspended in 0.9% saline) at a dose of 1.52 mg/kg bw by intratracheal instillation. After the exposure, antimony was detected at significant concentrations in the lung and liver, with smaller amounts in the kidney, stomach, and trachea. Pulmonary elimination was found to be biphasic. In an initial phase, about 20% of antimony(III) was eliminated during the first 20 hours. The calculated half-lives were about 40 hours for the initial phase and 20–40 days for the second phase (Leffler et al., 1984).

Pentavalent antimony

Rhesus monkeys were treated with meglumine antimoniate(V) at a dose of 5 or 20 mg/kg bw per day by intramuscular injection for 21 days. Antimony speciation in plasma on post-treatment days 1–9 indicated that although total antimony concentrations declined, the proportion of antimony(V) remained at 11–20%, whereas that of antimony(III) increased from 5% on day 1 to 50% on day 9. On post-treatment days 55 and 95, antimony was detected in various tissues, including the thyroid, liver, gall bladder, and spleen (Friedrich et al., 2012).

In Wistar rats treated with a single dose of meglumine antimoniate(V) at a concentration of 75 mg/kg bw by intramuscular injection, a sharp fall in antimony blood concentration (half-life, 0.6 hours) was observed, and antimony was cleared from the body within 6–12 hours. Exposure of rats to meglumine antimoniate(V) at an antimony(V) concentration of 300 mg/kg bw by subcutaneous injection once per day for 21 days resulted in a steady increase of antimony in the blood. Three months after dosing, antimony blood concentrations fell from 51 µg/g on day 22 to 36 µg/g on day 126. Antimony was found to accumulate in the spleen, bone, thyroid, kidney, and liver, with the highest amount being detected in the spleen. Antimony was mainly detected in whole blood but not plasma (Coelho et al., 2014).

In Wistar rats treated with a single intravenous injection of antimony(III) potassium tartrate at a dose of 1.72 mg/kg bw as antimony or given feed containing antimony(III) potassium tartrate, potassium pyroantimonate(V), or antimony(III) oxide at a dose of about 30 mg/kg bw per day as antimony for up to 17 weeks, antimony was distributed in the blood, principally accumulating in erythrocytes, and was integrated into Hb, regardless of oxidative state (III) or (V) (Wu et al., 2018).

A group of beagle dogs was treated with meglumine antimoniate(V) (Glucantime) at a dose of 100 mg/kg bw, equivalent to an antimony dose of 27.2 mg/kg bw, by intravenous injection initially, by intramuscular injection after 30 days, and by subcutaneous injection

after a further 30 days. After intravenous injection, the plasma concentration of total antimony decreased rapidly: about 78% of the antimony administered was excreted in the urine in the first 3 hours. After intramuscular and subcutaneous injections, plasma concentrations were similar, showing a rapid absorption phase, with a half-life of 40 minutes and T_{max} of 80 minutes (Valladares et al., 1996).

4.1.2 Metabolism

(a) Humans

The data on the metabolism of trivalent or pentavalent antimony in humans were limited.

Conversion of the valence state of antimony has been observed in clinical studies. One study showed that both trivalent and pentavalent antimony were detected in the urine of patients with leishmaniasis who had been treated with meglumine antimoniate(V) (Glucantime) (Miekeley et al., 2002). [The Working Group noted that the effects of *Leishmania* infection on the interconversion/metabolism of trivalent and pentavalent antimony are unclear.] About 23.3% systemic conversion to trivalent antimony was observed after pentavalent antimony was administered at a dose of 5 mg/kg bw by single intramuscular injection in 5 healthy adult volunteers (Vásquez et al., 2006). However, Patterson et al. (2003) reported that in cultured human keratinocytes, conversion of antimony from the pentavalent oxidation state to the trivalent oxidation state was not detected.

Treatment of human blood (collected from healthy donors) with pentavalent antimony showed that in the presence of glutathione (GSH), pentavalent antimony was reduced to trivalent antimony in the plasma and in the cytoplasm of erythrocytes. Trivalent antimony was found to be unstable and could be re-oxidized to pentavalent antimony (López et al., 2015).

(b) Experimental systems

Conversion of pentavalent antimony to trivalent antimony was observed in one study in rhesus monkeys (see Section 4.1.1(iii)). After administration of meglumine antimoniate(V) by intramuscular injection at a dose of 5–20 mg/kg bw once per day for 21 days, both trivalent and pentavalent antimony were detected in the plasma. The proportion of pentavalent antimony remained at 11–20% on post-treatment days 1–9, but that of trivalent antimony increased from 5% on post-treatment day 1 to 50% on day 9 (Friedrich et al., 2012).

In one study, two in vitro experiments showed interconversion of the valence states of antimony. Pentavalent antimony from a pentavalent antimony-based drug (sodium stibogluconate, Pentostam) was reduced to trivalent antimony in the human macrophage cell line Mono Mac 6 (Hansen et al., 2011).

Other in vitro experiments showed that thiols such as GSH prompted the reduction of pentavalent antimony to trivalent antimony, and that the oxidation–reduction reaction is favoured by acidic pH and elevated temperature (Frézard et al., 2001; Ferreira et al., 2003; Quiroz et al., 2013; Barrera et al., 2016).

4.1.3 Excretion

(a) Humans

Trivalent and pentavalent antimony are eliminated in the urine, regardless of the route of exposure (inhalation, injection, or ingestion). Increases in urinary concentrations of antimony have been reported in workers occupationally exposed to trivalent antimony by inhalation (Lüdersdorf et al., 1987; Kentner et al., 1995; Kim et al., 1999; Iavicoli et al., 2002; Dartey et al., 2017; El Shanawany et al., 2017) and in workers exposed to pentavalent antimony, including antimony(V) oxide and sodium antimonate(V) (Bailly et al., 1991). In general, urinary excretion

in workers exposed to antimony was related to the level of exposure.

(i) Inhalation

Trivalent antimony

Kim et al. (1999) reported that concentrations of antimony in urine were higher in workers directly exposed to antimony(III) oxide. Urinary antimony concentrations of 411, 113, and 28 μg/g creatinine were reported in workers exposed to antimony (mean air level, 766 μg/m^3), employees who worked in the same factory but not near the source of antimony, and healthy volunteers not exposed to antimony, respectively.

Analysis of urine samples collected from workers after exposure to antimony(III) by inhalation (7 workers from the casting area exposed to antimony(III) oxide and 14 workers from the lead plates stibine-formation production area exposed to both stibine and antimony(III) oxide) indicated that both trivalent antimony compounds showed similar levels of pulmonary absorption and renal elimination (see also Section 1.4.2). The median concentrations of antimony in urine of workers from the two groups were 15.2 and 3.9 μg/g creatinine, respectively. The half-life of renal elimination was approximately 4 days (Kentner et al., 1995). Lüdersdorf et al. (1987) measured the concentrations of antimony in blood and urine samples from 109 workers employed in four different fields of a glass-producing industry using trivalent antimony. Median concentrations were 0.4–3.1 μg/L (blood) and 0.2–15.7 μg/L (urine), depending on the fields in which the individuals worked (see also Section 1.4.2(c)). Iavicoli et al. (2002) assessed the personal exposure values for airborne antimony(III) oxide and urinary concentrations of antimony of workers exposed to antimony(III) oxide (see also Section 1.4.2(d)). Mean urinary concentrations were 0.31–0.35 μg/L; however, the personal exposure values (antimony < 0.01–0.55 μg/m^3) were much lower than international occupational standards (see Section 1.5) (Iavicoli et al., 2002). In a group of 7 workers accidentally exposed to radioactive antimony (^{125}Sb) oxide aerosols, pulmonary biphasic clearance was observed. There was a first rapid clearance phase of 7 days followed by a slower second phase. Half-lives were 600–1100 days for non-smokers and 1700–3700 days for smokers (Garg et al., 2003).

Pentavalent antimony

Bailly et al. (1991) showed that urinary excretion of antimony was related to the intensity of exposure by the analysis of urine samples of 22 workers in a smelter producing antimony(V) oxide and sodium antimonate(V) (see also Section 1.4.2(a)). A significant correlation was observed between the airborne concentrations of antimony and the concentrations in urine samples collected from workers post-shift (r = 0.83, P < 0.0001). It was estimated that after 8 hours exposure at 500 μg/m^3 the increase in urinary antimony concentration at the end of the shift amounted on average to 35 μg/g creatinine (Bailly et al., 1991).

(ii) Other exposure routes

Trivalent antimony

The urinary excretion of antimony was investigated in four patients who had accidentally ingested antimony(III) potassium tartrate (850–2500 mg/patient). Urinary excretion occurred in 8 hours, and the total amount of antimony excreted by the four patients during the first 3 days was 2 mg (Lauwers et al., 1990).

Pentavalent antimony

In patients treated with meglumine antimoniate(V) at a dose of 5 mg/kg bw per day by intramuscular injection for 30 or 60 days, the urinary concentration of antimony reached 60 mg/g creatinine 24 hours after administration. Rapid blood clearing occurred during the first 3 days after administration, and more than 50% of antimony was excreted by urine. The half-life for this rapid excretion phase was 24–72 hours,

and the half-life was greater than 50 days for the slow phase that followed (Miekeley et al., 2002). After administration of pentavalent antimony at a dose of 5 mg/kg bw by single intramuscular injection to five adult volunteers, it was reported that antimony elimination was biphasic; the first rapid elimination phase was about 4 hours, and the second slower phase extended for more than 24 hours. About 60% of the drug remained to be eliminated 24 hours after administration (Vásquez et al., 2006).

(b) Experimental systems

In Sprague-Dawley rats treated with antimony(III) trichoride by single intravenous or intraperitoneal injection, about 45–55% of the administered antimony was excreted within 4 days, with most being eliminated within the first day via both faeces and urine. Depletion of GSH before antimony exposure decreased faecal excretion and increased urinary excretion (Bailly et al., 1991). In Wistar rats, 2 hours after being treated with antimony(III) potassium tartrate at a dose of 50 µmol/kg bw by single intravenous injection, 55% of the administered antimony was excreted into the bile, and GSH promoted the process (Gyurasics et al., 1992).

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether trivalent and pentavalent antimony are electrophilic or can be metabolically activated to an electrophile; are genotoxic; induce oxidative stress; induce chronic inflammation; and alter cell proliferation, cell death, or nutrient supply. Evidence is also reported as to whether trivalent and pentavalent antimony alter DNA repair or cause genomic instability; induce epigenetic alterations; are immunosuppressive; modulate receptor-mediated effects; or cause immortalization.

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

(a) Humans

(i) Exposed humans

No data were available to the Working Group.

(ii) Human cells in vitro

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

Trivalent or pentavalent antimony compounds

In studies of acute toxicity, Wistar rats were treated with antimony(III) potassium tartrate at a dose of 1.72 mg/kg bw by intravenous injection and killed 10 minutes or 1, 4, 24, or 48 hours after exposure. At 10 minutes after exposure, most of the antimony was distributed in erythrocytes, with antimony levels being much higher in erythrocytes than in plasma or Hb, indicating that the in vivo distribution of trivalent antimony was initially determined by the membrane proteins on erythrocytes or the free-state fraction in the cytoplasm of erythrocytes, but not by Hb and plasma proteins (Wu et al., 2018). However, the profile curves of antimony in erythrocytes and Hb virtually overlapped 4–48 hours after exposure and were significantly higher than that of antimony in plasma. At 48 hours after exposure, 99% of antimony in the blood was sequestered by erythrocytes and over 93% was integrated into Hb. The metabolized form of antimony, rather than the parental form, might be responsible for the increased levels of antimony in Hb (Wu et al., 2018).

In studies of subchronic toxicity, rats were given feed containing antimony(III) potassium tartrate, potassium pyroantimonate(V), or antimony(III) oxide at a dose of 500 mg/kg bw for

13 weeks, followed by 1–4 weeks of recovery. Both trivalent and pentavalent antimony were predominantly sequestered by erythrocytes and structurally integrated into Hb after biotransformation (Wu et al., 2018).

(ii) Non-human mammalian cells in vitro

Trivalent or pentavalent antimony compounds

Erythrocytes have been shown to sequester antimony. Concentrations of trivalent and pentavalent antimony significantly increased in erythrocytes after exposure to elevated levels of trivalent or pentavalent antimony in an erythrocyte-incubation system (Wu et al., 2018). Exposure of rat cardiac myocytes to antimony(III) potassium tartrate at a concentration of 50 or 100 μM for 4 hours induced alterations in thiol homeostasis (including decreased protein thiol levels) and adenine nucleotide status (Tirmenstein et al., 1997).

(iii) Acellular systems

Trivalent or pentavalent antimony compounds

The interaction of trivalent and pentavalent antimony with herring fish DNA was measured by Li et al. (2011). The findings showed that trivalent antimony had a strong binding affinity to DNA, but no interaction of pentavalent antimony with DNA was observed. Wu et al. (2018) showed that binding of the parent forms of trivalent and pentavalent antimony, at a concentration of 100, 200, 300, or 400 μM, to Hb was negligible in a pure-Hb (acellular) system. This indicated that Hb, the most abundant protein in erythrocytes, did not contribute to the sequestration of the parent forms of antimony compounds by erythrocytes. The interaction (binding) of trivalent and pentavalent antimony with bovine serum albumin (BSA) was reported by Verdugo et al. (2017) and Gu et al. (2021). Verdugo et al. (2017) showed that BSA protein aggregates and conformational changes were increased in the presence of trivalent antimony, when compared with pentavalent antimony, and that GSH was protective against the effects of trivalent antimony on BSA protein conformational changes by modifying the interaction. However, Gu et al. (2021) showed that both trivalent and pentavalent antimony forms were able to competitively bind to BSA, and that the binding of either to BSA caused changes in the secondary structure of BSA.

4.2.2 Is genotoxic

(a) Humans

(i) Exposed humans

See Table 4.1.

The association between urinary antimony metal concentrations and sperm DNA damage, as measured by comet assay, of partners of patients at a fertility clinic in China was assessed in a cross-sectional study by Wang et al. (2016). No significant (or suggestive) associations were found between urinary antimony concentrations and sperm DNA integrity parameters after adjustment for age, BMI, abstinence time, smoking status, daily cigarette consumption, urinary creatinine, and other metals, nor for multiple testing. [The Working Group noted that although the sample size in this study was large (n = 1052), the range of antimony exposure levels in urine was small (first urine sample: median, 0.17 μg/L; interquartile range, 0.12–0.23; and second urine sample: median, 0.17 μg/L; interquartile range, 0.11–0.23), reducing the ability of the study to detect an exposure–response effect.]

In a study of 25 antimony-exposed rayon workers involved in polyester polymerization in Egypt, DNA damage in whole blood, expressed as an increase in apurinic/apyrimidinic sites, was compared with controls after adjusting for age and smoking status. Antimony exposure was found to significantly predict apurinic/apyrimidinic sites of DNA damage ($P < 0.001$) (El Shanawany et al., 2017).

Table 4.1 Genetic and related effects of trivalent or pentavalent antimony in exposed humans

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
DNA damage (comet assay)	Sperm DNA	China, partners of patients at fertility clinic, cross-sectional		No associations between urinary Sb levels and sperm DNA integrity parameters after adjustment for multiple testing (FDR-adjusted P for trend > 0.10)	Age, BMI, abstinence time, smoking status, daily cigarette consumption, and urinary creatinine	Exposure assessment critique: Urine samples collected at two close points in time on the same day as semen sample limits the findings.	Wang et al. (2016)
DNA damage (increased apurinic/ apyrimidinic sites)	Whole blood	Egypt, rayon workers, cross-sectional	25 rayon workers; 25 non-exposed controls	Significant positive correlation between urinary Sb levels and the quantity of DNA damage (in the form of increased apurinic/ apyrimidinic sites) among workers ($r = 0.873$, $P < 0.001$)	Age, smoking	Exposure assessment critique: The evidence of Sb exposure contrast presented in this study is compelling and supported by occupational information and urinary biomonitoring. However, the lack of dilution correction of urinary Sb measurements and little information on co-exposures in the occupation under investigation does slightly weaken the informativeness of the findings. Those with a history of use of medicinal products containing Sb and exposure to other known genotoxic agents were excluded and smoking was quantified. However, information on other co-exposures in this occupation was lacking. Misclassification not suspected.	El Shanawany et al. (2017)

Table 4.1 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
DNA damage (comet assay, TM measured) Oxidative DNA damage, Fpg enzyme-modified comet assay, TM measured) Micronucleus formation Sister-chromatid exchange	PBLs	Rome, Italy, workers producing fire-retardant textiles, cross-sectional	23 antimony(III) oxide-exposed workers; Group A (high), $n = 17$; Group B (low), $n = 6$; 23 non-exposed controls	NS between exposed and controls Fpg enzyme-modified TM compared with non-enzyme-modified TM; increased in Group A ($P = 0.002$) NS between exposed and controls NS between exposed and controls	Age, smoking	Exposure assessment critique: A key strength was the collection of multiple personal exposure measurements in the breathing zones of textile workers over the work week. However, unclear if the differences in the number of repeated measurements between the two exposure groups may have influenced the results. Exposures were assessed at the same time as the end-points of interest. There is potential for co-exposures to other metals or carcinogens, although none were mentioned or evaluated. Misclassification not suspected. [The Working Group noted very low exposure; 0.12 μg/m^3 in "high" exposure group.] PEL, 500 μg/m^3.	Cavallo et al. (2002)
Micronucleus formation Chromosomal aberration, sister-chromatid exchange	PBLs	Belgium, patient with leishmaniasis, case report	Treatment with meglumine antimoniate(V)	8- to 9-fold increase post- vs pre-treatment for binucleated cells No change pre- vs post-treatment		Exposure assessment critique: Few/no limitations noted as an exact, consistent, and known dose of the agent was administered to the patient. However, information on potential impurities in the treatment was not reported. The addition of Sb biomonitoring would provide information on internal dose of the agent at the various study time points. No statistics shown.	Hantson et al. (1996)

Table 4.1 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Micronucleus formation	Peripheral blood	China, coke-oven workers, cross-sectional	$n = 888$	No effect of Sb on frequency of micronucleus formation	Age, alcohol drinking status (ever vs never), and smoking pack-years	Exposure assessment critique: Single spot urine samples were used to assess exposures to Sb and other metals, which likely introduced non-differential exposure misclassification. Mixture effects of metals and urinary PAH metabolites and PAH adducts were assessed using LASSO regression and BKMR analyses.	Bai et al. (2021)
mLOY (genomic instability)				Significant associations of increasing urinary levels of Sb with elevated mLOY (marked by decreased mLRR). Remained significant in the multiple-exposure model [β (95% CI) = −0.0058 (−0.0096 to 0.0019)], $P = 0.004$			

BKMR, Bayesian kernel machine regression; BMI, body mass index; CI, confidence interval; FDR, false discovery rate; Fpg, formamidopyrimidine DNA glycosylase; LASSO, least absolute shrinkage and selection operator; mLOY, mosaic loss of chromosome Y; mLRR, median log R ratio; NS, not significant; PAH, polycyclic aromatic hydrocarbon; PBL, peripheral blood lymphocyte; PEL, permissible exposure level; Sb, antimony; TM, tail moment; vs, versus.

In a cross-sectional study of Italian workers producing fireproof textiles who were exposed to antimony(III) oxide at two exposure levels (high, Group A; low, Group B) and compared with non-exposed controls, no differences were found in the frequency of sister-chromatid exchange and micronucleus formation between exposed workers and controls in peripheral blood lymphocytes (PBLs) after controlling for age and smoking. There was no difference in tail moment, as measured by comet assay, between antimony-exposed and non-exposed control groups (Cavallo et al., 2002). [The Working Group noted the low antimony exposure concentration, relatively small sample size (exposed and controls, n = 23), and lack of information provided about occupational co-exposures, which reduced the informativeness of this study.]

In a case report from Belgium of a patient with leishmaniasis undergoing antimony therapy (pentavalent antimony), Hantson et al. (1996) noted a post-treatment increase of 9-fold in the frequency of micronucleus formation in PBLs (upon bone marrow biopsy) but no change in either the induction of chromosomal aberration or the frequency of sister-chromatid exchange. [The Working Group noted that this provocative antimony finding may have been confounded by potential immunosuppression caused by visceral *Leishmania* infection. Thus, the genotoxicity could have been caused by the lack of immune surveillance or impaired repair capacity.]

In a study of coke-oven workers with mixed exposure to PAHs and multiple metals, including antimony, conducted in China, Bai et al. (2021) assessed associations between antimony exposure and micronucleus formation in PBLs and found no antimony-associated effects. [The Working Group noted that a strength of the study was in the use of LASSO regression and BKMR analyses to assess mixture effects, and the large sample size (n = 888).]

A study by Alrashed et al. (2021) examined heavy metal-induced genotoxicity and oxidative stress in women with recurrent pregnancy loss. [The Working Group deemed the study to be uninformative because the authors failed to control for confounding by abnormally high levels of gonadotropins and other hormones in the pregnancy-loss group.] [The Working Group noted that two of five studies in exposed humans showed some evidence of antimony-induced genotoxicity.]

(ii) Human cells in vitro

See Table 4.2.

Trivalent antimony compounds

In studies using primary cells, exposure of human PBLs to non-cytotoxic concentrations of antimony(III) oxide (0.5 μM) or antimony(III) chloride (1 μM) for 24 hours caused a significant increase in the frequency of sister-chromatid exchange (Gebel et al., 1997). Exposure of human PBLs to antimony(III) chloride (5 μM) caused a significant increase in DNA damage, as measured by comet assay, and in the frequency of micronucleus formation, but was negative for oxidative DNA damage (see Section 4.2.5), and no cytotoxicity was observed at concentrations of ≤ 50 μM (Schaumlöffel & Gebel, 1998). Treatment of human PBLs with antimony(III) oxide at a concentration of 100 μg/mL for 68 hours induced a significant increase in chromosomal damage (as measured by cytogenetic assay) with metabolic activation in cells from two donors, and without metabolic activation in cells from one donor (Elliott et al., 1998). Treatment of human leukocytes with a non-cytotoxic concentration of antimony(III) sodium tartrate (2.3×10^{-9} M) for 48 hours caused a significant increase in the incidence of chromosome breakage (Paton & Allison, 1972). In addition, 4-hour treatment with antimony(III) chloride at concentrations of > 50 μM caused a significant increase in the frequency of micronucleus

Table 4.2 Genetic and related effects of trivalent or pentavalent antimony in human cells in vitro

End-point	Cell type or line	Results[a]	Concentration (LEC or HIC), exposure duration	Comments	Reference
Trivalent antimony compounds					
Antimony(III) oxide (Sb_2O_3)					
Sister-chromatid exchange	Human PBLs	+	0.5 µM, 24 h	No positive control. 5 µM is cytotoxic.	Gebel et al. (1997)
Chromosomal aberration	Human PBLs	+	100 µg/mL, 68 h	Positive control. Tested cells from two donors. Positive with metabolic activation (+liver S9) in cells from both donors and without metabolic activation (–liver S9) in cells from one donor. Reported no decrease in mitotic activity.	Elliott et al. (1998)
Antimony(III) chloride ($SbCl_3$)					
Sister-chromatid exchange	Human PBLs	+	1 µM, 24 h	No positive control. 10 µM is cytotoxic.	Gebel et al. (1997)
Micronucleus formation	Human bronchial epithelial (BES-6) cells	+	> 50 µM, 4 h	LC_{50} of 80 µM (BES-6) and 40 µM (fibroblasts).	Huang et al. (1998)
	Human fibroblasts	+		Apoptosis and DNA fragmentation not detected.	
Micronucleus formation	Human PBLs	+	5 µM, 24 h	No positive control. No cytotoxicity (≤ 50 µM).	Schaumlöffel & Gebel (1998)
DNA damage (comet assay)		+		Co-exposure with antioxidants (SOD and CAT) with no effect on micronucleus formation [no role of oxidative stress in DNA-damage induction or chromosomal aberration].	
Induction of γH2AX	Human hepatoblastoma (HepG2) cells	+	100 µM, 24 h	97% cell viability (HepG2).	Kopp et al. (2018)
	Human colorectal epithelial adenocarcinoma (LS-174T) cells	+	250 µM, 24 h	72% cell viability (LS-174T).	
Decreased repair of irradiation-induced DNA double-strand breaks	Human cervical cancer (HeLa S3) cells	+	50 µM, 8 h		Koch et al. (2017)
Antimony(III) sodium tartrate ($C_8H_4Na_2O_{12}Sb_2$)					
Chromosomal aberration	Human leukocytes	+	2.3 nM, 48 h	Single dose tested. No positive control. 1×10^8 M is cytotoxic.	Paton & Allison (1972)

Table 4.2 (continued)

End-point	Cell type or line	Results[a]	Concentration (LEC or HIC), exposure duration	Comments	Reference
Pentavalent antimony compounds					
Potassium antimonate(V) ($KSbO_3$)					
Micronucleus formation	Human PBLs	+	360 µM, 24 h	PHA-stimulated. Tested cells from two donors.	Migliore et al. (1999)
Meglumine antimoniate(V) ($C_7H_{17}NO_5 \cdot H \cdot O_3Sb$)					
DNA damage (comet assay)	Human PBLs	–	15 mg/mL, 3 and 24 h		Lima et al. (2010)

CAT, catalase; γH2AX, phosphorylation of histone H2AX; HIC, highest ineffective concentration; LC_{50}, median lethal concentration; LEC, lowest effective concentration (units as reported); PBL, peripheral blood lymphocyte; PHA, phytohaemagglutinin; SOD, superoxide dismutase.

[a] +, positive; –, negative.

formation in primary human fibroblasts. The LC_{50} (median lethal concentration) was 40 μM for human fibroblasts, but no apoptosis or DNA fragmentation was detected (Huang et al., 1998).

In studies using cell lines, 4-hour treatment with antimony(III) chloride at concentrations of > 50 μM caused a significant increase in the frequency of micronucleus formation in the human bronchial epithelial cell line BES-6. The LC_{50} was 80 μM, and no apoptosis was observed after the 4-hour exposure period (Huang et al., 1998). In a high-throughput screening assay, exposure of the HepG2 cell line to antimony(III) chloride at a concentration of 100 μM (which resulted in 97% cell viability) or of the LS 174T cell line at a concentration of 250 μM (72% cell viability) for 24 hours significantly increased γH2AX induction, indicating that antimony(III) chloride caused DNA damage in the cells (Kopp et al., 2018).

Pentavalent antimony compounds

Exposure of phytohaemagglutinin-stimulated human PBLs from two donors to potassium antimonate ($KSbO_3$) at a concentration of 360 μM for 24 hours caused a significant increase in the induction of micronucleus formation, which was greater by 7- to 10-fold than in the control cells (Migliore et al., 1999).

Exposure of human PBLs to meglumine antimoniate(V) (Glucantime) at a concentration of 3.25, 7.5, or 15 mg/mL (corresponding to a pentavalent antimony concentration of 1.06, 2.12, or 4.25 mg/mL, respectively) for 3 or 24 hours did not cause DNA damage, as measured by comet assay (Lima et al., 2010).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3.

Trivalent antimony compounds

In an assay for unscheduled DNA synthesis using hepatocytes from male rats exposed by gavage to a single dose of antimony(III) oxide (at 3200 or 5000 mg/kg bw), sampled either 2 or 16 hours after treatment, no increase in net nuclear grains or the percentage of cells exhibiting evidence of DNA repair was observed (Elliott et al., 1998).

Elliott et al. (1998) reported that no statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes (PCEs) were observed in the bone marrow of CD-1 mice 24 or 48 hours after a single exposure to antimony(III) oxide at a dose of 5000 mg/kg bw by gavage or after repeated exposure to doses of 400, 667, or 1000 mg/kg bw by gavage once per day for 7, 14, or 21 days (Elliott et al., 1998). In a series of experiments performed in male and female Swiss Albino mice, Gurnani et al. (1992a, b, 1993) assessed the clastogenic effects of antimony(III) oxide and antimony(III) chloride. No clastogenic effects (i.e. chromosomal aberration) were observed in the bone marrow of male and female mice at 6, 12, 18, or 24 hours after a single exposure by gavage to antimony(III) oxide at doses of 400, 667.7, or 1000 mg/kg bw (Gurnani et al., 1992a). However, repeated exposures of male mice to the same doses of antimony(III) oxide for 7, 14, or 21 days significantly increased the frequency of chromosomal aberration in the bone marrow (except for the 21-day exposure to 1000 mg/kg bw, which was lethal) (Gurnani et al., 1992a, 1993), but did not cause sperm-head abnormalities in germ cells (Gurnani et al., 1993). Instead, acute exposure to a single dose of antimony(III) chloride at 70, 140, or 233.33 mg/kg bw caused a significant increase in the frequency of chromosomal aberration in the bone marrow of female mice at 6, 12, 18, and 24 hours after gavage (Gurnani et al., 1992b).

Table 4.3 Genetic and related effects of trivalent or pentavalent antimony in non-human mammals in vivo

End-point	Tissue, cell type	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Trivalent antimony compounds					
Antimony(III) oxide (Sb_2O_3)					
Chromosomal aberration	Bone marrow of Swiss albino mice	–	1000 mg/kg bw	Gavage, 6, 12, 18, or 24 h, single dose	Gurnani et al. (1992a, 1993)
	Bone marrow of Swiss albino male mice	+	400 mg/kg bw per day	Gavage, 7, 14, or 21 days, repeated doses	
Sperm head abnormalities	Germ cells of Swiss albino male mice	–	1000 mg/kg bw per day		
Micronucleus formation in PCEs	Bone marrow of CD-1 mice	–	5000 mg/kg bw	Gavage, 24 or 48 h, single dose	Elliott et al. (1998)
		–	1000 mg/kg bw per day	Gavage, 7, 14, or 21 days, repeated doses	
DNA repair (unscheduled DNA synthesis assay)	DNA from hepatocytes of male APfSD rats	–	5000 mg/kg bw	Gavage, 2 or 16 h, single dose	
Chromosomal aberration or micronucleus formation	Bone marrow of SD rats	–	1000 mg/kg bw per day	Gavage, 21 days, repeated doses	Kirkland et al. (2007)
Micronucleus formation in normochromatic erythrocytes	Mature erythrocytes from peripheral blood of $B6C3F_1$/N mice	+	30 mg/m^3	Inhalation, 6 h/day, 5 days/wk for 12 mo	NTP (2017)
DNA damage (comet assay)	Lung tissue of $B6C3F_1$/N mice	+			
	PBLs of $B6C3F_1$/N mice	–			
Micronucleus formation in PCEs	Reticulocytes from peripheral blood of Wistar Han rats	–	30 mg/m^3		
DNA damage (comet assay)	Lung tissue of Wistar Han rats	–			
	PBLs of Wistar Han rats	–			
Antimony(III) chloride ($SbCl_3$)					
Chromosomal aberration	Bone marrow of Swiss female albino mice	+	70 mg/kg bw	Gavage, 6, 12, 18, or 24 h, single dose	Gurnani et al. (1992b)
Antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$ or $K_2Sb_2(C_4H_2O_6)_2$)					
Chromosomal aberration (chromatid gaps, chromatid breaks, and centric fusions)	Bone marrow of male rats	+	2 mg/kg bw	Intraperitoneal injection, 6, 24, or 48 h (single dose) or for 5 consecutive days (repeated doses), 20 days	El Nahas et al. (1982)

Table 4.3 (continued)

End-point	Tissue, cell type	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Pentavalent antimony compounds					
Meglumine antimoniate(V) ($C_7H_{17}NO_5 \cdot H \cdot O_3Sb$)					
DNA-damage scores and frequency of nucleoids (comet assay)	PBLs and peritoneal macrophages of Swiss mice	+	212.5 mg/kg bw	Intraperitoneal injection, 3 h (macrophages) or 24 h (PBLs and bone marrow), 20 days	Lima et al. (2010)
Micronucleus formation in PCEs	Bone marrow of Swiss mice	+			
DNA-damage scores and frequency of nucleoids (comet assay)	PBLs of Swiss mice	+	425 mg/kg bw	Intraperitoneal injection, 24 h, 20 days	Cantanhêde et al. (2015)
Micronucleus formation in PCEs	Bone marrow of Swiss mice	+			
DNA-damage scores and frequency of nucleoids (comet assay with Fpg enzyme; oxidative DNA damage)	PBLs of BALB/c mice	+	20 mg/kg bw per day	Intraperitoneal injection, 20 days	Moreira et al. (2017)
Micronucleated PCEs	Bone marrow of BALB/c mice	+			
DNA-damage scores and frequency of the highest nucleoid classes (3 and 4) (comet assay with Fpg enzyme; oxidative DNA-damage)	PBLs of Swiss mice	+	810 mg/kg bw	Single intraperitoneal injection, 24 h	de Jesus et al. (2018)
Micronucleated PCEs	Bone marrow of Swiss mice	+			

bw, body weight; Fpg, formamidopyrimidine DNA glycosylase; HID, highest ineffective dose; LED, lowest effective dose; mo, month; PBL, peripheral blood leukocyte; PCE, polychromatic erythrocyte; SD, Sprague-Dawley; wk, week.

[a] +, positive; –, negative.

Kirkland et al. (2007) also did not find any chromosomal aberration or an increased frequency of micronucleus formation in the bone marrow of Sprague-Dawley rats after repeated exposure to antimony(III) oxide at doses of 250, 500, or 1000 mg/kg bw per day by gavage for 21 days. [The Working Group noted that exposure of the bone marrow was demonstrated by toxicokinetic data.]

Inhalation exposure of male and female B6C3F$_1$/N mice to antimony(III) oxide at a concentration of 3, 10, or 30 mg/m^3 for 12 months caused a significant increase in the frequency of micronucleus formation in mature erythrocytes (normochromatic erythrocytes), on the basis of significant statistical trend tests and significantly elevated frequencies of micronucleated normochromatic erythrocytes at the highest exposure concentration (NTP, 2017). There was also a significant increase in the percentage of reticulocytes (polychromatic erythrocytes, PCEs). In addition, significantly increased DNA damage (as measured by comet assay) was observed in the lung tissue of male and female mice, but not in PBLs (NTP, 2017). No genotoxic effects were observed in reticulocytes of Wistar Han rats (both sexes) after exposure to antimony(III) oxide at a concentration of 3, 10, or 30 mg/m^3 for 12 months (NTP, 2017). [The Working Group noted that concentrations of antimony in the blood of rats were much higher than those in mice; however, exposure to antimony(III) oxide did not increase the frequency of micronucleus formation in reticulocytes of rats.]

Exposure of male rats to tartar emetic (antimony(III) potassium tartrate; 36.5% trivalent antimony) at a dose of 2, 8.4, or 14.8 mg/kg bw by single intraperitoneal injection caused significant increases in the frequency of chromosomal aberrations such as chromatid gaps, chromatid breaks, and centric fusions in bone marrow at 6, 24, or 48 hours after treatment (except for the 48-hour exposure to 14.8 mg/kg bw), as did repeated intraperitoneal injections for 5 consecutive days (El Nahas et al., 1982).

Pentavalent antimony compounds

In Swiss mice exposed to meglumine antimoniate(V) (Glucantime) at a concentration of 425 or 810 mg/kg bw by single intraperitoneal injection, significant increases in DNA damage scores and the frequency of nucleoids, as measured by comet assay, were observed (including oxidative DNA damage measured by formamidopyrimidine DNA glycosylate, Fpg, enzymatic digestion) in PBLs (de Jesus et al., 2018), and significantly increased frequency of micronucleated PCEs, as assessed by micronucleus assay, in bone marrow after 24-hour exposure (Cantanhêde et al., 2015; de Jesus et al., 2018). Acute intraperitoneal injection of Swiss mice with Glucantime at a dose of 212.5, 425, or 850 mg/kg bw caused significantly increased DNA damage scores and frequencies of nucleoids in PBLs (at 24 hours) and resident peritoneal exudate macrophages (at 3 hours), as measured by comet assay, and significantly increased frequencies of micronucleated PCEs in bone marrow (at 24 hours) (Lima et al., 2010). In addition, exposure of BALB/c mice to Glucantime by intraperitoneal injection at a dose of 20 mg/kg bw per day for 20 days caused a significant increase in DNA damage scores and frequencies of nucleoids in PBLs, as measured by comet assay (with Fpg enzymatic digestion indicative of oxidative DNA damage), and of micronucleated PCEs in bone marrow (Moreira et al., 2017). [The Working Group noted that pentavalent antimony can be metabolized or converted to its more toxic trivalent form.]

(ii) Non-human mammalian cells in vitro

See Table 4.4.

Trivalent antimony compounds

Exposure of mouse embryonic stem cell lines, transfected with a series of green fluorescent protein reporters (ToxTracker assay), to six trivalent antimony compounds – antimony(III)

Table 4.4 Genetic and related effects of trivalent or pentavalent antimony in non-human mammalian cells in vitro

End-point	Species, tissue, cell line	Results[a]	Concentration (LEC or HIC), exposure duration	Comments	Reference
Trivalent antimony compounds					
Antimony(III) chloride ($SbCl_3$)					
DNA damage (comet assay)	Chinese hamster, lung, V79	+	1 µM, 24 h	Cell viability > 90% at 20 µM.	Gebel et al. (1998)
Micronucleus formation	Chinese hamster, lung, V79	+	25 µM, 24 h		
DNA damage (alkaline elution)	Chinese hamster, lung, V79	+	10 µM, 24 h	No results for 20 µM exposure.	
Micronucleus formation	Chinese hamster, ovary, CHO-K1	+	> 50 µM, 4 h	LC_{50} of 180 µM (DNA fragmentation and apoptosis observed after 4 h exposure).	Huang et al. (1998)
Decreased repair of irradiation-induced DNA double-strand breaks	Chinese hamster, ovary, CHO-K1	+	0.2 mM, 2 h	Mean cytotoxic concentration, 0.21 mM.	Takahashi et al. (2002)
Sister-chromatid exchange	Chinese hamster, lung, V79	+	5 µg/mL, 28 h	Cytotoxic concentration, 20 µg/mL.	Kuroda et al. (1991)
Antimony(III) oxide (Sb_2O_3)					
Sister-chromatid exchange	Chinese hamster, lung, V79	+	0.17 µg/mL, 28 h		Kuroda et al. (1991)
Antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$ or $K_2Sb_2(C_4H_2O_6)_2$)					
Decreased repair of irradiation-induced DNA double-strand breaks	Chinese hamster, ovary, CHO-K1	+	0.4 mM, 2 h	Mean cytotoxic concentration, 0.12 mM. Most of the cells treated with 0.4 mM antimony(III) potassium tartrate lost proliferative capacity.	Takahashi et al. (2002)
Pentavalent antimony compounds					
Antimony(V) chloride ($SbCl_5$)					
Sister-chromatid exchange	Chinese hamster, lung, V79	–	35 µg/mL, 28 h		Kuroda et al. (1991)
Antimony(V) oxide (Sb_2O_5)					
Sister-chromatid exchange	Chinese hamster, lung, V79	–	40 µg/mL, 28 h		Kuroda et al. (1991)
Trivalent or pentavalent antimony compounds					
Sb_2O_3, Sb_2S_3, $SbCl_3$, $Sb_2(C_2H_4O_2)_3$,$SbC_6H_9O_6$, and $Sb_2K_2C_8H_4O_{12}$ (trivalent), and $SbCl_5$, $KSb(OH)_6$, $NaSbO_3$, $NaSb(OH)_6$, and Sb_2O_5 (pentavalent)					
DNA damage (Bscl2 and Rtkn genes in ToxTracker assay)	Mouse embryonic stem cells	–	1–4.24 µg/mL (trivalent) and 3 to ~45 µg/mL (pentavalent), 24 h	Wild-type cells from C57/BL6 B4418 mice.	Boreiko et al. (2021)

Bscl2, BSCL2 lipid droplet biogenesis associated, serpin; HIC, highest ineffective concentration; LC_{50}, median lethal concentration; LEC, lowest effective concentration; Rtkn, rhotekin.

[a] +, positive; –, negative.

oxide, antimony(III) sulfide, antimony(III) chloride, antimony tris (ethylene) glycolate ($Sb_2(C_2H_4O_2)_3$), antimony triacetate ($SbC_6H_9O_6$), and antimony potassium tartrate ($Sb_2K_2C_8H_4O_{12}$) – did not induce activation of the Bscl2 and Rtkn reporter genes, which would have been indicative of DNA damage (genotoxicity) or impaired DNA replication (Boreiko et al., 2021).

Treatment of the Chinese hamster lung cell line V79 with antimony(III) chloride at a concentration of 1 or 10 µM for 24 hours resulted in significantly increased DNA damage, as measured by comet assay and alkaline elution, respectively, and treatment with antimony(III) chloride at 25 µM significantly increased the frequency of micronucleus formation (Gebel et al., 1998). Treatment of V79 cells with antimony(III) chloride or antimony(III) oxide at concentrations up to 20 or 0.34 µg/mL, respectively, induced a significant increase in the frequency of sister-chromatid exchange after exposure for 28 hours (Kuroda et al., 1991). Moreover, 4-hour treatment of the Chinese hamster ovary cell line CHO-K1 with antimony(III) chloride at concentrations of > 50 µM significantly increased the frequency of micronucleus formation. The LC_{50} was 180 µM, but DNA fragmentation and apoptosis were detected after the 4-hour exposure (Huang et al., 1998).

Pentavalent antimony compounds

Similarly to trivalent antimony compounds, in the study by Boreiko et al. (2021), five pentavalent antimony compounds – antimony(V) chloride ($SbCl_5$), potassium hexahydroxoantimonate ($KSb(OH)_6$), sodium antimonate, sodium hexahydroxoantimonate, and antimony(V) oxide – did not induce a DNA damage response, as assessed by ToxTracker assay, in mouse embryonic stem cells exposed for 24 hours.

Treatment of the V79 cell line with antimony(V) chloride or antimony(V) oxide at concentrations up to 35 or 40 µg/mL, respectively, did not increase the frequency of sister-chromatid exchange after a 28-hour exposure (Kuroda et al., 1991).

(iii) Non-mammalian experimental systems

See Table 4.5.

Trivalent antimony compounds

Acute exposure of *Chironomus sancticaroli* to antimony(III) oxide at 50 or 800 µg/L for 48 hours, or subchronic exposure at 50 µg/L for 8 days, caused significantly increased DNA damage scores, as measured by comet assay (Morais et al., 2019).

Exposure of budding yeast (*Saccharomyces cerevisiae*) to trivalent antimony at 0.08–1 mM caused various forms of DNA damage including chemical modification of DNA bases, replication-associated DNA lesions, DNA double-strand breaks, and telomere damage (Litwin et al., 2021). Trivalent antimony also induced both replication-dependent and -independent DNA lesions in yeast, and trivalent antimony-induced DNA damage triggered the formation of RAD52 foci (Litwin et al., 2021).

Exposure to antimony(III) chloride or antimony(III) oxide caused DNA damage, as assessed by rec assay in *Bacillus subtilis*, which was reflected by the greater inhibition zone length of the Rec^- strain of *B. subtilis* than that of the wildtype (Rec^+) strain (Kanematsu et al., 1980; Kuroda et al., 1991). However, these trivalent antimony compounds did not exhibit mutagenicity, as assessed by spot tests, in *Escherichia coli* and *Salmonella typhimurium* strains with or without metabolic activation (liver S9) (Kanematsu et al., 1980; Kuroda et al., 1991; Elliott et al., 1998). In contrast, Nishioka (1975) reported that exposure to antimony(III) chloride did not cause DNA damage, as assessed by rec assay in *B. subtilis*. Antimony(III) chloride was not genotoxic, as assessed by SOS chromotest with *E. coli* strain PQ37 (Lantzsch & Gebel, 1997). Exposure to antimony(III) chloride did not cause mutagenicity, as assessed by *umu* genotoxicity assay

Table 4.5 Genetic and related effects of trivalent or pentavalent antimony in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]	Concentration (LEC, HIC, or range)	Comments	Reference
Trivalent antimony compounds					
Antimony(III) oxide (Sb_2O_3)					
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	0.05 M		Kanematsu et al. (1980)
Escherichia coli B/r WP2 *try*$^-$ and WP2 *hcr*$^-$ *try*	DNA reverse mutation	–	0.05 M		
Salmonella typhimurium his$^-$ strains TA98, TA100, TA1535, TA1537, and TA1538	DNA reverse mutation	–	0.05 M		
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	0.3–1.1 µg/disc		Kuroda et al. (1991)
Salmonella typhimurium TA98 and TA100	DNA reverse mutation	–	0.43–1.71 µg/plate	With and without metabolic activation (liver S9).	
Escherichia coli WP2P and WP2P*uvrA*		–	10 000 µg/plate	With and without metabolic activation (liver S9).	Elliott et al. (1998)
Salmonella typhimurium TA98, TA100, TA1535, and TA1537	DNA reverse mutation	–	10 000 µg/plate	With and without metabolic activation (liver S9).	
Antimony(III) chloride ($SbCl_3$)					
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	–	0.05 M		Nishioka (1975)
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	0.01 M		Kanematsu et al. (1980)
Escherichia coli B/r WP2 *try*$^-$ and WP2 *hcr*$^-$ *try*	DNA reverse mutation	–	0.01 M		
Salmonella typhimurium his strains TA98, TA100, TA1535, TA1537, and TA1538	DNA reverse mutation	–	0.01 M		
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	6.3–23 µg/disc		Kuroda et al. (1991)
Salmonella typhimurium TA98 and TA100	DNA reverse mutation	–	625–5000 µg/plate	With and without metabolic activation (liver S9).	
Escherichia coli PQ37	SOS chromotest	–	11–707 µM		Lantzsch & Gebel (1997)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]	Concentration (LEC, HIC, or range)	Comments	Reference
Salmonella typhimurium TA1535/pSK1002 (*umu* test)	DNA mutation	–	1.6×10^6 to 8.2×10^4 M	With and without metabolic activation (liver S9).	Yamamoto et al. (2002)
Salmonella typhimurium TA98 and TA100	DNA reverse mutation	–	1 mM	With and without metabolic activation (liver S9).	Kubo et al. (2002)
Antimony(III) potassium tartrate ($C_8H_{10}K_2O_{15}Sb_2$ or $K_2Sb_2(C_4H_2O_6)_2$)					
Salmonella typhimurium TA97, TA98, TA100, and TA1535	DNA reverse mutation	–	10–10 000 mg/plate	With and without metabolic activation (liver S9).	NTP (1992)
Pentavalent antimony compounds					
Antimony(V) chloride ($SbCl_5$)					
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	–	0.05 M		Nishioka (1975)
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	NR (0.03 mL)		Kanematsu et al. (1980)
Escherichia coli B/r WP2 *try*$^-$ and WP2 *hcr*$^-$ *try*	DNA reverse mutation	–	NR (0.03 mL)		
Salmonella typhimurium his strains TA98, TA100, TA1535, TA1537, and TA1538	DNA reverse mutation	–	NR (0.03 mL)		
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	+	65–260 µg/disc	Killing zone was not observed with negative results. With and without metabolic activation (liver S9).	Kuroda et al. (1991)
Salmonella typhimurium TA98 and TA100	DNA reverse mutation	–	54–864 µg/plate		
Antimony(V) oxide (SbO_5)					
Bacillus subtilis H17 (Rec$^+$, *arg*$^-$ *try*$^-$); M45 (Rec$^-$, *arg*$^-$ *try*$^-$)	DNA damage, rec assay	–	60 µg/disc	Killing zone was not observed with negative results. With and without metabolic activation (liver S9).	Kuroda et al. (1991)
Salmonella typhimurium TA98 and TA100	DNA reverse mutation	–	50–200 µg/plate		

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported.

[a] +, positive; –, negative.

with or without metabolic activation (liver S9) (Yamamoto et al., 2002). Kubo et al. (2002) also reported that exposure to antimony(III) chloride did not cause mutagenicity, as assessed by Ames test with *S. typhimurium* strains TA98 and TA100 with or without metabolic activation (liver S9). Antimony(III) potassium tartrate was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, and TA1535 with or without metabolic activation (liver S9) (NTP, 1992).

Pentavalent antimony compounds

Exposure of invertebrates (*Chironomus tentans* larvae) to sediment spiked with antimony(V) oxide nanoparticles (NPs) at a concentration of 5000 µg/kg for 10 days caused DNA strand breakage (Oberholster et al., 2011).

Exposure to antimony(V) chloride caused DNA damage, as assessed by rec assay in *B. subtilis* (Kanematsu et al., 1980; Kuroda et al., 1991). However, antimony(V) chloride and antimony(V) oxide compounds were not observed to be mutagenic, as assessed by spot tests in *E. coli* and *S. typhimurium* strains with or without metabolic activation (liver S9) (Kanematsu et al., 1980; Kuroda et al., 1991). In contrast, Nishioka (1975) reported that exposure to antimony(V) chloride did not cause DNA damage, as assessed by rec assay in *B. subtilis*.

4.2.3 Alters DNA repair or causes genomic instability

(a) Humans

(i) Exposed humans

See Table 4.1.

In a study of coke-oven workers with mixed exposure to PAHs and multiple metals including antimony in China, Bai et al. (2021) measured mLOY in blood as an indicator of genomic instability. The calculation of mLOY was based on genome-wide single-nucleotide polymorphism genotyping and expressed as median log R ratio-Y. The results of this study consistently suggested significant positive dose–response relationships between urinary antimony levels and mLOY. [The Working Group noted that single spot urine samples were used to assess exposures to antimony, tungsten, and cobalt. Exposure and outcomes were assessed at the same time. A strength of the study was that mixture effects of metals and urinary PAH metabolites and adducts were assessed using LASSO regression and BKMR analyses.]

(ii) Human cells in vitro

Trivalent antimony compounds

Exposure of the human lung carcinoma A549 cell line to antimony(III) chloride at 250, 350, or 500 µM for 24 hours caused significant impairment of nucleotide excision repair (NER), as demonstrated by inhibition of the removal of ultraviolet C irradiation-induced cyclobutane pyrimidine dimers (Grosskopf et al., 2010). However, antimony(III) chloride did not affect the repair of benzo[*a*]pyrene diol epoxide- and 6–4 photoproduct-induced DNA adducts after exposure for 2 hours, or the removal of benzo[*a*]pyrene diol epoxide-induced DNA adducts (Grosskopf et al., 2010). Moreover, antimony(III) chloride exposure caused significantly decreased gene and protein expression of the NER pathway component XPE, and trivalent antimony interacted with the zinc finger domain of another NER protein, XPA. In a cellular system using A549 cells, the association/dissociation of XPA to/from damaged DNA was diminished in the presence of antimony(III) chloride, suggesting that trivalent antimony interferes with proteins involved in the NER pathway (Grosskopf et al., 2010).

Exposure of the HeLa S3 cell line to antimony(III) chloride at a concentration of 50 µM for 8 hours decreased repair of γ-irradiation-induced DNA double-strand breaks. BRCA1 and RAD51 were identified as molecular targets of antimony(III) chloride, suggesting that, in

addition to non-homologous end-joining, homologous recombination may also be impaired by exposure to antimony(III) chloride (Koch et al., 2017).

(b) Experimental systems

(i) Non-human mammals in vivo

No data were available to the Working Group.

(ii) Non-human mammalian cells in vitro

Trivalent antimony compounds

Pre-treatment of Chinese hamster ovary cells with trivalent antimony (antimony(III) chloride or antimony(III) potassium tartrate) at a concentration of 0.2, 0.4, 0.6, or 0.8 mM for 2 hours inhibited the repair (rejoining) of DNA double-strand breaks induced by γ-irradiation (Takahashi et al., 2002) [The Working Group noted that significant inhibition of repair was observed after exposure to antimony(III) chloride at 0.2 mM and antimony(III) potassium tartrate at 0.4 mM, but that the mean cytotoxic doses were 0.21 and 0.12 mM, respectively, and that most of the cells treated with antimony(III) potassium tartrate at 0.4 mM lost their proliferative capacity.]

(iii) Non-mammalian experimental systems

Trivalent antimony compounds

Trivalent antimony inhibited DNA double-strand break repair not only by non-homologous end-joining, but also by homologous recombination, two pathways that are important for the repair of DNA double-strand breaks (Litwin et al., 2021). Trivalent antimony exposure also strongly affected the morphology of microtubule (actin) filaments in yeast (Litwin et al., 2021). Alterations in the microtubule cytoskeleton (genomic instability) may cause nuclear disorganization and inhibit DNA repair in budding yeast, and regulation of astral microtubules may be coordinated with pathways that maintain genome integrity (Estrem & Moore, 2019).

4.2.4 Induces epigenetic alterations

(a) Humans

(i) Exposed humans

See Table 4.6.

In a study conducted in China of 360 healthy men employed as coke-oven workers who were exposed to PAHs and multiple metals including antimony, Deng et al. (2019) measured the expression of miRNAs in plasma to explore their associations with urinary metals and PAHs. The selection of miRNAs (let-7b-5p, miR-126-3p, miR-142-5p, miR-150-5p, miR-16-5p, miR-24-3p, miR-27a-3p, miR-28-5p, miR-320b, and miR-451a) was based on previous observations that the expression of these miRNAs is inversely associated with the PAH response, genetic damage, and oxidative stress. After adjusting for urinary PAHs and other metal exposures, antimony was significantly associated with a 13% decrease in all the miRNAs in both single- and multiple-metal models. [The Working Group noted that the strength of this study was that antimony was significantly associated with miRNA expression, not only in single-metal models adjusted for PAH exposure, but also in multiple-metal models simultaneously adjusted for PAHs and other metals. However, the Working Group noted that the correlation between biomarkers of genetic damage or oxidative stress (DNA strand-break levels in lymphocytes, cytokinesis-blocked micronuclei, and indicators of oxidative stress) and miRNAs was adjusted for the sum of metals and PAHs, thus it was not possible to discriminate the effect of antimony alone. In addition, the Working Group noted that the urinary levels of antimony in the exposed group were not different ($P = 0.447$) from those in the control group.]

In a subset of the Aragon Workers Health study conducted in Spain, Riffo-Campos et al. (2018) used DNA Infinium Methylation 450 K data obtained from whole-blood samples from 23 of 73 middle-aged men without clinically evident cardiovascular disease to identify differentially

Table 4.6 Epigenetic alterations in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
miRNAs	Plasma	China, coke-oven workers, cross-sectional	$n = 360$	Inverse association of urinary Sb concentration with 10 miRNA expression measurements ($P < 0.05$)	PAHs, other metals		Deng et al. (2019)
DMRs	Whole blood	Spain, Aragon Workers Health Study, cross-sectional	DNA Infinium Methylation 450 K data were obtained from 23 out of 73 middle-aged men without clinically evident CVD	Of 303 genes annotated to metal DMRs, 42 were uniquely associated with Sb exposure; among the nearest genes to the identified DMRs, 46% of the metal-DMR genes overlapped with atherosclerosis-DMR genes ($P < 0.001$).	Adjusted by age, smoking status, BMI, hypertension, dyslipidaemia, and diabetes	Exposure assessment critique: Single urine samples were used to assess exposures to metals concurrently with the assessment of the end-point of interest. Urinary biomarkers of Sb represent recent exposure. Reliance on a single urine sample likely resulted in imprecise estimates of (recent) exposure. Sb levels are in normal range. Relationships between DMRs with respect to subclinical atherosclerosis in coronary, carotid, and femoral territories, metal concentrations, sociodemographic characteristics, and different cell types were evaluated using a big-data approach (i.e. bump hunter methodology). Sb effect is not characterized as positive or negative, rather as an overlapping of genes. Qualitative description of data only.	Riffo-Campos et al. (2018)

Table 4.6 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
DNA methylation and hydroxymethylation	Leukocytes from frozen specimens	USA, Strong Heart Cohort Study	48 Strong Heart Study participants for which selected metals had been measured in urine at baseline and DNA from leukocytes was available from 1989–1991 (visit 1) and 1998–1999 (visit 3)	Positive cross-sectional associations for Sb with global DNA methylation and hydroxymethylation were found, although the association with global DNA hydroxymethylation was weaker. *P*-values NR, but all CIs go through 1. Positive prospective associations for Sb with global DNA methylation in two different models Using urinary Sb above and below 0.27 µg/g creatinine: OR, 1.93 (95% CI, 1.07–3.47); OR, 2.15 (95% CI, 1.15–4.01) *P*-values, NR	Age, adiposity, smoking, and metal exposure	Exposure assessment critique: Biomonitoring being undertaken at a single time point limits the quality of this exposure assessment. Information on the source of Sb exposure was not available.	Tellez-Plaza et al. (2014)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DMR, differentially methylated region; miRNA, microRNA; NR, not reported; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; Sb, antimony.

methylated regions. Of 303 genes annotated to differentially methylated regions associated with exposure to metals, 42 were uniquely associated with antimony exposure.

Tellez-Plaza et al. (2014) assessed the association between antimony exposure and global DNA methylation and hydroxymethylation in leukocytes from frozen blood samples collected from participants in a US cohort study of cardiovascular disease. Also collected were baseline urine samples in which metal levels, including antimony, were measured. After controlling for age, adiposity, smoking, and metal exposure in cross-sectional analyses, odds ratios were elevated for associations between antimony and global DNA methylation and hydroxymethylation, although the association with hydroxymethylation was weaker (or lower). Although *P*-values were not reported, all confidence intervals overlapped. However, in a prospective analysis examining associations between urinary antimony levels and global DNA methylation, a positive association for antimony exposure was observed in two different models when using a urine antimony cut-point of 0.27 µg/g creatinine, giving odds ratios of 1.93 (95% CI, 1.07–3.47) and 2.15 (95% CI,1.15–4.01) (*P*-values not reported). [The Working Group noted that all the three studies above showed some evidence of antimony-induced epigenetic effects in exposed humans.]

(ii) Human cells in vitro

Trivalent antimony compounds

Exposure of the human bronchial epithelial cell line BEAS-2B to antimony(III) chloride at a concentration of 10–25 µM for 24 hours caused apoptosis through significant trivalent antimony-induced sirtuin 1 (SIRT1) gene downregulation and protein degradation, which was also linked to trivalent antimony-induced oxidative stress (increased reactive oxygen species, ROS) (see Section 4.2.5) and ERK (also known as MAPK1) activation (Zhao et al., 2018). SIRT1 can deacetylate histones and several non-histone substrates (Lin & Fang, 2013); furthermore, it acts as either a tumour suppressor or promoter depending on its targets in specific signalling pathways or cancers (Lin & Fang, 2013).

Exposure of human keratinocytes to trivalent antimony at a concentration of 3 µM for 1 week caused significant downregulation of miR-203, miR-143, and miR-146a. miR-203 is an inhibitor of cell proliferation, whereas miR-143 and miR-146a are inducers (Phillips et al., 2016).

Chronic exposure of the LNCaP cell line to low (non-cytotoxic) concentrations of antimony(III) potassium tartrate at a concentration of 1 or 2 µM for 20 weeks induced upregulation of the long non-coding RNA PCA3, which targets the miR-132-3P/SREBP1 (also known as SREBF1) signalling pathway, resulting in a significant increase in cell growth/proliferation and colony formation (Guo et al., 2021b).

(b) Experimental systems

(i) Non-human mammals in vivo

No data were available to the Working Group

(ii) Non-human mammalian cells in vitro

Trivalent antimony compounds

Exposure of CGR8 mouse embryonic stem cells to antimony(III) chloride at a concentration of 5 µM for 24 hours caused significantly decreased levels of 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine in both DNA and RNA (Xiong et al., 2017). The decrease in 5-hydroxymethylcytosine has been reported to be associated with early stages of carcinogenesis in rat liver where critical epigenetic modifications may occur (Lian et al., 2015).

4.2.5 Induces oxidative stress

(a) Humans

(i) Exposed humans

See Table 4.7.

In the cross-sectional study by Cavallo et al. (2002) (see Section 4.2.2 and Table 4.1) involving exposure to antimony(III) oxide, oxidative DNA damage was assessed by tail moment measurements of PBLs, as measured by Fpg enzyme-modified comet assay, compared with non-enzyme-modified tail moment measurements. The Fpg-modified tail moment measurements were significantly increased in the "high dose" antimony-exposed workers (group A) after adjusting for age and smoking ($P = 0.002$), suggesting oxidative DNA damage. [The Working Group noted the low antimony exposure concentration, relatively small sample size (exposed and controls, $n = 23$), and lack of information provided about occupational co-exposures, which reduced the informativeness of this study.]

In the study by El Shanawany et al. (2017), antimony exposure (exposed and controls, $n = 25$) was reported to significantly predict apurinic/apyrimidinic sites of DNA damage (see Section 4.2.2) but not total oxidant capacity in blood (Table 4.7), suggesting that antimony may have direct genotoxic effects independent from causing oxidative damage.

In a cross-sectional general-population study in Spain, several urinary markers of oxidative stress (oxidized to reduced glutathione ratio GSSG/GSH, malondialdehyde (MDA), and 8-oxo-deoxyguanine) were examined in 1440 participants and compared with urinary levels of metals, including antimony. No statistically significant differences in geometric mean ratios for any of the three oxidative stress end-points were observed when comparing the first and fifth quintiles of urinary antimony exposure (Domingo-Relloso et al., 2019).

In a study of 50 patients with cutaneous leishmaniasis in Saudi Arabia, markers of oxidative stress before and after administration of sodium stibogluconate and meglumine antimoniate(V) by intramuscular injection were assessed and compared with responses in 30 healthy controls (Seif & Al-Mohammed, 2021). For superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), all values were decreased in patients with cutaneous leishmaniasis compared with controls ($P < 0.001$). All values returned to close to normal ranges after antimony treatment ($P < 0.001$). Other measures of oxidative enzyme activity including nitric oxide, L-arginase, myeloperoxidase, adenosine deaminase, and MDA were all elevated before treatment compared with controls ($P < 0.001$–0.0001) except for GSH, which was markedly lower than control values ($P < 0.0001$). After antimony treatment, all values (except GSH) declined markedly towards normal values ($P < 0.001$–0.0001). [The Working Group noted that a strength of this study was its relatively large size. The study was unusual in comparing the effect of antimony on a cohort of people with systemic parasitic disease with healthy controls. However, the interpretation was complex, given the perturbations related to oxidative stress that are associated with leishmaniasis itself.]

Two studies reviewed by the Working Group examined the potential association between heavy metal-induced oxidative stress in women with either recurrent pregnancy loss (Alrashed et al., 2021) (see also Section 4.2.2) or PCOS (Kirmizi et al., 2021). [Both studies were deemed uninformative by the Working Group. Alrashed et al. (2021) failed to control for confounding by abnormally high levels of gonadotropins and other hormones in the pregnancy-loss group. Kirmizi et al. (2021) assessed a population with PCOS, which is reported to be associated with chronic low-dose inflammation and oxidative stress, thus it is difficult to assess the antimony-induced effect.]

(ii) Human cells in vitro

Trivalent antimony compounds

Primary erythrocytes from a healthy donor were treated with antimony(III) potassium tartrate (2 mM) for 1 hour resulting in the rapid

Table 4.7 Oxidative stress in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Total oxidant capacity	Whole blood	Egyptian rayon workers, cross-sectional	25 rayon workers, 25 non-exposed controls	No Sb effect The mean TOCs for workers and controls were 0.28 ± 0.11 and 0.27 ± 0.07 mmol/L, respectively (t = 0.167, P = 0.868)	Age, smoking	Exposure assessment critique: The evidence of Sb exposure contrast presented in this study is compelling and supported by occupational information and urinary biomonitoring. However, the lack of dilution correction of urinary Sb measurements and little information on co-exposures in the occupation under investigation does slightly weaken the informativeness of the findings. Those with a history of use of medicinal products containing Sb and exposure to other known genotoxic agents were excluded, and smoking was quantified. However, information on other co-exposures in this occupation was lacking. Misclassification not suspected.	El Shanawany et al. (2017)
Oxidative stress markers (GSSG/GSH, MDA, 8-oxo-dG)	Urine	Spain, general population, cross-sectional	n = 1440	No Sb effect NS differences in GMRs in any of the 3 end-points when comparing 1st and 5th quintile urinary Sb exposure	Diabetes, smoking	Exposure assessment critique: Population-based cross-sectional nature of the study and biomonitoring being undertaken at a single time point limits the quality of this exposure assessment. Information on the source of Sb exposure was not available. No details given for statistical methods; report regressions performed but no details.	Domingo-Relloso et al. (2019)

Table 4.7 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Oxidative stress markers (SOD, CAT, GPX) Oxidative enzyme activity (L-arg, MPO, ADA, GSH, NO, MDA)	Blood	Saudi Arabia, patients with CL Evaluation of pre/post markers after intramuscular injections of sodium stibogluconate and meglumine antimoniate(V)	50 patients with CL; 30 healthy controls	All values ↓ in patients with CL compared with controls; $P < 0.001$ All values return to normal range post-Sb treatment; $P < 0.001$ Untreated patients with CL: all values markedly ↑ compared with controls ($P < 0.001$–0.0001); except for GSH, ↓ compared with controls, $P < 0.0001$ All values mildly elevated in Sb-treated compared with controls; $P < 0.01$–0.0001 Except GSH; lower than controls ($P < 0.001$)		Strength of this study was its relatively large size.	Seif & Al-Mohammed (2021)

↓, decreased; ↑, increased; ADA, adenosine deaminase; CAT, catalase; CL, cutaneous leishmaniasis; GMR, geometric mean ratio; GPX, glutathione peroxidase; GSH, glutathione; GSSG/GSH, oxidized to reduced glutathione ratio; L-arg, L-arginase; MDA, malondialdehyde; MPO, myeloperoxidase; NO, nitric oxide; NS, not significant; 8-oxo-dG, 8-oxo-deoxyguanine; Sb, antimony; SOD, superoxide dismutase; TOC, total oxidant capacity.

movement of trivalent antimony across the cell membrane and the formation of intracellular trivalent antimony–GSH complexes, which may protect the cells against trivalent antimony-induced oxidative damage (Sun et al., 2000).

Poon & Chu (2000) showed that exposure of human erythrocytes to trivalent antimony (0.2–1.2 mM) for 5 minutes inhibited the activity of glutathione-*S*-transferase with a 50% inhibition concentration (IC_{50}) of 0.05 mM, which was not reversed by the antioxidant *N*-acetylcysteine (NAC) and may promote oxidative stress (Poon & Chu, 2000).

Antimony(III) chloride (10–25 µM) significantly decreased SIRT1 messenger RNA (mRNA) and protein expression in human bronchial epithelial (BEAS-2B) cells and increased apoptosis after 24 hours of exposure. Treatment with the antioxidant NAC restored SIRT1, which decreased apoptosis, suggesting a role for ROS in the suppression of SIRT1 (Zhao et al., 2018).

Viana et al. (2021) showed that exposure of the human acute promyelocytic leukaemia cell line NB4 to antimony(III) oxide (300, 400, and 500 µg/mL) for 72 hours caused increased cytotoxicity and ROS levels.

In the human bladder cancer EJ cell line, exposure to antimony(III) potassium tartrate (0.8 µM) for 48 hours caused significant induction of ROS and mitochondrial damage – with significantly decreased matrix metalloproteinase, mitochondrial respiratory enzyme complex (I/II/III/IV) activity, and ATP levels, and an increased ADP/ATP ratio – and the induction was inhibited by NAC exposure (Lou et al., 2021).

In human A549 lung cells, antimony(III) chloride (200 µM) significantly increased autophagy (and cell death) after 24 hours; this was inhibited by NAC, suggesting that the autophagy was ROS-dependent (Zhao et al., 2017).

In the HEK-293 cell line, antimony(III) oxide (8 and 16 µM) significantly induced ROS (with increased apoptosis) in a dose-dependent manner, with the peak effect being at 6 hours after exposure. These effects were inhibited by NAC. Induction and nuclear translocation of NRF2 and GADD45B expression (with downstream activation/phosphorylation of MAPKs) were also increased, and GADD45B was shown to play a protective role in the induction of oxidative stress and apoptosis by antimony(III) oxide (Jiang et al., 2016).

In human acute promyelocytic leukaemia cells, antimony(III) oxide (1–3 µM) significantly induced ROS (with increased apoptosis) after exposure for 24 hours (Mann et al., 2006).

In the human macrophage cell line THP-1, antimony(III) potassium tartrate (105 µg/mL) significantly induced ROS (and early apoptosis), decreased intracellular GSH levels, and inhibited glutathione reductase (resulting in an accumulation of glutathione disulfide) after 4-hour exposure. Pentavalent antimony had no effect, suggesting that macrophages cannot reduce pentavalent antimony to trivalent antimony (Wyllie & Fairlamb, 2006).

Antimony(III) potassium tartrate inhibited cell proliferation after 72 hours of exposure in four human acute myeloid leukaemia cell lines – HL-60 (LC_{50}, 3.57 ± 1.25 µM), K562 (LC_{50}, 16.71 ± 6.07 µM), KG-1a (LC_{50}, 20.47 ± 4.85 µM), and U937 (LC_{50}, 14.92 ± 5.28 µM). Treatment of the HL-60 cells with antimony(III) potassium tartrate at 10 µM significantly decreased matrix metalloproteinase (at 8 hours) and increased apoptosis (at 24–48 hours) and ROS generation (at 24 hours), which was inhibited by NAC (Lecureur et al., 2002).

In HEK-293 cells, antimony(III) oxide significantly decreased cell viability (measured by mitochondrial activity; LC_{50} after 24-hour exposure, 9.15 µM), and more so than the pentavalent antimony compound potassium hexahydroxoantimonate. Although exposure to antimony(III) oxide at 1 and 5 µM or potassium hexahydroxoantimonate at 1, 5, and 10 µM for 24 hours significantly reduced ROS levels, a

trend of increasing ROS generation was observed with increasing concentrations of pentavalent or trivalent antimony (Verdugo et al., 2016).

Lösler et al. (2009) showed that antimony(III) oxide (5 μM) increased apoptosis in the human myeloid and lymphatic cell lines Loucy, CCRF-CEM, and HL-60, but not K562, after exposure for 16 days or less. Apoptosis was enhanced after exposure to antimony(III) oxide at 1 or 5 μM for 7 or 14 days in the presence of DL-buthionine-(*S,R*)-sulfoximine, which is a modulator of the cellular GSH redox system and an inhibitor of the GSH-synthesis enzyme γ-glutamylcysteine synthetase (an enzyme involved in oxidative stress detoxification). The incubation with DL-buthionine-(*S,R*)-sulfoximine also enhanced the loss of mitochondrial membrane potential in HL-60 cells after 48 hours of exposure to antimony(III) oxide at 10 or 20 μM (Lösler et al., 2009).

As mentioned in Section 4.2.2, exposure of primary human PBLs to antimony(III) chloride at 5 μM for 24 hours significantly increased DNA damage and the frequency of micronucleus formation. However, these genotoxic effects were not inhibited by co-exposure to SOD or CAT, suggesting that oxidative stress may not play a role in the induction of DNA and chromosomal damage by antimony(III) chloride (Schaumlöffel & Gebel, 1998). [The Working Group noted that this study showed that ~8% of the dose of trivalent antimony was oxidized to pentavalent antimony after 24 hours.]

Chronic exposure of LNCaP cells to antimony(III) potassium tartrate at low (non-cytotoxic) concentrations of 1 or 2 μM for 20 weeks had no effect on intracellular ROS production (Guo et al., 2021b).

Pentavalent antimony compounds

In human whole blood and isolated polymorphonuclear leukocytes, exposure to sodium stibogluconate at 1, 10, or 100 μg/mL for 1 hour significantly enhanced the generation of ROS induced by the protein kinase C activator phorbol myristate acetate (PMA) or zymosan. It was also observed that in isolated polymorphonuclear leucocytes, sodium stibogluconate caused a concentration-dependent increase in superoxide production induced by PMA. The effect of sodium stibogluconate (at 10 μg/mL only) was also observed on superoxide production induced by zymosan, and to a lesser extent by platelet-activating factor, or *N*-formylmethionine-leucyl-phenylalanine (Rais et al., 2000).

Redox reactivity involving the partial reduction of pentavalent antimony to trivalent antimony (in the presence of GSH) was observed in human blood plasma after a 45-minute exposure of whole blood to potassium hexahydroxoantimonate (200 ng/mL). This pentavalent antimony compound also significantly reduced the GSH:glutathione disulfide ratio and GPX activity, and increased SOD activity (López et al., 2015).

Poon & Chu (2000) showed that exposure of human erythrocytes to sodium stibogluconate for 5 minutes did not inhibit the activity of glutathione-*S*-transferase (Poon & Chu, 2000).

(b) Experimental systems

(i) Non-human mammals in vivo

Trivalent antimony compounds

In a study of subchronic toxicity, groups of male and female Sprague-Dawley rats were given drinking-water containing antimony(III) potassium tartrate at a concentration of 0.5, 5, 50, or 500 ppm for 13 weeks. Hepatic glutathione-*S*-transferase and ethoxyresorufin-*O*-deethylase activity were significantly increased in the liver of the groups at 500 ppm (Poon et al., 1998).

Antimony(III) chloride at a dose of 250 μmol/kg bw administered by subcutaneous injection potently induced haem oxygenase levels in the liver and kidney of male Sprague-Dawley rats (peak, 16 hours) (Drummond & Kappas, 1981).

Male Kunming mice were treated with antimony(III) oxide at a dose of 15 mg/kg bw by gavage for 60 days. The results showed that total antioxidant capacity was significantly decreased and levels of MsrA, MsrB1, and MDA increased in the testis after exposure. Levels of SOD were also decreased, but the change was not statistically significant compared with the control group (Wu et al., 2021).

Kunming mice treated with antimony(III) chloride by intraperitoneal injection (40 mg/kg bw) for 28 days exhibited significantly decreased levels of SOD and GPX, and increased levels of MDA, in liver mitochondria (Wang et al., 1998).

Zhang et al. (2021) reported that the expression of inducible nitric oxide synthase (iNOS) was significantly increased in the brain tissue of male ICR mice treated with antimony(III) potassium tartrate trihydrate at doses of 10 or 20 mg/kg bw by intraperitoneal injection for 8 weeks.

Pentavalent antimony compounds

Phorbol myristate acetate- or zymosan-induced ROS were increased in blood samples collected on day 21 from BALB/c mice treated with sodium stibogluconate at doses of 100, 200, or 400 mg/kg bw by subcutaneous injection on days 14, 16, and 18 (Rais et al., 2000).

Induction of oxidative DNA damage in PBLs of Swiss mice was observed 24 hours after administration of meglumine antimoniate(V) (Glucantime) at a dose of 810 mg/kg bw by intraperitoneal injection (see Section 4.2.2). The induction was inhibited by the antioxidants genistein (administered by gavage 3 days prior to meglumine antimoniate(V)) and ascorbic acid (administered by intraperitoneal injection either as co-exposure with meglumine antimoniate(V) or 24 hours after meglumine antimoniate(V)) (de Jesus et al., 2018).

Exposure of BALB/c mice to meglumine antimoniate(V) administered by intraperitoneal injection at a dose of 20 mg/kg bw per day for 20 days caused a significant increase in oxidative DNA damage in PBLs (see Section 4.2.2). SOD and CAT activities were significantly increased and GPX activity was decreased in serum, which are indicative of oxidative stress (Moreira et al., 2017).

Oxidative stress was induced in the heart, liver, spleen, and brain (no significant effects in kidney) of CF-1 mice treated with meglumine antimoniate(V) at a dose of 20, 60, or 120 mg of antimony(V)/kg per day by subcutaneous injection for 3 consecutive days. The oxidative stress biomarkers measured – protein carbonylation (in heart, spleen, and brain at the highest exposure level) and lipid peroxidation, as assessed by MDA levels (in liver and brain at all exposure levels) – were significantly increased. Imbalances in SOD activity (decreased in heart and brain and increased in spleen at doses of 20 and 60 mg of antimony(V)/kg) and decreases in CAT activity (decreased in liver and brain at all exposure levels) were also observed (Bento et al., 2013).

Antimony(V) chloride, at a dose of up to 250 µmol/kg bw administered by intravenous injection, did not induce haem oxygenase in the liver and kidney of male Sprague-Dawley rats (Drummond & Kappas, 1981).

(ii) Non-human mammalian cells in vitro

Trivalent antimony compounds

Treatment of rat cardiac myocytes with antimony(III) potassium tartrate at a concentration of 100 µM for 4 and 18 hours significantly increased lipid peroxidation (as measured via the release of thiobarbituric acid-reactive substances), which was inhibited by pre-treatment with antioxidants, including vitamin E. Antimony(III) potassium tartrate (50 and 100 µM) also significantly decreased GPX activity as early as 1 hour, increased oxidized GSSH levels at 2 hours (at 100 µM), and decreased GSH levels at 4 hours. The addition of GSH partially protected the cells from lipid peroxidation induced by antimony(III) potassium

tartrate (100 μM) after 18 hours of exposure or less (Tirmenstein et al., 1995).

Exposure of mouse embryonic stem cell lines to six trivalent antimony compounds for 24 hours significantly induced an oxidative stress response (indicated by activation of the Srxn1 and Blvrb gene reporters relevant to a Nrf2 response and ROS production), as measured by ToxTracker reporter assay (see also Section 4.2.2) at non-cytotoxic concentrations: antimony(III) oxide (peak response, 0.32–0.96 μg/mL), antimony(III) sulfide (peak response, 0.56–1.4 μg/mL), antimony(III) chloride (peak response, 0.2–0.8 μg/mL), antimony triacetate (peak response, 2.12 μg/mL), antimony(III) potassium tartrate (peak response, 0.4–0.6 μg/mL), and antimony tris (ethylene) glycolate (peak response, 0.35–0.7 μg/mL) (Boreiko et al., 2021).

Exposure of the rat PC12 cell line to antimony(III) potassium tartrate trihydrate at concentrations of 25–100 μM for 24 hours significantly increased ROS and MDA levels, resulting in increased apoptosis and autophagy (via inhibition of Akt/mTOR signalling), which was reversed by treatment with the antioxidant NAC (Wang et al., 2019b).

Similarly, exposure of PC12 cells to antimony(III) potassium tartrate trihydrate at 50 or 75 μM for 24 hours significantly induced apoptosis (at 75 μM only) and the activation (phosphorylation) of cyclic adenosine monophosphate response element-binding (CREB) protein (via JNK activation), which is protective against oxidative stress/apoptosis by regulating target genes such as uncoupling protein-2 and Nrf2 (Zhi et al., 2020).

Treatment of neonatal rat cardiac myocytes with antimony(III) potassium tartrate at non-cytotoxic concentrations (5 and 10 μM) for 18 hours significantly increased GSH levels and haem oxygenase 1 (HMOX1) activity, indicative of increased oxidative stress (Snawder et al., 1999).

Exposure of the rat C6 glioma cell line (astrocytes) to antimony(III) potassium tartrate trihydrate at concentrations of > 0.625 μmol/L for 24 hours significantly increased iNOS protein and mRNA levels (Zhang et al., 2021).

Pentavalent antimony compounds

In the study by Boreiko et al. (2021), exposure of mouse embryonic stem cells to two pentavalent antimony compounds – antimony(V) chloride (peak response, 1.6–4 μg/mL) and potassium hexahydroantimonate (38 μg/mL) – significantly induced an oxidative stress response (indicated by activation of the Srxn1 and Blvrb gene reporters) at non-cytotoxic doses, as assessed by ToxTracker assay, after exposure for 24 hours. Sodium antimonate induced a weak response (activation of Srxn1 only) at 3 μg/mL. Sodium hexahydroxoantimonate and antimony(V) oxide gave negative results for oxidative stress.

Treatment of mouse peritoneal macrophages with the non-cytotoxic pentavalent antimonial anti-leishmaniasis drug sodium antimony(V) gluconate at a concentration of 60 μg/mL for 24 hours induced significantly increased production of nitric oxide (only in the presence of interferon gamma) and intracellular ROS (Ghosh et al., 2013). In addition, significantly enhanced generation of ROS (after 3 and 6 hours) and nitric oxide (after 48 hours) was observed after exposure to sodium antimony(V) gluconate at 10 μg/mL (Mookerjee Basu et al., 2006).

4.2.6 Induces chronic inflammation

(a) Humans

(i) Exposed humans

See Table 4.8.

In a study of antimony-smelter workers from Serbia and Montenegro, Potkonjak & Pavlovich (1983) reported findings relating to 51 workers exposed to airborne dust containing high concentrations of antimony(III) oxide over a period of 9–31 years. Abnormalities observed by

Table 4.8 Chronic inflammation in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Pneumoconiosis	CXR	Serbia and Montenegro, Sb-smelting plant, cross-sectional	51 workers exposed to high concentrations of antimony(III) oxide (≤ 88% of Sb species present); 9–31 yr duration	Frequency of clinical outcomes On CXR: pulmonary punctate opacities in > 67% of patients On physical examination: 35% with upper airway irritation, 27% with conjunctivitis	None	[The Working Group noted that these represent clinical findings of chronic inflammation and are unique for Sb vs silica exposure.]	Potkonjak & Pavlovich (1983)
Pneumoconiosis	CXR	USA, Sb smelters, cross-sectional	28 workers exposed to Sb ore and antimony(III) oxide, CXR post-smelting	8/28 had suspect or clear CXR abnormalities with predominantly small pulmonary opacities No consistent PFT abnormalities	None		Cooper et al. (1968)

CXR, chest X-ray; PFT, pulmonary function test; Sb, antimony; vs, versus; yr, year.

chest X-ray were described as small pulmonary punctate opacities (primarily in the mid-lung fields) in > 67% of patients, consistent with pneumoconiosis, which arises from a chronic inflammatory response to respirable insoluble mineral dusts in the deep lung. These antimony-specific findings on chest X-ray were different from findings for antimony miners, who have a mixed exposure to silica and thus may develop the classic findings of silicosis. On physical examination, 35% of patients also had evidence of upper-airway irritation, and 27% had evidence of conjunctivitis, which is consistent with chronic exposure to irritant dust. [The Working Group noted that the chest X-ray findings reported may or may not indicate chronic lung inflammation in the absence of a clinical history and may have a broader differential diagnosis. But, given that this is a population finding (and not an individual observation) with exposure histories included, it is reasonable to ascribe the findings to a pro-inflammatory response.]

In another study of antimony smelters exposed to antimony(III) oxide at a plant in the USA, Cooper et al. (1968) described antimony pneumoconiosis, exhibiting predominantly small pulmonary opacities, in 8 of 28 workers. However, there were no consistent abnormalities in pulmonary function.

The effect of antimony exposure was examined in a population of women with PCOS (Kirmizi et al., 2021). [As also reported in Section 4.2.5, the Working Group deemed the study to be uninformative regarding either potential antimony-induced oxidative stress or chronic inflammation.]

In two case reports of patients with leishmaniasis, Costa et al. (2018) and Torrús et al. (1996) compared the effects of antimony-containing topical medication before and after treatment, without normal controls. [The Working Group considered the perturbed inflammatory state before treatment to be poorly suited to examination of the antimony effect. In addition, the two patients in the study by Torrús et al. (1996) were reported to have additional immunocompromised states, with one patient coinfected with HIV and hepatitis C, and one patient being treated with immune modifiers (post-kidney transplant), including cyclosporin (which is *carcinogenic to humans*, IARC Group 1).]

Lobanova et al. (1996) assessed the pathogenic effects of antimony exposure in miners, reporting various markers of inflammation. [The Working Group considered the study to be minimally informative, because standard pro-inflammatory markers of interest are not included, and no statistical methods or controls for other co-exposures are described.]

(ii) Human cells in vitro

Trivalent antimony compounds

Guildford et al. (2009) investigated the potential role of different types of metal NPs, including antimony(III) oxide NPs (size, 41–91 nm), in activating elements of the clotting system (with incubation for 30 minutes in platelet-rich human plasma) and human primary blood-derived monocytes/macrophages. It was observed that exposure of monocytes/macrophages to antimony(III) oxide NPs at 0.05 mg/mL (preconditioned with plasma) for 20 hours activated the monocytes/macrophages via the promotion of fibrin polymerization and the aggregation and fragmentation of platelets; however, cellular secretion of TNFα and PDGF-BB were not significantly increased. [The Working Group noted that nano-scale antimony compounds have the potential to induce a pro-inflammatory response via activation of monocytes/macrophages. The Working Group also noted that this is not a chronic effect.]

Pentavalent antimony compounds

HIV-1 transcription, replication, and viral production were significantly increased in human primary CD4+ T-cells and ex vivo primary thymic histocultures exposed to

sodium stibogluconate at concentrations of 50–500 µg/mL for 3–6 and 14 days, respectively. The effect of sodium stibogluconate was dose-dependent and occurred by cellular activation of NF-κB (also known as NFKB1), AP-1 (also known as JUND), and the Syk, Jun, and MAPK/ERK signalling pathway (Barat et al., 2007). [The Working Group noted that sodium stibogluconate induced T-cell activation, which enhanced HIV-1 infection, but the relevance to chronic inflammation is unclear.]

(b) Experimental systems

(i) Non-human mammalian in vivo

Trivalent antimony compounds

Exposure of male and female B6C3F$_1$ mice to drinking-water containing antimony(III) potassium tartrate at a dose of 407 mg/kg bw for 14 days induced focal areas of ulceration in the forestomach, with necrosis and inflammation of the squamous mucosa, which were most apparent in females. In contrast, exposure to antimony(III) potassium tartrate at a dose of 50 mg/kg bw administered by intraperitoneal injection over the course of 16 days (12 injections) induced increased hepatocellular necrosis and liver capsule inflammation and fibrosis, which were most apparent in male mice. No such effects were induced by antimony(III) potassium tartrate in F344/N rats (Dieter et al., 1991; NTP, 1992). [The Working Group noted that no statistics were reported.] In 90-day studies of subchronic toxicity, exposure of B6C3F$_1$ mice and F344/N rats to antimony(III) potassium tartrate by oral administration in drinking-water induced inflammatory cell infiltrates in the pancreas, intestine, and mesenteric lymph nodes in mice, but not in rats (dose and sex not specified). Exposure of male and female F344/N rats to antimony(III) potassium tartrate at doses of ≥ 6 mg/kg bw administered by intraperitoneal injection (every other day for 90 days) induced hepatocellular degeneration and necrosis (with a minimal inflammatory cell infiltrate), as well as liver capsule inflammation and fibrosis at doses of ≥ 3 mg/kg bw (Dieter et al., 1991; NTP,1992). [The Working Group noted that no statistics were reported.]

Male and female Fischer 344 rats were exposed by inhalation (whole-body) to antimony(III) oxide at a concentration of 0, 0.25, 1.08, 4.92, or 23.46 mg/m^3 for 6 hours per day, 5 days per week for 13 weeks (with or without an observation period of 27 weeks) in a study of subchronic toxicity, and to 0, 0.06, 0.51, or 4.5 mg/m^3 for 52 weeks (with or without an observation period of 1 year) in a study of chronic toxicity. Subchronic and chronic histopathological changes in the lung of males and females included increased numbers of alveolar/intra-alveolar macrophages and subacute–chronic interstitial and granulomatous inflammation, which were all mostly apparent at the highest exposure concentrations (Newton et al., 1994).

In subacute studies, Wistar Han rats and B6C3F$_1$/N mice were exposed by inhalation (whole-body) to antimony(III) oxide aerosol at a concentration of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours per day (5 days per week) for 12–13 exposure days during a 16–17-day period. Significantly increased incidence of chronic active inflammation in the lung was observed in male and female rats exposed to antimony(III) oxide at 30 and 60 mg/m^3, but not in mice (NTP, 2017).

In 2-year studies of chronic toxicity, Wistar Han rats and B6C3F$_1$/N mice were exposed by inhalation (whole-body) to antimony(III) oxide aerosols at a concentration of 0, 3, 10, or 30 mg/m^3 for 6 hours per day (5 days per week) for 105 weeks or less. The incidence of chronic active inflammation in the lung was significantly increased in male and female rats and mice at all exposure concentrations. The incidence of cellular infiltration of lymphocytes in the lung was significantly increased in male and female mice, in female rats at all exposure concentrations, and in male

rats at 3 and 10 mg/m^3. The incidence of suppurative alveolar and pleural inflammation was also significantly increased in rats and mice (in both males and females), respectively, at all exposure concentrations. There was a significantly increased incidence of chronic active inflammation in the (respiratory epithelium of the) nose of male mice (3 and 10 mg/m^3) and larynx of female rats (3 mg/m^3). The incidence of chronic active inflammation in the arteries of multiple organs/tissues combined (including pancreas, lung, kidney, mediastinum, and mesentery) was significantly increased in male and female rats at the highest exposure concentration. In addition, the incidence of chronic active inflammation in the epicardium of the heart was significantly increased in male and female mice at the two highest exposure concentrations, as was the incidence of chronic active inflammation of the forestomach in males at the highest exposure concentration (NTP, 2017).

Potkonjak & Pavlovich (1983) reported that exposure of female Wistar albino rats to antimony(III) oxide dust (50 mg) administered intraperitoneally or intratracheally induced non-collagenous (non-fibrotic) pneumoconiosis 2 months after the exposure.

Exposure of female Fischer 344 (CDF) rats to antimony(III) oxide by inhalation (whole-body) at a concentration of 1.6 ± 1.5 or 4.2 ± 3.2 mg/m^3 (6 hours per day and 5 days per week) for 1 year or less caused a significant increase in the incidence of multinucleated giant cells, cholesterol clefts, pigmented macrophages, and focal fibrosis in the lung (after 3–6 months of exposure), and chronic interstitial nephritis in the kidney (Watt, 1983).

In a study of subchronic toxicity, male and female Sprague-Dawley rats were given drinking-water containing antimony(III) potassium tartrate at a concentration of 0.5, 5, 50, or 500 ppm for 13 weeks. Monocytes were significantly increased in the blood of the female rats at 500 ppm (Poon et al., 1998).

Lung inflammation was not reported in rats and rabbits exposed to antimony(III) oxide (100–125 mg) by inhalation for ~50 and ~14 days, respectively, although the alveolar spaces in rabbits contained some macrophages (Gross et al., 1955b).

Pentavalent antimony compounds

Potkonjak & Pavlovich (1983) also reported that antimony(V) oxide dust (50 mg) administered intraperitoneally or intratracheally to female Wistar albino rats induced non-collagenous (non-fibrotic) pneumoconiosis 2 months after the exposure.

In BALB/c mice exposed to sodium antimony gluconate administered by a single intravenous injection (16 mg/kg bw), peritoneal macrophages isolated 2 days after injection exhibited significantly increased T-cell-stimulating activity (with increased interleukin-2 production), which is relevant to enhanced antigen presentation, and production of interleukin-12 and tumour necrosis factor alpha (TNFα) (Ghosh et al., 2013).

(ii) Non-human mammalian cells in vitro

Trivalent antimony compounds

Exposure of the rat C6 glioma cell line (astrocytes) to antimony(III) potassium tartrate trihydrate at a concentration of 0.1–5.0 μmol/L for 24 hours significantly increased cell activation/proliferation as well as phosphorylation/nuclear translocation of p65 (also known as RELA; NF-κB signalling) and expression of the pro-inflammatory cytokines interleukin IL-1β (also known as IL1B), IL-6, and TNFα at exposure concentrations of ≥ 1.25 μmol/L. Antimony also induced increased phosphorylation of TGFβ-activated kinase 1 (TAK1, also known as MAP3K7) thus increasing its activity, whereas TAK1 inhibition alleviated antimony(III) potassium tartrate trihydrate-induced p65 phosphorylation and subsequent C6 cell activation (Zhang et al., 2021). [The Working Group noted that the link between astrocyte proliferation and the activation of

NF-κB or TAK1 is missing, since no cell proliferation markers were investigated after the cells were treated with NF-κB or TAK1 inhibitors.]

Treatment of the murine haematopoietic Baf3 cell line with antimony(III) potassium tartrate (10 µg/mL) did not enhance IL-3-induced Jak2/Stat5 tyrosine phosphorylation or IL-3-induced proliferation (Pathak & Yi, 2001).

Pentavalent antimony compounds

Treatment of peritoneal macrophages derived from BALB/c mice with a non-cytotoxic dose of sodium antimony gluconate (60 µg/mL) induced significantly increased T-cell-stimulating activity (with increased IL-2 production) (after 24- and 72-hour exposures) and production of interleukin-12 and TNFα (after 24-hour exposure) (Ghosh et al., 2013). [The Working Group noted that acute immune activation may or may not be linked to chronic inflammation.]

Treatment of murine haematopoietic Baf3 cells with sodium stibogluconate (10 µg/mL) increased IL-3-induced Jak2/Stat5 tyrosine phosphorylation, and IL-3-induced Baf3 proliferation (at day 3) was significantly increased at concentrations of sodium stibogluconate between 0.3 and 200 µg/mL, with a maximal effect concentration of ~40 µg/mL (Pathak & Yi, 2001).

4.2.7 Is immunosuppressive

(a) Humans

(i) Exposed humans

See Table 4.9.

Kim et al. (1999) assessed antimony-induced alterations of the immune system – including the concentrations of the IgG subclasses, IgE, IL-2, interferon gamma (IFNG), and IL-4 – in samples of sera collected from workers (n = 34) exposed to antimony(III) oxide during manufacture. Serum IgG1 levels were significantly lower ($P < 0.05$) in workers in the group exposed to the highest concentration (n = 12) than those moderately (n = 22) and not exposed (control, n = 33). Serum IgE concentrations in the group exposed to the highest concentration were also significantly lower ($P < 0.05$) than the control (3.6-fold) group and the group exposed to the lowest concentration (5.2-fold). Workers in the group exposed to the highest concentration also had significantly lower serum interferon gamma ($P < 0.05$) and IL-2 levels than the group exposed to the lowest concentration and controls (although, for IL-2, the difference did not reach statistical significance).

In an NHANES study, which is a nationally representative survey of the civilian population in the USA, Scinicariello & Buser (2016) reported leukocyte telomere length in blood samples collected from study participants as a function of antimony exposure. [The Working Group noted that critically shortened telomeres may signal replicative senescence and apoptosis in cells.] Exploring several effect models – and considering covariates and adjustments including age, ethnicity, education, weight status, and lead exposure – higher antimony concentrations in urine were reported to be significantly associated with shorter leukocyte telomere length. Individuals in the third and fourth quartiles of the urinary antimony distribution had significantly shorter leukocyte telomere lengths (quartile 3, −4.78%; 95% CI, −8.42 to −0.90; and quartile 4, −6.11%; 95% CI, −11.04 to −1.00) than the lowest reference antimony quartile with evidence of a dose–response (P for trend, 0.03). [The Working Group noted that increased antimony-induced apoptosis of circulating leukocytes could be linked to immunosuppressive effects.]

Wu & Chen (2017) studied 99 industrial workers employed at five plants – involved in industries including the manufacture of glass and engineered plastics – exposed to antimony(III) oxide and 42 administrative staff (non-exposed controls) from the same plants. Mean urinary antimony concentrations in all industrial workers (9.28 µg/g creatinine) were significantly higher ($P < 0.001$) than non-exposed controls (2.26 µg/g

Table 4.9 Immunosuppression in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Ig subclasses, cytokines	Serum	Republic of Korea, Sb workers, cross-sectional	Group A, $n = 12$ high antimony(III) oxide exposure Group B, $n = 22$ moderate antimony(III)oxide exposure Group C, $n = 33$ non-exposed controls	↓ Serum IgG1 ($P < 0.05$) in Group A compared with Groups B or C ↓ Serum IgE ($P < 0.05$) in Group A compared to Groups B (5.2-fold) or C (3.6-fold) ↓ Serum IFNG ($P < 0.05$) and IL-2 (NS) in Group A compared with Groups B or C	None	Exposure assessment critique: The evidence of Sb exposure contrast presented in this study is very compelling and supported by multiple methods of exposure assessment. The differences in Sb exposure between comparison groups is indisputable.	Kim et al. (1999)
Leukocyte telomere length	Blood, leukocytes	USA, NHANES, cross-sectional		↓ LTL with increased Sb exposure; individuals in the 3rd and 4th quartiles of urinary Sb distribution had significantly shorter LTL (−4.78%, 95% CI, −8.42 to −0.90; and −6.11%, 95% CI, −11.04 to −1.00, respectively) compared with the lowest reference quartile with evidence of a dose–response (P for trend = 0.03)	3 models, multiple covariates and adjustments including age, ethnicity, education, weight status, and Pb	Exposure assessment critique: Population-based cross-sectional nature of the study and biomonitoring being undertaken at a single time point limits the quality of this exposure assessment. Information on the source of Sb exposure was not available.	Scinicariello & Buser (2016)

Table 4.9 (continued)

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Ig subclasses	Serum	Taiwan, China, industrial workers, cross-sectional	$n = 99$ industrial workers from 5 plants $n = 14$ with higher Sb exposure compared with the others $n = 42$ administrative staff (non-exposed controls) from the same plants Mean urinary Sb in workers = 9.28 μg/g creatinine vs in controls = 2.26 μg/g creatinine ($P < 0.001$)	↓ Mean serum IgG, IgA, and IgE levels among all industrial workers compared with controls ($P \leq 0.001$) ↓ Monocyte counts for total participants ($n = 133$) with ↑ Sb levels in blood and urine ($P < 0.001$ and $P < 0.05$, respectively)	Authors note that the prevalence rates of smoking, drinking, betel nut chewing, and allergy were alike for the Sb-exposed workers and controls	Exposure assessment critique: Area air sampling was conducted during work shifts using standard methods. There were insufficient details about the strategy for collecting air (area) samples, particularly in terms of how many air samples were collected each day and whether sampling occurred on multiple days. Levels of Sb in air samples and in urine, blood, and hair were measured at the same time as the end-points of interest. Co-exposures to other metals and chemicals were not evaluated.	Wu & Chen (2017)

↓, decreased; ↑, increased; CI, confidence interval; Ig, immunoglobulin; IFNG, interferon gamma; IL-2, interleukin 2; LTL, leukocyte telomere length; NHANES, National Health and Nutrition Examination Survey; NS, not significant; Pb, lead; Sb, antimony.

creatinine), and mean serum IgG, IgA, and IgE levels in all industrial workers were significantly lower ($P \leq 0.001$). Monocyte counts for all study participants ($n = 133$) were negatively correlated with antimony in blood and urine ($P < 0.001$ and $P < 0.05$, respectively). [The Working Group noted that there were possible co-exposures to other metals and carcinogens in these plants that were not addressed in the analyses reported, but that the three studies showed some evidence of antimony-induced immunosuppression in exposed humans.]

(ii) Human cells in vitro

No data were available to the Working Group.

(b) Experimental systems

In a study conducted by the NTP (2017) (see Section 4.2.6(b)(i)), chronic exposure to antimony(III) oxide by inhalation caused a significant increase in the incidence of cellular depletion in the thymus of male and female B6C3F$_1$/N mice at the two highest exposure concentrations (10 and 30 mg/m^3).

White Leghorn chick embryo eggs were injected with antimony(III) chloride or antimony(III) potassium tartrate on days 7 and 14 as follows: (a) 0.0 ppm (in 0.5 or 1.0 mL of vehicle), (b) 1.0 ppm (in 0.5 or 1.0 mL), and (c) 5.0 ppm (in 0.5 mL of vehicle). Blood was collected 20 days after injection. The results showed that injection of 1 ppm/mL antimony decreased the number of leukocytes by 47%, but that injection of 2 or 10 ppm/mL did not (Newkirk et al., 2014). [The Working Group noted that there were high standard deviations in this study.]

4.2.8 Modulates receptor-mediated effects

(a) Humans

(i) Exposed humans

See Table 4.10.

In the Hangzhou Birth Cohort Study conducted in China, thyroid hormone levels in 915 pregnant women were examined by tertiles of level of exposure to six metals: arsenic, cobalt, manganese, nickel, antimony, and selenium. For antimony, in a single-metal model, an inverse association was found with FT4 in blood across tertiles of antimony exposure after controlling for multiple testing (false discovery rate-adjusted P for trend, < 0.05). In a multiple-metal model, significantly decreased changes in percentage levels of thyroid hormones were demonstrated between FT4 and the third tertile of antimony exposure (–1.99%; 95% CI, –3.44% to 0.52%; P for trend, 0.006). Results of spline regression models indicated that FT4 decreased throughout the range of antimony concentrations with a significant linear trend (P for overall association, 0.001; P for nonlinearity, 0.716). Covariates considered included maternal age, education, household income, working during pregnancy, exposure to second-hand smoke in pregnancy, drinking during pregnancy, gestational age at measurement of thyroid hormones, parity, history of hyperglycaemia during pregnancy, and pre-pregnancy BMI (Guo et al., 2018).

In a study of 824 pregnant women in the Rhea Birth Cohort, conducted in Greece, Margetaki et al. (2021) assessed women with high (third tertile) urinary antimony concentrations and found that they had a 12.5% lower (95% CI, 1.8–22.0%) level of thyroid-stimulating hormone in blood than women in the first and second tertiles, which was statistically significant ($P < 0.05$). Covariates considered included trimester at blood sampling, maternal age, parity, smoking early in pregnancy, maternal education, maternal pre-pregnancy BMI, iodine status, and family history of thyroid disease. In a combined exposure model including other metals (cadmium and lead exposure), the thyroid-stimulating hormone effect reported was a change of –9.8% (95% CI, –19.7 to 1.3; $P < 0.1$).

The association of urinary metal concentrations with reproductive hormone levels was

Table 4.10 Modulation of receptor-mediated effects in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Thyroid hormone levels	Blood	China, Hangzhou Birth Cohort Study, cross-sectional	n = 915 pregnant women	Negative associations of tertiles of Sb exposure with FT4 ($P < 0.05$; FDR = 0.018) Negative associations of 3rd tertile of Sb exposure in multiple-metal model for FT4 (–1.99%, 95% CI, –3.44 to –0.52%; P for trend = 0.006) Results of spline regression models indicated that thyroid hormones decreased throughout the range of Sb concentrations with a significant linear trend (P for overall association = 0.001, P for nonlinearity = 0.716)	Maternal age, education, household income, working during pregnancy, second-hand smoke during pregnancy, drinking during pregnancy, gestational age at measurement of thyroid hormone levels, parity, history of hyperglycaemia in pregnancy, and pre-pregnancy BMI	Exposure assessment critique: Single blood samples were used to assess exposures to metals concurrently with the assessment of the end-point of interest. Co-exposures to other metals (As, Co, Se, Mn, and Ni) were evaluated in the statistical analyses if they produced statistically significant results ($P < 0.05$) when evaluated one at a time. Logistic regression results presented for Mn, Ni, and Sb with FT4.	Guo et al. (2018)
Thyroid hormone levels	Serum	Greece, Rhea Birth Cohort	n = 824 pregnant women	↓ TSH with ↑ urinary Sb (3rd tertile); 12.5% ↓ TSH (95% CI, 1.8–22.0%) compared with women with lower (2nd and 1st tertile) urinary Sb ($P < 0.05$) in a single exposure model and -9.8% change (95% CI, –19.7 to 1.3) for a combined exposure model ($P < 0.1$)	Trimester at blood sampling, maternal age, parity, smoking early in pregnancy, maternal education and maternal pre-pregnancy BMI, iodine status, and family history of thyroid disease	Exposure assessment critique: Single urine samples were used to assess exposures to metals concurrently with the assessment of the end-point of interest. Urinary biomarkers of Sb represent recent exposure. Co-exposures to Cd and Pb were evaluated using BKMR. Reliance on a single urine sample likely resulted in imprecise estimates of (recent) exposure.	Margetaki et al. (2021)
Reproductive hormone levels	Serum	China, partners of patients at a fertility clinic, cross-sectional	n = 511	No associations between urinary Sb levels and serum reproductive hormones after adjustment for multiple testing (FDR-adjusted P for trend) for each hormone ranging from > 0.50 to 0.99)	Age, BMI, abstinence time, smoking status, daily cigarette consumption, and urinary creatinine	Exposure assessment critique: Urine samples collected at two close points in time on the same day as semen sample limits the findings.	Wang et al. (2016)

↓, decreased; ↑, increased; As, arsenic; BKMR, Bayesian kernel machine regression; BMI, body mass index; Cd, cadmium; CI, confidence interval; Co, cobalt; FDR, false discovery rate; FT4, free T4 (thyroxine); Mn, manganese; Ni, nickel; Pb, lead; Sb, antimony; Se, selenium; TSH, thyroid-stimulating hormone.

also assessed in the partners of patients at a fertility clinic in China in a cross-sectional study conducted by Wang et al. (2016). No associations between urinary antimony concentrations and serum reproductive hormones after adjustment for multiple testing were observed (with false discovery rate-adjusted *P* for trend for each hormone ranging from > 0.50 to 0.99). [The Working Group noted that cadmium and lead were also measured in urine samples, and co-exposures were assessed using BKMR analysis.] [The Working Group noted that two of the two studies that assessed the effects of antimony on different thyroid hormone measurements reported inverse associations.]

(ii) Human cells in vitro

Trivalent antimony compounds

Zhang et al. (2018a, b) demonstrated that exposure of androgen-dependent human prostate cancer cell lines to low (non-cytotoxic) doses of antimony(III) potassium tartrate for 48–72 hours (LNCaP cells, 0.5 μM; PC3 cells, 8 μM) significantly promoted cell growth/proliferation, invasion (into Matrigel), and migration, as assessed by wound-healing assay with PC3 cells only. In LNCaP cells, treatment with antimony(III) potassium tartrate triggered the phosphorylation of the androgen receptor, which transcriptionally regulated the expression of many androgen-associated genes, including upregulation of PSA and NKX3.1, thus mimicking androgen activity (Zhang et al., 2018a). In the study with PC3 cells, antimony(III) potassium tartrate regulated the expression of Ctbp2, which resulted in the transcriptional regulation of RhoC (a Rho GTPase family member) expression, increased ROCK1 kinase activity, and increased stability of the c-Myc oncogenic protein (Zhang et al., 2018b).

Chronic exposure of LNCaP cells to antimony(III) potassium tartrate at low (non-cytotoxic) concentrations of 1 and 2 μM for 20 weeks significantly increased cell growth/proliferation, colony formation, and triglyceride and cholesterol levels, indicative of lipid metabolic disequilibrium induced by upregulation of the long non-coding RNA PCA3, which targets the miR-132-3P/SREBP1 receptor signalling pathway, in response to antimony(III) potassium tartrate exposure (Guo et al., 2021b).

Patterson & Rice (2007) found that exposure of spontaneously immortalized keratinocyte (SIK) cells to antimony(III) potassium tartrate (5 μM) for 3 or 9 days resulted in the stabilization of the epidermal growth factor (EGF) receptor, which preserved its ability to signal and thus the proliferative capacity of the cells. In the presence of AG1478, an EGF receptor inhibitor, exposure to antimony(III) potassium tartrate for 3 days did not increase the colony-forming efficiencies of SIK cells and primary normal human epidermal keratinocytes, which indicates that antimony has an EGF receptor-dependent effect on cell proliferation. Treatment of the SIK cells with antimony(III) potassium tartrate also stabilized nuclear β-catenin protein and significantly altered (in the presence of EGF) β-catenin-dependent gene expression (Patterson & Rice, 2007).

Choe et al. (2003) used human MCF7 cells, which were stably transfected with the plasmid pTK-ERE containing a luciferase reporter gene under the control of an estrogen-responsive element (MCF7-ERE), and an E-Screen assay (also with MCF7 cells) to assess the estrogenicity of various heavy metals and their species. They found that treatment with antimony(III) chloride (1 μM) exhibited high estrogenicity in MCF7-ERE cells and the E-Screen assay after exposure for 36 hours and 6 days, respectively (Choe et al., 2003).

Comparison of the gene expression profiles of SIK cells exposed to trivalent arsenic (3 μM) or trivalent antimony (6 μM) for 1 week using next-generation sequencing revealed that both trivalent arsenic and antimony produced highly similar transcriptional responses in human keratinocytes (Phillips et al., 2016). mRNAs

downregulated by both antimony(III) and arsenic(III) included those encoding the leucine-rich repeats protein 1 (LRIG1), a negative regulator of EGFR signalling, and the ryanodine receptor 1 (RYR1), a positive regulator of calcium signalling that promotes cell differentiation (Phillips et al., 2016). Moreover, exposure of SIK cells to either trivalent antimony or arsenic also significantly attenuated bone morphogenetic protein-6 (BMP6)-induced DUSP2 and DUSP14 (Phillips et al., 2016), consistent with the maintenance of EGF receptor signalling.

Pentavalent antimony compounds

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

No data were available to the Working Group.

(ii) Non-human mammalian cells in vitro

No data were available to the Working Group.

4.2.9 Alters cell proliferation, cell death, or nutrient supply

(a) Humans

(i) Exposed humans

See Table 4.11.

Goi et al. (2003) assessed the activity of lysosomal glycohydrolases in plasma samples from a group of 26 Italian art-glass workers, of whom 16 were exposed to arsenic(III) oxide and 10 were exposed to antimony(III) oxide. No significant mean differences were found between the antimony-exposed workers and non-exposed controls ($n = 50$) in levels of the six enzymes measured (*N*-acetyl-β-D-glucosaminidase, β-D-glucuronidase, α-D-galactosidase, α-D-glucosidase, β-D-galactosidase, and α-D-mannosidase). There was also no evidence of metabolic, endocrinological, or haemolytic diseases, haemoglobinopathies, or diseases involving major organs. Furthermore, none of the workers had a family history of diabetes and all were HIV-negative.

(ii) Human cells in vitro

Trivalent antimony compounds

Goi et al. (2003) found that 24-hour exposure of human PBLs to trivalent, but not pentavalent, antimony (200–300 μg/L) caused significantly increased secretion of the lysosomal glycohydrolases *N*-acetyl-β-D-glucosaminidase and β-D-glucuronidase (Goi et al., 2003).

In vitro exposure of the human prostate cancer cell lines LNCaP and PC3 to antimony(III) potassium tartrate significantly promoted cell growth/proliferation and invasion, as assessed by Matrigel assay, and wound healing (Zhang et al., 2018a, b; Guo et al., 2021b), as well as lipid metabolic disorder (Guo et al., 2021b) (see Section 4.2.8).

Exposure of the human bladder cancer EJ cell line to low-dose antimony(III) potassium tartrate (0.8 μM) for 24–48 hours significantly increased cell proliferation, invasion (into Matrigel), and migration (in a wound-healing assay) (Lou et al., 2021). In addition, antimony(III) potassium tartrate significantly inhibited mitophagy in EJ cells by downregulating the expression of PINK1, Parkin, and p(ser65)-Parkin, which resulted in increased cell proliferation. Activation of the PINK–Parkin pathway by carbonyl cyanide 3-chlorophenylhydrazone significantly inhibited antimony(III) potassium tartrate-induced cell proliferation (Lou et al., 2021).

Treatment of human SIK cells with antimony(III) potassium tartrate (5 μM) or EGF alone for 3 days significantly increased their colony-forming efficiency by two- to three-fold compared with untreated (control) cultures. In SIK cells co-treated with both agents, the colony-forming efficiency increased by four-fold. (Patterson & Rice, 2007).

Pentavalent antimony compounds

No data were available to the Working Group.

Table 4.11 Alterations in cell proliferation, cell death, or nutrient supply in humans exposed to trivalent or pentavalent antimony

End-point	Biosample type	Location, setting, study design	Study population	Response (significance)	Covariates controlled	Comments	Reference
Lysosomal glycohydrolase levels	Plasma	Italy, art glass workers, cross-sectional	*n* = 10 antimony(III) oxide-exposed workers *n* = 16 arsenic(III) oxide-exposed-workers *n* = 50 non-exposed controls	NS between exposed workers and controls for *N*-acetyl-β-D-glucosaminidase, β-D-glucuronidase, α-D-galactosidase, α-D-glucosidase, β-D-galactosidase, and α-D-mannosidase	There was no evidence of metabolic, endocrinological, or haemolytic diseases, haemoglobinopathies, or diseases involving major organs; none of the workers had a family history of diabetes, and all were HIV-negative	Exposure assessment critique: Single urine samples were used to assess exposures to metals concurrently with the assessment of plasma levels of lysosomal enzymes. No correction of Sb (and As) concentrations for urinary dilution. No assessment for co-exposure to As in the statistical analyses. [The Working Group noted that it seemed that the workers were parsed by either As or Sb exposure, although other potential co-exposures were not mentioned.]	Goi, et al. (2003)

As, arsenic; HIV, human immunodeficiency virus; NS, not significant; Sb, antimony.

(b) Experimental systems

(i) Non-human mammals in vivo

Trivalent antimony compounds

In studies of subacute toxicity, Wistar Han rats and B6C3F$_1$/N mice were exposed by inhalation (whole-body) to antimony(III) oxide aerosol at a concentration of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours per day (5 days per week) for 12–13 days during a 16–17-day period. A significantly increased incidence of squamous metaplasia of the epiglottis was observed in the larynx of male and female mice, but not rats, after exposure to the two highest concentrations (30 and 60 mg/m^3) (NTP, 2017).

In 2-year studies of chronic toxicity, Wistar Han rats and B6C3F$_1$/N mice were exposed by whole-body inhalation to antimony(III) oxide aerosols at a concentration of 0, 3, 10, or 30 mg/m^3 for 6 hours per day (5 days per week) for 105 weeks or less. The incidence of alveolar and bronchiolar epithelial hyperplasia, as well as lymphoid hyperplasia of the bronchial lymph nodes, was significantly increased in male and female rats and mice at all concentrations. Lymphoid hyperplasia of the mediastinal lymph nodes was significantly increased at all exposure concentrations in male and female rats, and at the two highest concentrations in male and female mice. Bone marrow hyperplasia (predominantly because of increased erythroid precursors) was significantly increased in male and female rats at the highest concentration, and bone marrow hyperplasia (myeloid) was significantly increased in male and female mice at the two highest concentrations. The incidence of squamous metaplasia of the alveolar epithelium (at the lowest concentration) and of the nasal respiratory epithelium (at the highest concentration) was significantly increased in female rats and mice, respectively. Hyperplasia and squamous metaplasia of the respiratory epithelium of the nose and hyperplasia of the adrenal medulla were also significantly increased in male and female rats at the highest concentration. In addition, the incidence of hyperplasia and squamous metaplasia of the respiratory epithelium of the epiglottis in the larynx and of hyperplasia of the squamous epithelium was significantly increased in male and female mice at the highest concentration. There was also a significant increase in the incidence of haematopoietic cell proliferation in the spleen of female mice at the highest concentration (NTP, 2017).

In a study of chronic toxicity by Groth et al. (1986), male and female Wistar rats were exposed by inhalation (whole-body) to antimony(III) oxide (TWA, 45 mg/m^3) or antimony ore (TWA, 36–40 mg/m^3) for 7 hours per day, 5 days per week for 52 weeks or less. After exposure to antimony(III) oxide for 6 months, alveolar wall hyperplasia was increased in female rats, but not in males. After 12 months of exposure, the incidence of cuboidal and columnar (alveolar wall) cell metaplasia was increased in female and male rats (although less so in males). Similar effects in terms of metaplasia were reported after exposure to antimony ore.

Newton et al. (1994) reported an increase in the incidence of bronchioloalveolar hyperplasia in female, but not male, Fischer 344 rats exposed to antimony(III) oxide for 1 year by inhalation (whole-body) at the highest exposure level (23.5 mg/m^3) after a 1-year observation period. Minimal to no bronchioloalveolar hyperplasia was observed in male and female rats after exposure for 13 weeks (with or without a 27-week observation period) or 1 year.

Increased incidence and severity of bone marrow myeloid hyperplasia was reported by Poon et al. (1998) in male and female Sprague-Dawley rats given drinking-water containing antimony(III) potassium tartrate at a concentration of 0.5, 5, 50, or 500 ppm for females, and 50 or 500 ppm for males for 13 weeks. The incidence of bone marrow erythroid hyperplasia was also increased, but only in males exposed at the

highest concentration (500 ppm), and to a lesser degree than the myeloid type.

In a 13-week study, antimony(III) potassium tartrate administered by intraperitoneal injection caused an increase in the incidence of bile duct hyperplasia in the liver of Fischer 344 (primarily male) rats at the highest dose (24 mg/kg bw) (Dieter et al., 1991, NTP, 1992).

Watt (1983) reported a significant increase in the incidence of bile duct proliferation and pneumocyte hyperplasia in female CDF rats exposed by inhalation (whole-body) to antimony(III) oxide (1.6 ± 1.5 and 4.2 ± 3.2 mg/m^3) for up to 1 year.

In tumour implantation studies, male BALB/c immunodeficient (nude) mice were given drinking-water containing antimony(III) potassium tartrate (0.1 or 1.0 μg/mL) or potassium tartrate hemihydrate ($C_4H_6K_2O_7$, control compound) for 14 days, and then inoculated subcutaneously and bilaterally with prostate cancer (LNCaP or PC3) cells (in Matrigel), after which exposure to antimony(III) potassium tartrate or potassium tartrate hemihydrate in drinking-water was continued. Tumour sizes and volumes were monitored until days 21 (PC3) and 23 (LNCaP) and were found to be greater in mice treated with antimony(III) potassium tartrate (Zhang et al., 2018 a, b). Similar findings were reported by Lou et al. (2021) for exposure to antimony(III) potassium tartrate (0.8 μmol/mL) in a tumour implantation study using the bladder cancer cell line EJ, with tumour size/volume monitored for > 24 days. In the study by Guo et al. (2021), male BALB/c (nude) mice were inoculated with LNCaP cells by subcutaneous injection and then given drinking-water containing antimony(III) potassium tartrate (1.0 μg/mL) or potassium tartrate ($K_2C_4H_40_6$, control compound). Tumour sizes and volumes were monitored to day 40 and were found to be greater in mice treated with antimony(III) potassium tartrate. Serum triglyceride and total cholesterol levels were also significantly increased in the group treated with antimony(III) potassium tartrate, consistent with lipid metabolic disequilibrium.

Zhang et al. (2021) reported that the expression of glial fibrillary acidic protein (GFAP) and iNOS, two critical protein markers of reactive astrogliosis, were significantly increased in the brain tissue of male ICR mice treated with antimony(III) potassium tartrate trihydrate at a dose of 10 or 20 mg/kg bw by intraperitoneal injection for 8 weeks, indicating that antimony induced astrocyte activation in vivo. Although antimony(III) potassium tartrate induced astrocyte activation and proliferation in vitro (in the rat C6 glioma cell line) (Zhang et al., 2021) (see below), no cell proliferation markers were investigated in the brain tissue of the antimony-exposed mice.

Pentavalent antimony compounds

No data were available to the Working Group.

(ii) Non-human mammalian cells in vitro

Trivalent antimony compounds

Exposure of the rat C6 glioma cell line (astrocytes) to antimony(III) potassium tartrate trihydrate (0.1–5.0 μmol/L) for 24 hours significantly increased cell activation and proliferation, with increased expression of PCNA and cyclin D1 proteins (> 0.625 μmol/L). GFAP and iNOS protein and mRNA levels were also significantly increased (> 0.625 μmol/L) (Zhang et al., 2021).

Exposure of rat erythrocyte-derived phosphofructokinase (a rate-limiting enzyme of glycolysis in erythrocytes) to antimony(III) potassium tartrate hydrate (5 mM) for 3 minutes inhibited its activity by 95%. GSH and Hb partially protected phosphofructokinase against the inhibitory effect of antimony (most effectively at low antimony concentrations) (Poon & Chu, 1998).

Treatment of the Baf3 cell line with antimony(III) potassium tartrate (1–1000 μg/mL) did not result in detectable inhibition of protein tyrosine phosphatases, nor was enhanced

(IL-3-induced) proliferation observed (Pathak & Yi, 2001).

Pentavalent antimony compounds

Treatment of the Baf3 cell line with sodium stibogluconate (10–100 µg/mL) induced tyrosine phosphorylation of cellular proteins – including inhibition of the protein tyrosine phosphatases SHP-1, SHP-2, and PTP1B and increased (IL-3-induced) proliferation at concentrations between 0.3 and 200 µg/mL (maximal effect concentration, ~40 µg/mL) (Pathak & Yi, 2001). This suggests that only the pentavalent form of antimony acts as an inducer of Baf3 cell proliferation, which is inactivated when it is transformed into the trivalent form (Pathak & Yi, 2001).

Pathak et al. (2002) also showed that treatment of the NB4 cell line with sodium stibogluconate (25–100 µg/mL) inactivated SHP-1 protein tyrosine phosphatases.

4.2.10 Evidence on other key characteristics of carcinogens

(a) Causes immortalization

Exposure to antimony(III) acetate (1.6, 3.2, or 7.5 µM) significantly enhanced the frequency of transformation of Syrian hamster embryo cells by simian adenovirus SA7 (Casto et al., 1979).

(b) Multiple characteristics

(i) Human cells in vitro

In view of the chemical similarity of inorganic trivalent arsenic (arsenite) and antimony (antimonite), the responses of human epidermal keratinocytes to either trivalent antimony or arsenic were compared at the transcriptional and translational levels (Phillips et al., 2016, 2020). Human epidermal SIK cells were treated with sodium arsenate (Na_3AsO_4, 3 µM) or antimony(III) potassium tartrate (6 µM) for 7 days. Results from next-generation sequencing showed that exposure to trivalent arsenic and antimony induced highly similar transcriptional responses in SIK cells (Phillips et al., 2016). Furthermore, the gene expression changes were almost entirely in the same direction for the two treatments, although the degrees of change were sometimes different (Phillips et al., 2016). Both sodium arsenate and antimony(III) potassium tartrate induced suppression of RYR1 and LRIG1, as well as bone morphogenic protein-6 activity, which are linked to decreased differentiation and maintenance of EGF-dependent proliferative capacity. Both compounds also inhibited many miRNAs, including miR-203 (a suppressor of proliferation). On the basis of transcriptional and proteomic comparisons and Ingenuity Pathway Analysis (IPA), sodium arsenate and antimony(III) potassium tartrate were reported to share virtually the same signalling pathways and upstream regulators (Phillips et al., 2020). Of the merged top five pathways enriched for genes modulated by sodium arsenate and antimony(III) potassium tartrate in SIK cells, four were identical (Nrf2-mediated oxidative stress, glucocorticoid receptor signalling, xenobiotic metabolism signalling, and the γ-glutamyl cycle). Proteomic analysis also predicted the involvement of the Nrf2-mediated oxidative stress response as one of the most-affected pathways, and of the top five predicted upstream transcriptional regulators, three (Myc, EFNA4, and ROCK2) were affected by both sodium arsenate and antimony(III) potassium tartrate (Phillips et al., 2020).

Kawata et al. (2007) used DNA microarrays to classify the toxic effects of six heavy metals, including antimony, compared with those of the "model chemicals" 2,3-dimethoxy-1,4-naphthoquinone, phenol, and *N*-nitrosodimethylamine. Specific gene alterations in HepG2 cells and hierarchical clustering revealed that the effects of antimony were very similar to those of 2,3-dimethoxy-1,4-naphthoquinone, which has been reported to be an inducer of ROS and associated with the increased expression of genes, such as CCNB2 and UBE2C, involved in cell proliferative responses (Kawata et al., 2007).

Modulation of gene expression in the human monocytic THP-1 cell line by treatment with sodium stibogluconate (200 µg/mL) was measured by Affymetrix human DNA microarray and further validated by real-time PCR. The results showed that sodium stibogluconate induced the upregulation of endothelin receptor type B (EDNRB) (G-protein signalling coupled to the second messenger inositol trisphosphate), HMOX1, glutamate-cysteine ligase modifier subunit (GCLM) (GSH biosynthesis pathway in response to oxidative stress), melanoma antigen family B2 (MAGEB2) (protein binding), and 5′-nucleotidase, cytosolic II (NT5C2) gene expression, and downregulation of mannose receptor, C type 1 (MRC1) (receptor-mediated endocytosis) and selenoprotein W, 1 (SEPW1) gene expression (El Fadili et al., 2008). Induction of HMOX1 by sodium stibogluconate was also observed in primary human monocyte-derived macrophages (El Fadili et al., 2008). HMOX1 is a potent inducer of vascular endothelial growth factor, a critical factor that governs tumour angiogenesis, and has been recognized as a promoter of tumour metastasis (Cherrington et al., 2000).

(ii) Evaluation of high-throughput in vitro toxicity screening data

The analysis of the in vitro bioactivity of the agents reviewed in *IARC Monographs* Volume 131 was informed by data from high-throughput screening assays generated by the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al., 2018). Antimony was one of thousands of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes. Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is publicly available (US EPA, 2022).

The ToxCast/Tox21 high-throughput screening results are presented based on the assays that have been mapped to the key characteristics (Reisfeld et al., 2022). The detailed results are available in supplementary information for this volume (Annex 4, Supplementary material for Section 4, Evaluation of high-throughput in vitro toxicity screening data, web only, available from: https://publications.iarc.fr/618). Here, for brevity, assays for which there is a positive "hit call" are referred to as "active" assays. A summary of these results is given below as the number of active assays (without any caution flags)/total number of key characteristic-related assays for the chemical.

The results for the four trivalent antimony compounds screened are: (i) acetic acid, antimony(III) salt: 0/111; (ii) antimony(III) potassium tartrate trihydrate: 17/117; (iii) antimony(III) chloride: 13/170; and (iv) antimony(III) potassium tartrate hydrate: 6/38.

The active assays that appear for one or more of the compounds are as follows:

Key characteristic 2, "is genotoxic" (three assays): (i) DT40, a single-readout assay that uses DT40 (a chicken lymphoblast cell line); (ii) H2AX_HTRF_CHO_Agonist, a single-readout assay that uses the CHO-K1 cell line; and (iii) p53_BLA_p3, a single-readout assay that uses HCT 116 (a human intestinal cell line).

Key characteristic 5, "induces oxidative stress" (two assays): (i) HSE_BLA_Agonist, a single-readout assay that uses HeLa (a human cervix cell line); and (ii) ARE_BLA_Agonist, a single-readout assay that uses HepG2 (a human liver cell line).

Kay characteristic 8, "modulates receptor-mediated effects" (10 assays): (i) PPARd_BLA_Antagonist, a single-readout assay that uses HEK-293T (a human kidney cell line); (ii) PR_BLA_Antagonist, a single-readout assay that uses transfected HEK-293T cells; (iii) RORg_LUC_CHO_Antagonist, a single-readout assay that uses CHO-K1 cells; (iv) TR_LUC_GH3_Antagonist, a single-readout assay that uses GH3 (a rat pituitary gland cell line); (v) FXR_BLA_Antagonist, a single-readout assay that

uses HEK-293T cells; (vi) AR_BLA_Antagonist, a single-readout assay that uses HEK-293T cells; (vii) AR_LUC_MDAKB2_Antagonist, a single-readout assay that uses MDA-kb2 (a human breast cell line); (viii) ERR, a single-readout assay that uses ERR-HEK-293T (a human kidney cell line); and (ix) PGC_ERR, a single-readout assay that uses PGC/ERR HEK-293T (a human kidney cell line).

Key characteristic 10, "alters cell proliferation, cell death, or nutrient supply" (four assays): (i) TR_LUC_GH3_Antagonist, a single-readout assay that uses GH3 (a rat pituitary gland cell line); (ii) AP1_BLA_Agonist, a single-readout assay that uses ME-180 (a human cervix cell line); (iii) AR_LUC_MDAKB2_Antagonist, a single-readout assay that uses MDA-kb2 (a human breast cell line); and (iv) RORg_LUC_CHO_Antagonist, a single-readout assay that uses the CHO-K1 cell line.

For the pentavalent antimony compound antimony(V) sulfide, the assay results were as follows: 0/38 (no active assays for any key characteristic).

Overall, for trivalent antimony compounds, the results were uninformative, except for key characteristic 8, "modulates receptor-mediated effects".

For pentavalent antimony compounds, the results were uninformative for all key characteristics.

5. Summary of Data Reported

5.1 Exposure characterization

The following agents are considered in this monograph: the trivalent antimony compounds antimony(III) oxide, antimony(III) chloride, antimony(III) potassium tartrate, antimony(III) sulfide, antimony(III) ions, antimony(III) hydride; and the pentavalent antimony compounds antimony(V) oxide, meglumine antimoniate(V), and antimony(V) in sodium stibogluconate.

The major antimony form that is mined is antimony(III) sulfide, a High Production Volume chemical. Primary product compounds are typically antimony(III) oxide, antimony metal, or sodium antimonate, with other antimony products synthesized from those forms. Antimony compounds are mainly used in flame retardants, lead–acid batteries, lead alloys, plastics (as catalysts and stabilizers), glass and ceramics, as a lubricant in brake pads and clutch discs, and as an ammunition primer in explosives. Antimony(III) potassium tartrate has been widely replaced with meglumine antimoniate(V) and sodium stibogluconate in the treatment of leishmaniasis.

Releases of antimony into the environment occur from natural processes, such as the weathering of rocks, soil runoff, wind-blown dust, volcanic eruptions, sea spray, and forest fires, and from anthropogenic activities, including the mining and processing of ores, metal production, and other related industrial processes.

Inhalation of airborne dust is considered the primary route of occupational exposure to antimony; skin exposure and inadvertent ingestion may also occur. Occupational exposure may arise in various industrial sectors, such as smelting, production of antimony compounds and of other metals, glass manufacture, textile production, battery manufacture, and electronic and electrical waste processing. Workers may be exposed to multiple antimony compounds in the workplace and may also have co-exposure to other agents. Non-occupational exposures are typically relatively lower, arising from exposure to contaminated water, air, and soil, and use of consumer products, tobacco, and electronic cigarette liquids. Estimated dietary intakes are generally well below the current WHO-derived tolerable daily intake values. Both occupational and environmental exposure guidelines exist for antimony, as do reference values for

concentrations in urine and blood. Exposure assessments involving detailed characterization of antimony speciation and co-occurrence of other agents such as arsenic and lead, notably in airborne dusts, are limited.

5.2 Cancer in humans

The available body of evidence on antimony and cancers in humans comprised four occupational cohort studies, including one in glassblowers, two in antimony-smelter workers, and one in tin-smelter workers, as well as nine cohort, case–cohort, case–case, and case–control studies in the general population. The three most informative of these were the studies of lung cancer mortality in smelter workers, which consistently observed elevated standardized mortality ratios for workers exposed to antimony. In one of these studies, an elevated standardized mortality ratio among antimony or maintenance workers was observed, but not among those in other job categories. In another of the studies, standardized mortality ratios increased according to duration of employment. The most recent study found that excess lung cancer mortality risk increased with increasing weighted cumulative exposure to antimony.

The major limitation in these studies was the inability to control for exposure to arsenic (classified in IARC Group 1, *carcinogenic to humans*), which is present in both antimony and tin smelting. In all three studies, there was little evidence that co-exposure to arsenic was a convincing explanation for the observed associations between antimony and lung cancer among smelter workers. Nonetheless, although these studies observed a positive association between antimony exposure and lung cancer mortality, the possibility of confounding by exposure to arsenic or other known lung carcinogens could not be fully excluded.

Studies on other cancers were considered only minimally informative, too few in number, and without consistent evidence to contribute to the evaluation. Occupational exposure to antimony among smelter workers was considered to be exposure to trivalent antimony. All the general-population studies using biomarkers or estimates of air pollution considered antimony exposure without regard to chemical form. No epidemiological studies were identified that specifically evaluated exposure to pentavalent antimony.

5.3 Cancer in experimental animals

5.3.1 Trivalent antimony

Treatment with antimony(III) oxide caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms, in two species or in both sexes of a single species, in well-conducted studies that complied with Good Laboratory Practice.

Antimony(III) oxide was administered by inhalation (whole-body exposure) in one well-conducted study that complied with Good Laboratory Practice in male and female B6C3F$_1$/N mice. Antimony(III) oxide caused an increase in the incidence of bronchioloalveolar carcinoma in males and females, of fibrous histiocytoma of the skin and of histiocytoma or fibrosarcoma (combined) of the skin in males, and of malignant lymphoma (all organs) in females.

Antimony(III) oxide was administered by inhalation (whole-body exposure) in one well-conducted study that complied with Good Laboratory Practice in male and female Wistar rats. In females, antimony(III) oxide caused an increase in the incidence of cystic keratinizing epithelioma or squamous cell carcinoma (combined) of the lung, and of benign or malignant pheochromocytoma (combined) of the adrenal medulla.

Antimony(III) oxide administered by inhalation (whole-body exposure) in one study in female

Wistar rats caused an increase in the incidence of squamous cell carcinoma, scirrhous adenocarcinoma, and bronchioloalveolar adenoma or carcinoma (combined) of the lung.

Antimony(III) oxide administered by inhalation (whole-body exposure) in one study in female Fischer 344 (CDF) rats caused an increase in the incidence of lung scirrhous adenocarcinoma.

5.3.2 Pentavalent antimony

No data on pentavalent antimony were available to the Working Group.

5.4 Mechanistic evidence

Humans are primarily exposed occupationally to antimony via inhalation. The available data on the absorption and distribution of antimony in humans are limited. Antimony has been detected in the lung, blood, and urine of workers occupationally exposed to antimony in the air. Antimony particles accumulate in the lung of exposed humans and persist for long periods of time (from months to years). The available data in humans indicate that trivalent or pentavalent antimony is eliminated in the urine, regardless of the route of exposure. Ingested trivalent antimony is also excreted into the bile.

Inhalation studies with trivalent antimony in rodents indicate that antimony blood concentrations and lung burden increase with increasing levels of exposure. Pulmonary clearance of antimony is lung burden-dependent, and antimony remains in the lung for a long period of time. Sparse data from studies in experimental animals indicate that absorption of trivalent antimony is poor, whereas absorption of pentavalent antimony is rapid via the gastrointestinal tract. The distribution of antimony is similar for different routes of exposure. Trivalent or pentavalent antimony can accumulate in erythrocytes. The excretion of trivalent or pentavalent antimony is via the urine in rodent studies. The elimination of trivalent antimony from the blood or lung is generally biphasic, with a rapid and a slow phase.

The metabolism of antimony primarily involves the conversion of the valence state from +5 to +3.

5.4.1 Trivalent antimony

There is consistent and coherent evidence that trivalent antimony exhibits key characteristics of carcinogens.

Trivalent antimony is genotoxic. In exposed humans, there is suggestive evidence of genotoxicity in two of four studies of antimony exposure. There is consistent and coherent evidence in human primary cells in multiple studies and in human cell lines that trivalent antimony induces DNA damage, chromosomal aberration, micronucleus formation, and/or increased frequency of sister-chromatid exchange. Although the findings for the genotoxic potential of trivalent antimony were mixed in mice and rats in vivo, DNA damage and micronucleus formation were increased in mice exposed by inhalation. Trivalent antimony was genotoxic in hamster cell lines in several studies but gave negative results in one study in mouse embryonic stem cells. Findings for trivalent antimony were mixed in non-mammalian systems, including yeast and bacteria.

Trivalent antimony induces oxidative stress. The few available studies in exposed humans were either uninformative or did not suggest effects of trivalent antimony on oxidative stress parameters. However, there is consistent and coherent evidence in experimental systems that trivalent antimony induces oxidative stress, including findings of increased levels of reactive oxygen species, in human cell lines in several studies. One study in human primary cells gave negative results for oxidative DNA damage. Trivalent antimony also altered oxidative stress parameters in non-human mammalian systems in vivo and in vitro in multiple studies.

Trivalent antimony induces chronic inflammation. Suggestive evidence in exposed humans is provided by two studies in workers exposed to trivalent antimony, which reported radiographic evidence of pneumoconiosis. There is consistent and coherent evidence in experimental systems that trivalent antimony induces chronic inflammation. Multiple studies in mice and rats showed that subacute to chronic exposure via different routes caused chronic inflammation in multiple organs, including the lung. One study showed that intraperitoneal or intratracheal exposure to trivalent antimony caused non-collagenous pneumoconiosis in rats.

Trivalent antimony alters cell proliferation, cell death, or nutrient supply. One study in workers exposed to trivalent antimony reported negative results for this key characteristic; however, there is consistent and coherent evidence in experimental systems that trivalent antimony alters cell proliferation, cell death, or nutrient supply. Multiple studies showed that trivalent antimony induced increased cell proliferation in human cell lines. Tumour size increased in athymic nude mice injected with human cancer cells and exposed to antimony in a few studies. Trivalent antimony also induced increased cell proliferation and hyperplasia, including in the lung and bone marrow, after inhalation exposure in mice and rats in multiple studies.

There is suggestive evidence that trivalent antimony alters DNA repair or causes genomic instability. Human exposure to antimony was associated with an increased frequency of mosaic loss of chromosome Y in one study. Trivalent antimony decreased the capacity for DNA repair in human cell lines in a few studies but had no effect in vivo in rats in one study. Trivalent antimony decreased the capacity for DNA repair in hamster cells and yeast (single studies) but gave negative results in mouse cells in one study.

There is suggestive evidence in three human population studies that antimony exposure induces epigenetic effects. In two cohort studies, changes in DNA methylation were shown to be associated with antimony exposure. In a cohort study, antimony levels in urine samples were associated with decreased miRNAs in plasma. Trivalent antimony induced some epigenetic-related effects in human cell lines in a few studies and in mouse cells in one study. There were no studies in non-human mammals in vivo.

There is suggestive evidence that antimony is immunosuppressive on the basis of two studies of antimony exposure in human populations. Trivalent antimony also caused cellular depletion of the thymus in mice in one study.

There is suggestive evidence in experimental systems that trivalent antimony modulates receptor-mediated effects. Two studies in pregnant women exposed to antimony showed decreased thyroid hormone levels, but a third study in men found no antimony-associated effects on reproductive hormones. Trivalent antimony altered signalling pathways for androgen receptor, epidermal growth factor receptor, and/or miR-132-3P/SREBP1 receptor in human cell lines in multiple studies.

For other key characteristics of carcinogens, there is a paucity of data.

5.4.2 Pentavalent antimony

For pentavalent antimony, the mechanistic evidence is suggestive. There is suggestive evidence that pentavalent antimony is genotoxic. It gave mixed results in human primary cells in two studies. However, pentavalent antimony induced DNA damage and micronucleus formation in mice exposed by intraperitoneal injection in several studies. Findings for genotoxicity in bacteria were mostly negative. There is suggestive evidence that pentavalent antimony induces oxidative stress in rodent systems in vivo and in vitro in multiple studies, including oxidative DNA damage in vivo in mice in one study. For other key characteristics of carcinogens, there is a paucity of data.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of trivalent antimony. Positive associations have been observed between exposure to trivalent antimony and cancer of the lung.

There is *inadequate evidence* in humans regarding the carcinogenicity of pentavalent antimony.

6.2 Cancer in experimental animals

Trivalent antimony

There is *sufficient evidence* in experimental animals for the carcinogenicity of antimony(III) oxide.

Pentavalent antimony

There is *inadequate evidence* in experimental animals regarding the carcinogenicity of pentavalent antimony.

6.3 Mechanistic evidence

There is *strong evidence* in human primary cells and in experimental systems that trivalent antimony exhibits key characteristics of carcinogens.

For pentavalent antimony, there is *limited* mechanistic evidence.

6.4 Overall evaluation

Trivalent antimony is *probably carcinogenic to humans (Group 2A).*

Pentavalent antimony is *not classifiable as to its carcinogenicity to humans (Group 3).*

6.5 Rationale

The Group 2A evaluation for trivalent antimony is based on *limited evidence* for cancer in humans, *sufficient evidence* for cancer in experimental animals, and *strong* mechanistic evidence. There is *limited evidence* that exposure to trivalent antimony causes lung cancer in humans. Among the available human cancer studies, three occupational cohort studies among antimony- or tin-smelter workers were found to be most relevant for assessing trivalent antimony's association with cancer. A positive association was observed between trivalent antimony exposure and risk of lung cancer in all three studies, but confounding by exposure to arsenic or other known lung carcinogens could not be ruled out as an explanation for the findings. For all other cancer sites, the evidence is *inadequate*, because the studies were few in number, minimally informative, or did not show consistent positive associations. The *sufficient evidence* for cancer in experimental animals is based on an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms caused by antimony(III) oxide, in two species or in both sexes of a single species, in a well-conducted study that complied with Good Laboratory Practice. There is *strong evidence* of key characteristics of carcinogens in human primary cells; trivalent antimony is genotoxic. There is also *strong evidence* of key characteristics of carcinogens in experimental systems; trivalent antimony induces oxidative stress, induces chronic inflammation, and alters cell proliferation, cell death, or nutrient supply.

The evidence is *inadequate* regarding whether exposure to pentavalent antimony causes cancer in humans and in experimental animals because no studies were available. There is *limited evidence* in experimental systems that pentavalent antimony is genotoxic and induces oxidative stress.

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