# SULFUR DIOXIDE AND SOME SULFITES, BISULFITES AND METABISULFITES

## 1. Exposure Data

### 1.1 Chemical and physical data

1.1.1 *Synonyms and structural and molecular data*

***Sulfur dioxide***

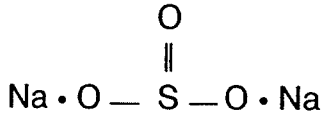
*Chem. Abstr. Serv. Reg. No.*: 7446-09-5
*Replaced CAS Nos.*: 8014-94-6; 12396-99-5; 83008-56-4; 89125-89-3
*Chem. Abstr. Name*; Sulfur dioxide
*IUPAC Systematic Name*: Sulfur dioxide
*Synonyms*: Sulfurous acid anhydride; sulfurous anhydride; sulfurous oxide; sulfur oxide ($SO_2$); sulfur superoxide; sulphur dioxide

$$O = S = O$$

$SO_2$ Mol. wt: 64.07

***Sodium sulfite***

*Chem. Abstr. Serv. Reg. No.*: 7757-83-7
*Alternate CAS No.*: 10579-83-6
*Replaced CAS No.*: 68135-69-3
*Chem. Abstr. Name*: Sulfurous acid, disodium salt
*IUPAC Systematic Name*: Sulfurous acid, disodium salt
*Synonyms*: Anhydrous sodium sulfite; disodium sulfite; sodium sulphite

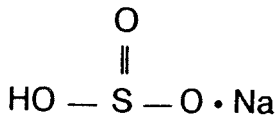


$Na_2SO_3$ Mol. wt: 126.04

***Sodium bisulfite***

*Chem. Abstr. Serv. Reg. No.*: 7631-90-5
*Replaced CAS Nos.*: 57414-01-4; 69098-86-8; 89830-27-3; 91829-63-9
*Chem. Abstr. Name*: Sulfurous acid, monosodium salt
*IUPAC Systematic Name*: Sulfurous acid, monosodium salt

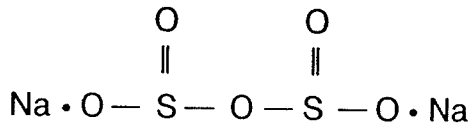
*Synonyms*: Hydrogen sulfite sodium; monosodium sulfite; sodium acid sulfite; sodium bisulphite; sodium hydrogen sulfite; sodium sulfite ($NaHSO_3$)



$NaHSO_3$ Mol. wt: 104.06

***Sodium metabisulfite***

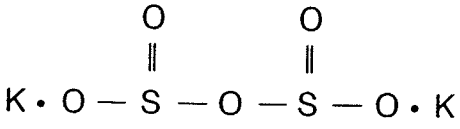
*Chem. Abstr. Serv. Reg. No.*: 7681-57-4
*Alternate CAS No.*: 7757-74-6
*Replaced CAS No.*: 15771-29-6
*Chem. Abstr. Name*: Disulfurous acid, disodium salt
*IUPAC Systematic Name*: Pyrosulfurous acid, disodium salt
*Synonyms*: Disodium disulfite; disodium metabisulfite; disodium pyrosulfite; sodium disulfite; sodium metabisulphite; sodium pyrosulfite



$.Na_2S_2O_5$ Mol. wt: 190.11

***Potassium metabisulfite***

*Chem. Abstr. Serv. Reg. No.*: 16731-55-8
*Alternate CAS No.*: 4429-42-9
*Chem. Abstr. Name*: Disulfurous acid, dipotassium salt
*IUPAC Systematic Name*: Pyrosulfurous acid, dipotassium salt
*Synonyms*: Dipotassium disulfite; dipotassium metabisulfite; dipotassium pyrosulfite; potassium disulfite; potassium metabisulphite; potassium pyrosulfite



$K_2S_2O_5$ Mol. wt: 222.33

### 1.1.2 *Chemical and physical properties*

The chemistry of sulfur dioxide in aqueous solutions involves complex equilibria among a number of species of sulfur oxidation state IV, including sulfite, bisulfite, metabisulfite and sulfurous acid. The composition of the mixture depends on the concentration of sulfur dioxide in the water, the pH and the temperature (Weil, 1983).

***Sulfur dioxide***

(*a*) *Description*: Colourless gas or liquid with sharp pungent (suffocating) odour (Sax & Lewis, 1987; Budavari, 1989; Weast, 1989)
(*b*) *Boiling-point*: –10 °C (Weast, 1989)
(*c*) *Melting-point*: –72.7 °C (Weast, 1989)

(*d*) *Density*: 1.434 g/ml (pressurized liquid at 0 °C); 2.927 g/l (gas) (Weast, 1989)
(*e*) *Solubility*: Soluble in water (g/100 g water at 760 mm Hg [101.3 kPa]): 23.0 at 0 °C, 11.6 at 20 °C and 5.9 at 40 °C; in ethanol, 25 g/100 g; in methanol, 32 g/100 g. Liquid sulfur dioxide is only slightly miscible with water; miscible in all proportions with liquid sulfur trioxide; readily dissolves in most organic liquids: acetone, benzene, carbon tetrachloride and formic acid; completely miscible in diethyl ether, carbon disulfide and chloroform (Weil, 1983; Sander *et al.*, 1984; Budavari, 1989). The solubility of sulfur dioxide in sulfuric acid first decreases with rising sulfuric acid concentration, reaching a minimum at a sulfuric acid concentration of about 85%; beyond this concentration, it increases again (Sander *et al.*, 1984).
(*f*) *Volatility*: Vapour pressure, 2477 mm Hg [330 kPa] at 20 °C; relative vapour density at 0 °C (air = 1), 2.263 (Weil, 1983)
(*g*) *Stability*: Extremely stable to heat, even up to 2000 °C; not explosive or inflammable in admixture with air (Weil, 1983)
(*h*) *Reactivity*: Oxidized by air and pure oxygen; can also be reduced by hydrogen and hydrogen sulfide. With hot metals, usually forms both metal sulfides and metal oxides (Weil, 1983)
(*i*) *Conversion factor*: $mg/m^3 = 2.62 \times ppm$[a]

***Sodium sulfite***

(*a*) *Description*: White powder or hexagonal prisms (Weast, 1989)
(*b*) *Melting-point*: Decomposes (Weast, 1989)
(*c*) *Density*: 2.633 g/ml at 15.4 °C (Weast, 1989)
(*d*) *Solubility*: Very soluble in water (12.54 g/100 ml at 0 °C; 28.3 g/100 ml at 80 °C); slightly soluble in ethanol; insoluble in acetone and most other organic solvents (Weil, 1983; Weast, 1989)
(*e*) *Stability*: Stable in dry air at ambient temperatures or at 100 °C; undergoes rapid oxidation to sodium sulfate in moist air; on heating to 600 °C, disproportionates to sodium sulfate and sodium sulfide; above 900 °C, decomposes to sodium oxide and sulfur dioxide (Weil, 1983)

***Sodium bisulfite***

(*a*) *Description*: White, monoclinic crystals, yellow in solution (Weast, 1989)
(*b*) *Melting-point*: Decomposes (Weast, 1989)
(*c*) *Density*: 1.48 g/ml (Weast, 1989)
(*d*) *Solubility*: Very soluble in cold and hot water; slightly soluble in ethanol (Weast, 1989)
(*e*) *Stability*: Unstable with respect to metabisulfite (Weil, 1983)

***Sodium metabisulfite***

(*a*) *Description*: White powder or crystal (Weast, 1989)
(*b*) *Melting-point*: Decomposes at > 150 °C (Weast, 1989)

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[a]Calculated from: $mg/m^3$ = (molecular weight/24.45) × ppm, assuming normal temperature (25 °C) and pressure (760 mm Hg [101.3 kPa])

(*c*) *Density*: 1.4 g/ml (Weast, 1989)
(*d*) *Solubility*: Soluble in water (54 g/100 ml at 20 °C; 81.7 g/100 ml at 100 °C) and glycerine; slightly soluble in ethanol (Weast, 1989)
(*e*) *Stability*: Decomposes in moist air with loss of part of its sulfur dioxide content and by oxidation to sodium sulfate; forms hydrates with water at low temperatures (Weil, 1983)

***Potassium metabisulfite***

(*a*) *Description*: Colourless, monoclinic plates (Weast, 1989)
(*c*) *Melting-point*: Decomposes at 190 °C (Weast, 1989)
(*d*) *Density*: 2.34 g/ml (Weast, 1989)
(*e*) *Solubility*: Slightly soluble in water and ethanol; insoluble in diethyl ether (Weast, 1989)

### 1.1.3 *Technical products and impurities*

The main grade of liquid sulfur dioxide (pressurized gas) is known as the technical, industrial or commercial grade. This grade contains a minimum of 99.98 wt% sulfur dioxide and is a water-white liquid, free of sulfur trioxide and sulfuric acid. It contains only a trace at most of nonvolatile residue. Its most important specification is the moisture content, which is generally set at a maximum of 100 ppm. The only other grade of liquid sulfur dioxide sold is the refrigeration grade, which is a premium grade of the same purity and specifications as the industrial grade but with a maximal moisture content specified as 50 ppm (Weil, 1983).

Sodium sulfite is available commercially in several grades (Catalyzed SULFTECH®, Catalyzed SULFTECH® with sodium metabisulfite, reagent ACS [American Chemical Society]), with the following ranges of specifications: purity, 94.5–98.5%; sodium chloride, 0.01–0.02%; iron (Fe), 0.001–< 0.002%; arsenic (see IARC, 1987), 1 ppm (mg/kg); heavy metals (as lead), 0.001%; and additives (cobalt salts (see IARC, 1991), 0.01%; anti-caking agent, 0.07%) (General Chemical Corp., undated a,b).

Sodium bisulfite is not sufficiently stable in the solid state to be marketed for commercial use. The 'sodium bisulfite' of commerce consists chiefly of sodium metabisulfite. A technical-grade aqueous solution is available commercially, with the following specifications: concentration, 40.0 wt%; sulfate, 0.7 wt% max; and iron, 15.0 ppm (mg/l) max (Weil, 1983; Calabrian Corp., undated).

Sodium metabisulfite is available commercially in several grades—food and non-food, photographic, technical and industrial—with the following ranges of specifications: purity, 95–98.7%; sodium sulfite, 0.6% max; sulfur dioxide, 65.5–66.5%; iron, 0.0005–0.0015%; selenium (see IARC, 1975), < 0.0005%; heavy metals (as lead), < 0.001–0.002%; chloride, < 0.02%; thiosulfate, < 0.01%; arsenic, < 2.0 ppm (mg/kg); and lead (see IARC, 1987), < 2.0 ppm (mg/kg) (Calabrian Corp., 1990a,b; Virginia Basic Chemicals Co., 1991; General Chemical Corp., undated c,d).

No data were available on technical products and impurities of potassium metabisulfite.

### 1.1.4 *Analysis*

Techniques for the detection and measurement of sulfur dioxide have been reviewed (Karchmer, 1970; Snell & Ettre, 1973). This compound can be recognized even at extreme

dilutions by its pungent smell. Solutions of sulfur dioxide, sulfites or bisulfites decolourize iodine and permanganate by reducing them. Sulfur dioxide and sulfites are reduced by zinc in a hydrochloric acid solution to hydrogen sulfide, which is readily detected by its smell. Sulfur dioxide can be determined chemically by iodometry, titrimetry, gravimetry or colorimetry (Sander *et al.*, 1984).

Routine monitoring of performance in plants usually entails continuous measurement of the sulfur dioxide content of, for instance, roaster gases, contact gases and tail gases in a sulfuric acid plant by automatic recording, based on some physical property, such as spectroscopic absorption in the infrared or ultraviolet range or electrical conductivity (Sander *et al.*, 1984).

The classical, manual method of iodometric determination (Reich, 1961) is still widely used in industrial practice. A partial stream of sulfur dioxide-containing gas is drawn through an iodide solution, and the sulfur dioxide concentration in the stream is calculated from the gas volume and the titrated iodine released. For titrimetric or gravimetric determination of sulfur dioxide, the gases to be analysed are passed through a hydrogen peroxide solution, which oxidizes sulfur dioxide to sulfuric acid; the sulfuric acid is either titrated with caustic soda solution against bromophenol blue or precipitated as barium sulfate and weighed (Sander *et al.*, 1984).

Typical methods for the analysis of sulfur dioxide in various matrices are summarized in Table 1.

## 1.2 Production and use

### 1.2.1 *Production*

Sulfur dioxide has been produced commercially from the following raw materials: elemental sulfur; pyrites; sulfide ores of non-ferrous metals; waste sulfuric acid and sulfates; gypsum and anhydrite; hydrogen sulfide-containing waste gases; and flue gases from the combustion of sulfurous fossil fuels (Sander *et al.*, 1984).

Elemental sulfur is the most important raw material for sulfur dioxide production worldwide. It is the raw material of choice in the production of 100% sulfur dioxide and of commercially important sulfites, such as calcium hydrogen sulfite solution used in cellulose production. The proportion of industrial sulfur dioxide production that is based on elemental sulfur varies in different countries. Of the total amount of sulfur in all forms used for producing sulfur dioxide-containing gases for sulfuric acid production in 1979, the share of elemental sulfur was about 80% in the USA, about 50% in Germany and probably less than 25% in the USSR (Sander *et al.*, 1984).

Sulfur dioxide is produced by burning molten sulfur in a special burner with a controlled amount of air. The burner gas, free of dust and cooled, is dissolved in water in two towers in series. In a third tower, the solution is sprayed at the top and flows down while steam is injected at the base. The gas issuing from the third tower is then cooled to remove most moisture and passed up a fourth tower against a countercurrent of sulfuric acid. The dried gas is liquefied by compression (Mannsville Chemical Products Corp., 1985).

Pyrites and other iron sulfide ores still constitute the main raw material for sulfur dioxide production in some countries, especially in the primary stage of sulfuric dioxide manufacture.

**Table 1. Methods for the analysis of sulfur dioxide**

| Sample matrix | Sample preparation | Assay procedure[a] | Limit of detection | Reference |
|---|---|---|---|---|
| Air | Collect on cellulose filter saturated with KOH preceded by a cellulose ester membrane; oxidize sulfite to sulfate with 30% w/v $H_2O_2$; elute with $NaHCO_3/Na_2CO_3$ | IC | 0.01 mg/ sample | Eller (1987) |
| | Absorb in 0.3N $H_2O_2$; titrate using bromocresol green and methyl red solution | Titration | Range, 0.01–10 ppm [0.026–26 mg/m$^3$] | Taylor (1977) |
| | Absorb in potassium or sodium tetrachloromercurate; complex heavy metals with EDTA; treat with 0.6% sulfamic acid; treat with formaldehyde and *para*-rosaniline; adjust pH to 1.6 with 3M $H_3PO_4$; read maximal absorbance at 548 nm | Colorimetry | 0.01 ppm (26 μg/m$^3$) | Taylor (1977); Kok *et al.* (1987a) |
| | Absorb in buffered formaldehyde solution; treat with 0.6% sulfamic acid; treat with NaOH and *para*-rosaniline; read maximal absorbance at 580 nm | Colorimetry | 26 μg/m$^3$ | Kok *et al.* (1987b) |
| | Draw air through bubbler containing 0.3N $H_2O_2$; add isopropanol; adjust pH with dilute $HClO_4$; titrate using 0.005M $Ba(ClO_4)_2$ and Thorin indicator | Titration | Range, 6.55–26.8 mg/m$^3$ | Taylor (1978) |
| | Adsorb onto Molecular Sieve 5A; desorb with heat | MS | 2 mg/m$^3$ | Taylor (1977) |
| Stack gases | Collect on impinger; absorb with 3% $H_2O_2$; titrate using NaOH and bromophenol blue indicator | AT | Range, 26–15 600 mg/m$^3$ | Knapp *et al.* (1987) |
| | Irradiate sample with pulsed ultraviolet light; pass emitted fluorescent light through broad-band optical filter; detect by photomultiplier tube | PFD | Range 2.6–13 000 mg/m$^3$ | Adams *et al.* (1987) |
| Beer | Add mercury stabilizing solution and 0.1N $H_2SO_4$; add 0.1N NaOH; add *para*-rosaniline and formaldehyde solutions | Colorimetric | Not reported | Helrich (1990) |
| Food[b] | Heat in refluxing 1N HCl; add nitrogen gas stream; condense gas into 3% $H_2O_2$ solution; titrate with NaOH and methyl red indicator | Titration | 10 ppm | US Food and Drug Administration (1987) |

[a]Abbreviations: AT, alkalimetric titration; IC, ion chromatography; MS, mass spectrometry; PFD, pulsed fluorescence detection

[b]Method is also applicable to the following sulfiting preservative agents: potassium metabisulfite, sodium bisulfite, sodium metabisulfite and sodium sulfite

The most important iron sulfide minerals are pyrite and marcasite, both $FeS_2$. The sulfur content of pyrite concentrates may be as high as 50%. In Japan and some other countries, all the pyrite ores produced are processed domestically; whereas other countries, especially Norway, Spain and the countries of the ex-USSR, still export pyrites as raw materials for sulfuric acid production (Sander *et al.*, 1984).

Non-ferrous metal sulfide ores are also important raw materials for sulfur dioxide production, as in the pyrometallurgical processing of sulfide ores for extraction of copper, nickel, zinc and lead, waste gases containing sulfur dioxide are inevitably produced (Sander *et al.*, 1984).

Sulfur dioxide is normally recovered from waste sulfuric acid and sulfates, from hydrogen sulfide-containing industrial waste gases and from power station flue gases only for environmental reasons. Industrial and public utility boilers can be significant sources of sulfur dioxide, which is a by-product of the combustion of fuel oil and coal. The concentration of sulfur dioxide in these gases is often low and difficult to recover economically. US government regulations restrict the emissions of sulfur dioxide from the stacks of utilities to 10.2 pounds [4.6 kg] per million British thermal units [1 055 055 kJ] of fuel burned (Sander *et al.*, 1984; Mannsville Chemical Products Corp., 1985).

Sulfur dioxide is also recovered commercially by liquefying gas obtained during smelting of non-ferrous metals such as lead, copper and nickel. Much of this smelter by-product is recovered and oxidized to sulfur trioxide for producing sulfuric acid (Sander *et al.*, 1984; Mannsville Chemical Products Corp., 1985).

Calcium sulfate, in the form of natural gypsum or anhydrite, was formerly used in a few small plants as a raw material for sulfur dioxide and sulfuric acid production; owing to the high energy consumption of such plants, however, they have been shut down or modified to process waste gypsum (for example, from phosphoric acid manufacture) (Sander *et al.*, 1984).

In a typical sodium sulfite manufacturing process, a solution of sodium carbonate is allowed to percolate downwards through a series of absorption towers through which sulfur dioxide is passed countercurrently. The solution leaving the towers is chiefly sodium bisulfite of, typically, 27 wt% combined sulfur dioxide content. The solution is then run into a stirred vessel, where aqueous sodium carbonate or sodium hydroxide is added until the bisulfite is entirely converted to sulfite. The solution may be filtered to attain the required product grade. A pure grade of anhydrous sodium sulfite can be crystallized at above 40 °C, since its solubility decreases with increasing temperature (Weil, 1983).

Sodium metabisulfite is produced by reacting an aqueous sodium hydroxide, sodium bicarbonate, sodium carbonate or sodium sulfite solution with sulfur dioxide. The solution is cooled, and the precipitated sodium metabisulfite is removed by centrifugation or filtration. Rapid drying, in a steam-heated shelf dryer or a flash dryer, avoids the excessive decomposition or oxidation to which moist sodium metabisulfite is susceptible. Potassium metabisulfite can be produced by a similar process (Weil, 1983).

Sulfur dioxide was produced for sale in the USA at a level of 64 thousand tonnes in 1960, 99 thousand in 1970, 124 thousand in 1980 and 118 thousand in 1985 (Mannsville Chemical Products Corp., 1985). Demand rose to 227 thousand tonnes in 1987 (Anon., 1988) and to 290 thousand tonnes in 1990 (Anon., 1991). Most of the sulfur dioxide produced worldwide is

for captive use in the sulfuric acid and wood pulp industries (Weil, 1983; Sander *et al.*, 1984). The numbers of companies producing sulfur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite and potassium bisulfite in various countries and regions are given in Table 2.

**Table 2. Numbers of companies producing sulfur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite and potassium bisulfite in different countries in 1988–90**

| Country or region | $SO_2$ | $Na_2SO_3$ | $NaHSO_3$ | $Na_2S_2O_5$ | $K_2S_2O_5$ |
|---|---|---|---|---|---|
| Argentina | – | 1 | 1 | 1 | – |
| Australia | 1 | – | – | – | – |
| Austria | 1 | 1 | – | – | 1 |
| Belgium | 1 | – | – | – | – |
| Brazil | 2 | 3 | 2 | 1 | – |
| Canada | 4 | 1 | – | – | – |
| Chile | 1 | – | – | – | – |
| China | – | 4 | – | 2 | – |
| Colombia | 1 | 1 | – | 1 | – |
| Czechoslovakia | – | 1 | – | – | 1 |
| Finland | 1 | – | – | – | – |
| France | 2 | – | 1 | – | – |
| Germany | 6 | 4 | 3 | – | 1 |
| Greece | 1 | – | – | – | – |
| India | 2 | 3 | 4 | 3 | 1 |
| Israel | – | – | 1 | – | – |
| Italy | 2 | 3 | 4 | 2 | 3 |
| Japan | 3 | 17 | 2 | 3 | 1 |
| Mexico | 3 | 2 | 1 | – | – |
| Netherlands | 1 | – | – | – | – |
| New Zealand | – | – | 1 | – | – |
| Norway | 1 | – | – | – | – |
| Philippines | 1 | – | – | – | – |
| Poland | 1 | 1 | – | 1 | – |
| South Africa | 1 | – | 1 | – | – |
| Spain | 4 | 3 | 2 | 2 | 4 |
| Sweden | 3 | – | – | – | – |
| Switzerland | 2 | 1 | 2 | – | – |
| Taiwan | 3 | 2 | – | 1 | – |
| Turkey | 1 | 1 | – | 1 | – |
| United Kingdom | 3 | 5 | 3 | 2 | 2 |
| USA | 7 | 5 | 4 | 3 | 1 |
| USSR | – | 1 | – | – | – |
| Yugoslavia | – | 1 | – | – | 1 |

From Anon. (1988, 1990); Chemical Information Services (1988); –, not known to be produced

### 1.2.2 *Use*

The commercial uses of sulfur dioxide are based on its function as an acid, as a reducing or oxidizing agent or as a catalyst (Mannsville Chemical Products Corp., 1985).

The dominant uses of sulfur dioxide are as a captive intermediate in the production of sulfuric acid and in the pulp and paper industry for sulfite pulping (see p. 145); it is also used as an intermediate for on-site production of bleaches, e.g., chlorine dioxide, by the reduction of sodium chlorate in sulfuric acid solution, and of sodium hydrosulfite (sodium dithionite) ($Na_2S_2O_4$), by the reaction of sodium borohydride with sulfur dioxide. Sulfur dioxide is often used in water treatment to reduce residual chlorine after chlorination and in filter bed cleaning (Weil, 1983; Sander *et al.*, 1984; Mannsville Chemical Products Corp., 1985).

In food processing, sulfur dioxide has a wide range of applications as a fumigant, preservative, bleach and steeping agent for grain. In the production of high-fructose corn syrup, sulfur dioxide is used to steep corn and remove the husks as the corn is prepared for processing. In the manufacture of wine, a small amount of sulfur dioxide is added to the must to destroy bacterial moulds and wild yeasts without harming the yeasts that produce the desired fermentation (Weil, 1983; Sander *et al.*, 1984; Mannsville Chemical Products Corp., 1985).

In petroleum technology, sulfur, most commonly as sodium sulfite, is used as an oxygen scavenger. Sulfur dioxide is used in oil refining as a selective extraction solvent in the Edeleanu process, in which aromatic components are extracted from a kerosene stream with sulfur dioxide, leaving a purified stream of saturated aliphatic hydrocarbons, which are relatively insoluble in sulfur dioxide. Sulfur dioxide acts as a cocatalyst or catalyst modifier in certain processes for oxidation of *ortho*-xylene or naphthalene to phthalic anhydride (Weil, 1983).

In mineral technology, sulfur dioxide and sulfites are used as flotation depressants for sulfide ores. In electrowinning of copper from leach solutions containing iron, sulfur dioxide is used to pre-reduce ferric to ferrous ions to improve current efficiency and copper cathode quality. Sulfur dioxide also initiates precipitation of metallic selenium from selenous acid, a by-product of copper metallurgy (Weil, 1983). In chrome waste disposal, it is used to reduce hexavalent chromium (Mannsville Chemical Products Corp., 1985).

Sulfur dioxide is also used to reduce coloured impurities in clay processing. In the bromine industry, it is used as an antioxidant in spent brine to be reinjected underground. In agriculture, it increases water penetration and the availability of soil nutrients by virtue of its ability to acidulate saline–alkali soils. In glass container manufacture, it is used as a surface alkali neutralizer which improves resistance to scratching and prepares leach-resistant bottles for medicinals, blood plasma and detergents (Weil, 1983).

Sodium sulfite is used in neutral semi-chemical pulping, in acid sulfite pulping, in high-yield sulfite cooling and in some kraft pulping processes; in the chemical industry as a reducing agent and source of sulfite ion; as an antioxidant in water treatment chemicals; in the food industry as an antioxidant and enzyme inhibitor in the processing of fruit and vegetables; in the photographic industry as a film and stain preservative during developing; in the textile industry as a bleach and antichlor; and to remove oxygen from water used in

boilers, oil-well flooding, oil-well drilling muds and other situations in which it is important to remove oxygen to reduce corrosion (Weil, 1983; General Chemical Corp., undated a,b).

Estimated uses of sulfur dioxide in 1988 and of sodium sulfite in 1990 in the USA are presented in Table 3.

**Table 3. Estimated percentage uses of sulfur dioxide and sodium sulfite in the USA**

| Use | Sulfur dioxide 1988[a] | Sodium sulfite 1990[b] |
|---|---|---|
| Hydrosulfites and other chemicals | 40 | – |
| Pulp and paper | 20 | 59 |
| Food and agriculture (mainly corn processing) | 16 | – |
| Textile bleaching, food preservatives, chemical intermediate, ore flotation, oil recovery | – | 10 |
| Water treatment | 10 | 11 |
| Photography | – | 5 |
| Metal and ore refining | 6 | – |
| Petroleum refining | 4 | – |
| Export | – | 15 |
| Miscellaneous | 4 | – |

–, not used or not exported
[a]From Anon. (1988)
[b]From Anon. (1990)

Sodium metabisulfite is used in chemical processing to activate polymerization of acrylonitrile and in waste treatment to reduce chrome wastes; in fruit and vegetable processing as a bleach and preservative; in photoprocessing as a preservative for thiosulfate fixing baths and as a reductant for reversal developing; in tanneries to accelerate the depilatory action of lime for unhairing hides; in the textile industry as an antichlor following chlorine bleaching of cotton and following shrink proofing of wool and as a mordant; in dye manufacture to inhibit oxidation of sensitive amine groups, to replace chlorine groups with the sulfite radical and as an aid in the formation of naphthylamine derivatives; in water treatment as an antichlor; and in the manufacture of explosives and detergents (Weil, 1983; Virginia Basic Chemicals Co., 1991; General Chemical Corp., undated c,d).

The uses of potassium metabisulfite are similar to those of sodium metabisulfite; it is used especially in the processing and preserving of foods and beverages (Sax & Lewis, 1987).

## 1.3 Occurrence

### 1.3.1 *Air*

Anthropogenic activities result in a significant contribution to the atmospheric burden of sulfur compounds regionally and on a global scale. By 1976, it was estimated that global gaseous sulfur emissions from anthropogenic combustion sources were about 90 million tonnes per year. This estimate may be compared with the 90 million tonnes per year contributed by all natural sources of gaseous sulfur compounds, principally biogenic, in

addition to 40 million tonnes per year as sulfate in sea-spray particles (Winchester, 1983). In another study, it was estimated that approximately 65 million tonnes of sulfur, mostly as sulfur dioxide, are released into the global atmosphere yearly from the burning of fossil fuels and the roasting of metal sulfide ores; the same authors estimated that the total natural releases of sulfur to the atmosphere were approximately 80 million tonnes per year (Turner & Liss, 1983).

Sulfur occurs in a variety of compounds in the atmosphere, many of which participate in the sulfur cycle. Hydrogen sulfide is believed to be emitted into the atmosphere in large but uncertain quantities, mainly from natural sources such as swamps and estuaries; most of it is rapidly oxidized to sulfur dioxide and sulfuric acid by a number of reactions involving reactive oxygen species. Sulfur dioxide is not only a product of hydrogen sulfide oxidation, it constitutes about 95% of the sulfur compounds produced by the burning of sulfur-containing fossil fuels. The major anthropogenic sources of sulfur dioxide are the combustion of coal and fuel oil; production, refining and use of petroleum and natural gas; industries using and manufacturing sulfuric acid and other sulfur products; and smelting and refining of ores (Krupa, 1980).

Natural sources of sulfur include sea spray, volcanic activity, decay of animal and plant tissue, marine algae, anaerobic microbiological activity and other soil processes. Biogenic sulfur compounds originate from nonspecific bacterial reduction of organic sulfur, i.e., plant decomposition, and from specific sulfate-reducing bacteria. Sulfated sea spray accounts for approximately 10% of the natural sulfur emissions, volcanic activity for another 10% and biogenic activity for the balance (Aneja *et al.*, 1982).

Because all sulfur species are eventually oxidized to sulfur dioxide and sulfates, the concentration of atmospheric sulfur dioxide gives a general indication of the original total concentration of other sulfur compounds. In a remote, moist equatorial forest in the Ivory Coast, the atmospheric sulfur dioxide concentration was approximately 30 $\mu g/m^3$. Such levels of sulfur dioxide are secondary reaction products from the decomposition of organic litter and humus. The concentration is comparable to that in industrial zones and higher than those reported for rural areas in the USA and Europe. In comparison, marine concentrations of sulfur dioxide in the air near the Ivory Coast were 0.1–0.5 $\mu g/m^3$ (Aneja *et al.*, 1982).

The average concentration of sulfur dioxide in the dry, unpolluted atmosphere is generally in the range of $10^{-5}$–$10^{-4}$ ppm (0.03–0.3 $\mu g/m^3$), with an approximate residence time in the atmosphere of 10 days (Harrison, 1990).

Sulfur dioxide in the atmosphere can contribute to environmental corrosion and can influence the pH of precipitation both by acting as a weak acid itself and by its conversion to the strong acid, sulfuric acid. Sulfur dioxide is a stronger acid than carbon dioxide and at a concentration of only 5 ppb (13 $\mu g/m^3$) in air will, at equilibrium, decrease the pH of rainwater to 4.6 at 15 °C. In many instances, however, low pH is not attained, owing to severe kinetic constraints upon achievement of equilibrium, as is the case with many atmospheric trace gases. Dissolved sulfur dioxide may contribute appreciably to measured total sulfate and acidity in urban rainwater (Harrison, 1990).

The mechanisms by which sulfur dioxide is oxidized to sulfates are important because they determine the rate of formation of sulfate, the influence of the concentration of sulfur

dioxide on the reaction rate and, to some extent, the final form of sulfate. Because atmospheric oxidation of sulfur dioxide proceeds *via* a range of mechanisms, depending upon the concentrations of the responsible oxidants, the oxidation rate is extremely variable with space and time; typically, it is 1–5% per hour (Wilson, 1978; Harrison, 1990).

Several mechanisms have been investigated for the gas-phase oxidation of sulfur dioxide. The major pathway appears to involve the hydroxy radical, and gives rise to sulfur trioxide and ultimately sulfuric acid (Wilson, 1978; Harrison, 1990).

In the presence of water droplets, in the form of fog, clouds, rain or hygroscopic aerosols, sulfur dioxide dissolves, so that aqueous-phase oxidation can give rise to bisulfite and sulfite. These equilibria are sensitive to pH, and $HSO_3^-$ is the predominant species over the pH range of 2–7. The other consequence of these equilibria is that the more acidic the droplet, the greater the degree to which the equilibria move towards gaseous sulfur dioxide and limit the concentrations of dissolved sulfur[IV] species (Harrison, 1990).

Estimated sulfur dioxide emissions in 22 countries in 1980 are shown in Table 4. In the United Kingdom, it was estimated that sulfur dioxide contributes 71% of the total atmospheric acidity, compared to 25% from nitrogen oxides and 4% from hydrochloric acid. In the rest of western Europe, sulfur dioxide is estimated to contribute 68%, nitrogen oxides, 30% and hydrochloric acid, 2% (Lightowlers & Cape, 1988). It should be noted, however, that production quantities or emission inventories are not reliable indicators of atmospheric concentrations for a region or country, due to cross-boundary air transport of sulfur dioxide (US Environmental Protection Agency, 1986).

It was estimated that, in 1985, anthropogenic sources contributed approximately 21 million tonnes of sulfur dioxide in the USA, while emissions in Canada were approximately 4 million tonnes. Contributions from different emission sources in the USA and Canada, respectively, were: electric utilities, 69% and 19%; industrial and manufacturing processes, 13% and 69%; industrial combustion, 11% and 8%; transportation, 4% and 3%; and commercial, residential and other combustion, 3% and 1%. Most emissions of sulfur dioxide come from large utility and industrial sources (Placet, 1990).

Between 1900 and 1970, annual estimated sulfur dioxide emissions in the USA increased from 9 to 28 million tonnes; in 1970–87, emissions decreased by an estimated 28%. Natural sources have been estimated to contribute 1–5% of total US sulfur dioxide emissions; they do not appear to make a significant contribution to the sulfate component of acidic deposition in the USA or Canada (Placet, 1990). Total US sulfur dioxide emissions from electric utilities decreased by 16% between 1973 and 1982, from almost 17 million tonnes to slightly under 14.5 million tonnes. Of the sulfur dioxide emissions from utilities in 1982, more than 93% came from coal-fired utilities and less than 7% from oil-fired utilities (Pechan & Wilson, 1984).

Concentrations of sulfur dioxide in ambient air have been measured in many different locations worldwide. Some examples are given in Table 5. Average concentrations of sulfur dioxide have generally been found to be highest in and around large cities (WHO, 1979).

**Table 4. Sulfur dioxide emissions in 1980**

| Country or region | Emission (thousand tonnes) |
|---|---|
| USSR | 25 500 |
| USA | 23 000 (21 200 in 1984) |
| United Kingdom | 4 680 |
| Italy | 3 800 |
| Germany (western) | 3 580 |
| France | 3 270 |
| Czechoslovakia | 3 100 |
| Yugoslavia | 3 000 |
| Poland | 2 755 |
| Hungary | 1 663 |
| Bulgaria | 1 000 |
| Belgium | 809 |
| Greece | 700 |
| Finland | 600 |
| The Netherlands | 487 |
| Sweden | 450 |
| Austria | 440 |
| Denmark | 399 |
| Romania | 200 |
| Portugal | 149 |
| Norway | 137 |
| Switzerland | 119 |

From US Environmental Protection Agency (1986)

**Table 5. Sulfur dioxide concentrations in ambient air**

| Location | Year | $SO_2$ concentration ($\mu g/m^3$) | Reference |
|---|---|---|---|
| Rural NY, USA | 1984–86 | 3.38–7.44 | Kelly *et al.* (1989) |
| PA, USA | 1983 | 26–31 | Pierson *et al.* (1989) |
| Rural PA, USA | 1984 | 3–131 | Lewin *et al.* (1986) |
| Bermuda | 1982–83 | 0–1.67 | Wolff *et al.* (1986) |
| Coastal DE, USA | 1985 | 13.4 | Hastie *et al.* (1988) |
| Bermuda (mid-ocean) | 1985 | 0.7 | Hastie *et al.* (1988) |
| Northwest Territories, Canada | Nov–Dec 1981 | 0.33–0.69 | Hoff *et al.* (1983) |
| Northwest Territories, Canada | Feb 1982 | 2.3–4.3 | |
| Ontario, Canada | 1982 | 8.4–16.2 | Anlauf *et al.* (1985) |
| Ontario, Canada | 1984 | 0.1–62.8 | Barrie (1988) |
| Near $H_2SO_4$ producer, United Kingdom | 1981 | 0.5–120 | Harrison (1983) |

1.3.2 *Occupational exposure*

The uses of sulfur dioxide described above indicate its widespread occurrence in the work place. It also occurs in the work environment as a result of oxidation (e.g., burning) of sulfuric ores, sulfur-containing fuels and other materials. Table 6 is a list of occupations entailing frequent exposure to sulfur dioxide. The number of workers exposed to sulfur dioxide in the USA in 1974 was estimated to be about 500 000 (US National Institute for Occupational Safety and Health, 1974), which is 0.2% of the total population. The corresponding figure in Finland in 1991 was 10 000 (Kangas, 1991), which is similarly 0.2% of the population. On the basis of these estimates and of the characteristics of the populations and industrial development on the five continents, the global number of exposed workers is probably several million.

**Table 6. Occupations in which there is potential exposure to sulfur dioxide**

| | |
|---|---|
| Beet sugar bleaching | Oil bleaching |
| Blast furnace tending | Oil processing |
| Brewery work | Ore smelting |
| Diesel engine operation | Organic sulfonate manufacture |
| Diesel engine repair | Papermaking |
| Disinfectant manufacture | Petroleum refinery work |
| Disinfection | Preservative manufacture |
| Fire-fighting | Refrigeration |
| Flour bleaching | Straw bleaching |
| Food bleaching | Sugar refining |
| Food protein manufacture | Sulfite manufacture |
| Foundry work | Sulfur dioxide work |
| Fruit bleaching | Sulfuric acid manufacture |
| Fumigant manufacture | Sulfuryl chloride manufacture |
| Fumigation | Tannery work |
| Furnace operation | Textile bleaching |
| Gelatin bleaching | Thermometer manufacture |
| Glass making | Thionyl chloride manufacture |
| Glue bleaching | Wickerware bleaching |
| Grain bleaching | Winemaking |
| Ice making | Wood bleaching |
| Industrial protein manufacture | Wood pulp bleaching |
| Meat preserving | |

From US National Institute for Occupational Safety and Health (1974)

Sulfur dioxide has been measured in many industries, but most of the data come from pulp manufacture by the acidic (sulfite) process (see IARC, 1987) and the manufacture of basic metals. Some data are available from the chemical industry (e.g., sulfuric acid manufacture), oil refining and the petrochemical industry, textile processing, refrigerator production, food preparation, the rubber industry (see IARC, 1987), the glass industry, the brick industry, mineral fibre production (see IARC, 1988), photography, silicon carbide production, power plants and fire fighting. Exposure may occur also in the pharmaceutical

industry, in mining, in water treatment, in chrome-waste treatment and during fumigation and other operations (US National Institute for Occupational Safety and Health, 1974; US National Institute for Occupational Safety and Health/Occupational Safety and Health Administration, 1981), but no data on levels of exposure were available to the Working Group, nor was any information available on occupational exposure to sulfites, bisulfites or metabisulfites.

The methods used to take occupational hygiene measurements have varied over the years. Detector tubes showing the crude concentration of sulfur dioxide in work-room air during measurement, which usually lasts 1–2 min, were used commonly in the 1950s and 1960s. An older method that allows longer sampling is based on liquid absorption of sulfur dioxide and determination by titration. More recently, long-term detector tubes, passive dosimeters and other methods have been used. Most samples have been collected from static sampling points at sites that workers visit occasionally or regularly; some measurements are made during relatively brief episodes when high-peak exposures are expected to occur. Long-term personal sampling has rarely been done because liquid absorption sampling is difficult under these conditions and because the aim of measurements has traditionally been to identify acute risks of exposure to sulfur dioxide. Therefore, many of the reported results reflect mainly short-term exposure and are overestimates of the exposure levels experienced by workers during longer periods (Smith *et al.*, 1978; Broder *et al.*, 1989).

(*a*) *Pulp industry*

Large amounts of sulfur dioxide are used in the preparation of cooking liquor in sulfite pulp mills. Sulfur dioxide gas is reacted with water and calcium carbonate or other carbonate minerals in an absorption tower ('acid' tower), where the cooking liquor containing sulfurous acid, bisulfites and sulfur dioxide is formed. The cooking acid and wood chips are charged into a continuous or batch-type digester where the lignin of the wood dissolves in liquor during cooking under raised temperature and pressure. Pulp is dropped or 'blown' from the digester into covered or uncovered pits to be washed. This operation often releases large amounts of sulfur dioxide into the work-room air; in addition, the raw pulp contains residues of cooking liquor, which contribute to the emissions. Sulfur dioxide is thus a major air contaminant in sulfite pulp mills, and nearly all process workers involved in the preparation of cooking liquor or cooking, washing and other operations are exposed. Work in acid plants is usually continuous, and exposure occurs during the whole work day. In other areas, exposure varies, being relatively low in control rooms (where most time is spent) but high episodically during certain operations and during leakages of the process equipment (Feiner & Marlowe, 1956; Jäppinen, 1987). Sulfur dioxide may also be used in the bleaching departments of pulp and paper plants to neutralize residual chemicals and during final acidification to remove metallic ions from the pulp. Occasionally, mechanically produced pulp is bleached with sodium dithionite, which may release sulfur dioxide (Kangas, 1991). Occupational exposure measurements in the pulp industry are given in Table 7.

Sulfite pulp workers were exposed for shorter or longer periods in the 1950s to measured concentrations of sulfur dioxide well above 26 mg/m$^3$. The scarce data available on daily mean exposures suggest levels of 13 mg/m$^3$ or more; but these data represent only the situation in digesting and pulp storage in one mill at one period of time. Measurements in the

**Table 7. Measurements of sulfur dioxide in the pulp industry**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Five sulfite pulp mills | | | | 1954–67 | Finland | FIOH (1990) |
| Burning of pyrite, acid plants, digesting, blow pits | 156 | 68.1 | ND–560 | | | |
| Sulfite pulp mills | | | | 1972–74 | Finland | Skyttä (1978) |
| Acid departments | 3 | | 7.1–66 | | | |
| Blow pits | 2 | | 12.6–37 | | | |
| Digesting departments | 2 | | 20–34 | | | |
| Filtering | 1 | | < 0.3 | | | |
| Burning of sulfur | 2 | | 6.6–13.6 | | | |
| Power plants | 2 | | 2.4–3.4 | | | |
| Chimney sweeping | 1 | | 17.0 | | | |
| Four sulfite pulp mills | | | | 1978–85 | Finland | Kangas (1991) |
| Acid departments | 31 | | | | | |
| Control rooms | NR | < 1.3 | 0.3–2.6 | | | |
| Other sites | NR | 12.6 | 2.1–86.5 | | | |
| Digesting, washing | 196 | | | | | |
| Control rooms | NR | 2.1 | NR–16.5 | | | |
| Digesters, blow pits | NR | 5.8 | NR–60.3 | | | |
| Evaporation | | | | | | |
| Winter | | | 5.5 | | | |
| Summer | | | 3.9 | | | |
| Bleaching | | < 5.2 | NR | | | |
| Four sulfite pulp mills | | | | NR | USA | Feiner & Marlow (1956) |
| Sulfur burner rooms | 3 | 13.1 | 5.2–31.4 | | | |
| Blow valve floors | 5 | NR | 13.1– > 131 | | | |
| Blow pit floors | 3 | 79 | 52.4–131 | | | |
| Digester loading floors | 4 | NR | 5.2– > 131 | | | |
| Acid plant | 1 | | 52.4 | | | |
| Four sulfite pulp mills | | | | NR | Norway | Skalpe (1964) |
| Acid towers | 6 | 46.3 | 26.2–94.3 | | | |
| Digester plants | | | | | | |
| Top floors | 4 | 17.2 | 3.1–31.4 | | | |
| Middle floors | 2 | 20 | 3.1–36.7 | | | |
| Bottom floors | 5 | 27 | 13.1–49.8 | | | |
| Sulfite pulp mill | | | | 1958–63 | USA | Ferris *et al.* (1967) |
| Digester loading room | 13 | 14.2 | ND–29 | | | |
| Blow pit floor | 2 | | ND | | | |
| Recovery boiler | 2 | 8.5 | 3.9–13 | | | |
| Washer operating floor | 2 | 0.7 | ND–1.31 | | | |
| Evaporators | 1 | | 10.5 | | | |
| Dryers | 1 | | < 0.3 | | | |
| Lower floor | 6 | 9.2 | 2.6–15.7 | | | |
| Pyrite plant | 3 | 1.5 | ND–4.45 | | | |
| Acid room | 5 | 15.1 | Traces–26.2 | | | |
| Bleaching plant | 1 | | 3.7 | | | |
| Blower house | 2 | 85.2 | 83.8–86.5 | | | |

**Table 7 (contd)**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Sulfite pulp mill | | | | NR | Sweden | Stjernberg *et al.* (1984) |
| Digester room and wood pulp storage | | | | | | |
| > 50% of daily means | NR | 14.28 (TWA) | NR | | | |
| Maximal daily means | NR | NR | 114–140 | | | |
| Semichemical pulp mill | NR | < 3 | NR | NR | Finland | Kangas (1991) |
| Sulfate pulp mill | | | | 1963 | USA | Ferris *et al.* (1967) |
| Digester loading room | 1 | 2.6 | | | | |
| Washer operating floor | 3 | 2.0 | ND–4.7 | | | |
| Evaporators | 1 | 3.7 | | | | |
| Other sites | 2 | | ND | | | |
| Mechanical pulp mills | | | | NR | Finland | Kangas (1991) |
| Dosing of dithionite in bleaching departments | 12 | 3.34 | 0.8–39.3 | | | |
| Pulp mill, general plant | | | | 1963 | USA | Ferris *et al.* (1967) |
| Wood chipper room | 1 | | ND | | | |
| Barker drum plant | 1 | | ND | | | |
| Power plant | 1 | | 0.3 | | | |

ND, not detected; NR, not reported

[a]Measurements based on long-term sampling and given as the average concentration over about one working day or longer are indicated as TWA (time-weighted average concentration).

1980s suggested lower levels, especially in control rooms (Table 7). Other agents present in the work environment of sulfite pulp mills include sulfur, ammonia, limestone, sulfurous acid, calcium bisulfite, calcium oxide, carbon monoxide, lignosulfonates, methanol, acetic acid, formic acid, formaldehyde (see IARC, 1987), furaldehyde and cymene (Jäppinen, 1987).

### (*b*) *Metallurgy*

In the basic metal industries, in which steel, copper, nickel, zinc, cobalt, aluminium and other metals are produced, sulfur dioxide occurs when sulfidic ores or sulfuric impurities of the ores are sintered, roasted or melted. Impurities of coal, coke, heavy fuel oils and other materials used in the processes may also contribute to emissions of sulfur dioxide. The exposure level in a specific mill depends on many factors, including the composition of the raw materials, temperatures and other parameters of the processes, intensity of the production, tightness of the furnaces and other process equipment, ventilation and use of respirators. The concentration of sulfur dioxide in the air also varies over time, with the operations carried out and possible leakages of the process equipment. Occupational exposure measurements in metallurgy are given in Table 8.

## Table 8. Measurements of sulfur dioxide in metallurgy

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Copper smelter (furnaces, converters, etc.) | 36 | 17.5 | 1.57–100 | 1951–57 | Finland | FIOH (1990) |
| Copper smelter | | | | NR | Sweden | Lundgren (1954) |
| Roaster | NR | ~ 222 | 66–550 | | | |
| Reverberatory furnace | NR | ~ 152 | 0–500 | | | |
| Converter hall | NR | ~ 24 | 0–52.4 | | | |
| Copper smelter | | | | 1972 | USA | US National Institute for Occupational Health (1974) |
| Reverberatory furnaces | 3 | 16 | 2.6–26.3 | | | |
| Other sites | 8 | < 3 | NR | | | |
| Reverberatory furnaces, chargers floor | 20 | 60 | 4.2–118 | | | |
| Main floor opposite skimming end | 20 | 6.6 | 0.8–23.6 | | | |
| Skimmers' platforms | 21 | 25.1 | 2.1–68 | | | |
| Copper smelter | | | | 1940–74 | USA | Smith *et al.* (1978) |
| Reverberatory furnace | | | | | | |
| Area measurements, 1940–74 | NR | 20.5[b] TWA | 2.0–75.4[b]cTWA | | | |
| Stationary measurements, 1972–74 | 181 | 10.6[b] TWA | 1.1–62.0[c] TWA | | | |
| Personal monitoring, 1973–74 | NR | 3.1[b] TWA | 2.7–3.5[c] TWA | | | |
| Converter | | | | | | |
| Area measurements, 1940–74 | NR | 7.0[b] TWA | 1.2–30.9[c] TWA | | | |
| Stationary measurements, 1972–74 | 198 | 3.7[b] TWA | 1.5–14[c] TWA | | | |
| Personal monitoring, 1973–74 | NR | 2.6[b] TWA | 2.6[c] TWA | | | |
| Reverberatory furnace and converter area | | | | | | |
| Personal monitoring, 1973–74 | | | | | | |
| Supervisors | NR | 2.6 TWA | NR | | | |
| Maintenance workers | NR | 1.7 TWA | NR | | | |
| Anode plant | | | | | | |
| Area measurements, 1959–74 | NR | 3.2[b] TWA | 1.4–4.2[c] TWA | | | |
| Stationary measurements, 1972–74 | 100 | 3.9 TWA | NR–7.3 (SD, 1.8) | | | |
| Personal monitoring, 1973–74 | NR | 2.5 TWA | NR | | | |

**Table 8 (contd)**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | mean | range | | | |
| Copper smelter (contd) | | | | | | Smith *et al.* (1978) (contd) |
| Acid plant | | | | | | |
| Area measurements, 1940–74 | NR | 3.5[b] TWA | 0.4–9.4[c] TWA | | | |
| Stationary measurement, 1972–74 | 53 | 5.4 TWA | NR (SD, 3.6) | | | |
| Personal monitoring, 1973–74 | NR | 4.2 TWA | NR | | | |
| Truck shop | | | | | | |
| Area measurements, 1973–74 | 91 | < 0.2 TWA | NR | | | |
| Unspecified smelter area | | | | | | |
| Personal monitoring, 1973–74 | NR | 2.1 TWA | NR | | | |
| Copper smelter | | | | | USA | Rom *et al.* (1986) |
| Old plant | | 4.5 TWA | 0.5–17.6 TWA | 1976 | | |
| New plant | | 6.0 TWA | 0.5–14.7 TWA | 1982 | | |
| Copper/nickel mill (furnaces, converters) | 23 | 5.9 | 0.3–34.1 | 1968 | Finland | FIOH (1990) |
| Copper/nickel mill | | | | NR | Finland | Kangas (1991) |
| Reverberatory furnaces | | ~ 3 | NR–10.5 | | | |
| Converters | | ~ 3 | NR–7.9 | | | |
| Casting of copper anodes | | < 3 | NR–5.2 | | | |
| Pretreatment of precious metal ores | | < 3 | NR–13.1 | | | |
| Nickel smelter | NR | 1.8 TWA | 0.05–9.4 TWA | 1985 | Canada | Broder *et al.* (1989) |
| Steel mill | | | | 1968 | Finland | FIOH (1990) |
| Blast furnace | 4 | 0.3 | 0.3 | | | |
| Steel smelter | 4 | 1.1 | 0.26–1.8 | | | |
| Rolling mill | | | | | | |
| Crane | 4 | 9.4 | 0.26–19.1 | | | |
| Other sites | 3 | 0.8 | 0.3–1.8 | | | |
| Two steel mills | | | | 1964–68 | United Kingdom | Warner *et al.* (1969) |
| Blast furnace | | | | | | |
| Mill 1 | 51 | 1.8 TWA | NR | | | |
| Mill 2 | 75 | 1.5 TWA | NR | | | |

**Table 8 (contd)**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | mean | range | | | |
| | | | | | | Warner *et al.* (contd) |
| Converters | | | | | | |
| Mill 1 | 97 | 0.30 TWA | NR | | | |
| Mill 2 | 87 | 0.35 TWA | NR | | | |
| Open hearths | | | | | | |
| Mill 1 | 37 | 0.18 TWA | NR | | | |
| Mill 2 | 96 | 0.33 TWA | NR | | | |
| Hot mill | | | | | | |
| Mill 1 | 136 | 0.99 TWA | NR | | | |
| Mill 2 | 93 | 0.21 TWA | NR | | | |
| Cold mill | | | | | | |
| Mill 1 | 217 | 1.50 TWA | NR | | | |
| Mill 2 | 75 | 0.28 TWA | NR | | | |
| Power plant | | | | | | |
| Mill 1 | 26 | 0.84 TWA | NR | | | |
| Mill 2 | 38 | 0.06 TWA | NR | | | |
| Sinter, coke ovens, quarries, lime burning, central electrical workshops, engineering workshops, stores, laboratories, and offices (both mills) | 338 | 0.08 TWA | NR | | | |
| Steel mills | | | | NR | Finland | Kangas (1991) |
| Sintering | NR | NR | 0–26.2 | | | |
| Blast furnace | | | | | | |
| Usually | NR | NR | 1.05–2.6 TWA | | | |
| Occasionally | | NR | 26.2–52.4 | | | |
| Steelmaking, mixers | | | | | | |
| Usually | NR | NR | 0.3–2.4 TWA | | | |
| Occasionally | | NR | 13.1–39.3 | | | |
| Rolling mill 1 | | | | | | |
| Usually | NR | NR | 1.31–2.1 TWA | | | |
| Rolling mills 2 & 3 | 47 | 4.2 | 1.31–42 | | | |

**Table 8 (contd)**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Zinc mill | | | | NR | Finland | Kangas (1991) |
| Roasting department | | | | | | |
| Personal monitoring | NR | ~ 3 TWA | NR | | | |
| Static sampling | NR | ~ 5 TWA | NR | | | |
| Cobalt mill | | | | 1968 | Finand | FIOH (1990) |
| Roasting department | 14 | 12.8 | 0.6–44.5 | | | |
| Dissolving department | 4 | 0.6 | 0.6 | | | |
| Aluminium smelter | | | | 1979–80 | Canada | Chan-Yeung *et al.* (1983) |
| Potroom workers (personal samples) | 121 | 2.0 TWA | SD, 1.5 | | | |
| Aluminium foundry (personal monitoring) | NR | 2.6 TWA | 0.5–7.9 TWA | NR | Sweden | Sorsa *et al.* (1982) |
| Foundries | | | | NR | Finland | Kangas (1991) |
| Steel foundry using furan resins | 14 | 5.8 | < 1.3–2.1 | | | |
| Other steel foundries | 7 | < 3 | NR | | | |
| Light metal foundry | 1 | < 3 | NR | | | |
| Brass/bronze foundry | 7 | 12 | NR | | | |

NR, not reported; ND, not detected; SD, standard deviation

[a]Measurements based on long-term sampling and given as the average concentration over about one working day or longer are indicated as TWA (time-weighted average concentration).

[b]Mean of means

[c]Range of means

In copper smelters, the mean level of sulfur dioxide is often between 2.6 and 26 mg/m$^3$; high concentrations, well above 26 mg/m$^3$, may occur occasionally. In nickel, zinc and aluminium smelters, as well as in steel mills, lower mean concentrations have been measured (2.6 mg/m$^3$ or less) (Table 8). In most cases, sulfur dioxide is only one of the agents present in work-room air. Other agents that may occur simultaneously include iron, nickel, copper, aluminium, cobalt, zinc, lead, cadmium and arsenic and their compounds. Burning of raw materials and fuels also releases carbon monoxide, other combustion gases and particulates into the air. The airborne particulates may contain a complex mixture of polycyclic aromatic hydrocarbons and sometimes silica.

(*c*) *Other miscellaneous industries and operations* (see Table 9)

Sulfur dioxide is used as an intermediate in the production of sulfuric acid (see the monograph on occupational exposure to mists and vapours from sulfuric acid and other strong inorganic acids, p. 47). The mean levels of sulfur dioxide in long-term samples have varied between < 3 and 5 mg/m$^3$; peak exposure to a level of 26 mg/m$^3$ or more may occur occasionally (Table 9). Sulfur dioxide may in some cases be carried over to departments in which sulfuric acid is used as a raw material in the production of other chemicals, such as superphosphate fertilizers.

Workers manufacturing refrigerators in which sulfur dioxide was used as a refrigerant were reported to have experienced frequently brief but high (> 26 mg/m$^3$) exposures in the charging department and during the storage and distribution of sulfur dioxide. No other inhalatory exposure was mentioned (Kehoe *et al.*, 1932).

Crude oil contains varying amounts of sulfur compounds which are partly removed during petroleum refining. Even though oxidative processes are avoided, exposure to sulfur dioxide may occur during recovery of sulfur and in the vicinity of furnaces and flares. A wide variety of other agents including benzene (see IARC, 1987), asbestos (see IARC, 1987), 1,3-butadiene (see monograph, p. 237) and polycyclic aromatic compounds (see IARC, 1983) are present in oil refineries and related petrochemical plants (IARC, 1989).

Silicon carbide is produced by heating petroleum coke and silica sand in an electric furnace. The sulfur impurities of coke form sulfur dioxide during burning. Other agents present include dusts of raw materials (coke, silica (see IARC, 1987)) or products (silicon carbide) and furnace emissions (e.g., carbon monoxide and various hydrocarbons) (Smith *et al.*, 1984).

Vulcanization of rubber containing sulfur compounds as ingredients may also release sulfur dioxide. In addition, the air in the breathing zone of personnel working at vulcanization presses may contain a complex mixture of gases and vapours, including styrene, 1,3-butadiene, carbon monoxide, oil mist, acrylonitrile (see IARC, 1987), aromatic amines, formaldehyde, acrolein (see IARC, 1987), ammonia and methanol (Volkova & Bagdinov, 1969).

Sulfur dioxide, together with numerous other agents, is used in leather tanneries as a biocide in the beamhouses and as a chrome tanning chemical (IARC, 1981).

In the production of glass, porcelain, ceramics, bricks and mineral fibres, as well as in power plants, the source of sulfur dioxide is fuel that is burned in order to melt or dry raw

materials or products. Occasionally, raw materials may also contain sulfur impurities (Kangas, 1991).

Fixing solutions for films usually contain sodium thiosulfate as an ingredient, which, under certain conditions, may release sulfur dioxide (Kangas 1991).

In addition to its limited use in the bleaching of pulp, sulfur dioxide has been used directly to bleach coir (coconut fibres) (Uragoda, 1981). Bisulfites that release sulfur dioxide are also used as finishing agents in the bleaching of wool.

### 1.3.3 *Food and beverages*

In food and beverage industries, sulfur dioxide may be used as a bleaching agent, preservative and sterilization agent. According to the few measurements of the Finnish Institute of Occupational Health (1990), the concentrations during some short-term tasks may be high (Table 9).

Sulfur dioxide and sulfite occur naturally in some foods and are added as preservatives. *Allium* and *Brassica* vegetables contain naturally occurring sulfur dioxide-producing components: The concentration of sulfur dioxide was 17 ppm (mg/kg) in fresh onions, 60 ppm in dried onions, 4 ppm in canned, boiled onions, 121 ppm in dried garlic, 7 ppm in dried leek soup mix and 10–30 ppm in dried onion soup mixes. Non-sulfited soya bean protein contained 20 ppm, sulfited soya bean proteins, 80–120 ppm, cherries, 24 ppm, white wine, 14 ppm, and 'burgundy' wine, 150 ppm of sulfur dioxide (Fazio & Warner, 1990). The concentrations of sulfite (measured by the Monier-Williams method and calculated as $SO_2$) were 173–197 ppm in mashed potatoes, 1977 ppm in dehydrated apricots, < 1–564 ppm in raisins, 1072 ppm in dried peaches, 5.2 ppm in corn syrup, < 1 ppm in frozen shrimps, 26 ppm in canned shrimps, 71 ppm in onion flakes, 126 ppm in garlic powder, 177 ppm in red wine, 138–218 ppm in white wine and 261 ppm in lemon juice (Lawrence & Chadha, 1988).

The total content of sulfur dioxide in wines from 12 countries ranged from 60 to 170 mg/l (Ough, 1986); 33–47 ppm were found in conventional corn syrups and 5–33 ppm in specialty starches (Coker, 1986). The US population has been estimated to consume an average of 10–15 mg/person of sulfiting agents daily. The daily intake varies widely depending on the diet and may be 120 mg or more (Allen, 1985; Emerson & Johnson, 1985).

## 1.4 Regulations and guidelines

Occupational exposure limits for sulfur dioxide in some countries are shown in Table 10.

WHO (1987) recommended ambient air quality guidelines for sulfur dioxide: Short-term exposures should not exceed 500 $\mu g/m^3$, based on a 10-min average, which corresponds to a 1-h maximal value of 350 $\mu g/m^3$. Guideline values for combined exposure to sulfur dioxide and particulate matter in a 24-h period should not exceed 126 $\mu g/m^3$ sulfur dioxide, 125 $\mu g/m^3$ black smoke, 120 $\mu g/m^3$ total suspended particulates and 70 $\mu g/m^3$ particles in the thorax. Guideline values for exposure to combined sulfur dioxide and particulate matter averaged over one year should not exceed 60 $\mu g/m^3$ sulfur dioxide and 60 $\mu g/m^3$ black smoke.

**Table 9. Measurements of sulfur dioxide in miscellaneous industries and operations**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Four sulfuric acid plants (furnaces, dilution, gas purification, tower room, etc.) | 35 | 14.4 | ND–79 | 1951–61 | Finland | FIOH (1990) |
| Sulfuric acid plant | NR | NR | 0.34–12.0 | | China | Meng & Zhang (1990a) |
| Sulfuric acid plant | | | | 1969–84 | Sweden | Englander *et al.* (1988) |
| Stationary samples | NR | 9.1[b] TWA | 2.4–12.4 | | | |
| Breathing zone samples | NR | 3.6[b] TWA | 1.1–2.3 | | | |
| Sulfuric acid plants | | | | NR | Finland | Kangas (1991) |
| Long-term samples | NR | < 3 TWA | NR | | | |
| Occasionally | NR | NR | NR–26.2 | | | |
| Superphosphate plant (conveyors, mixing, etc.) | 6 | 3.7 | 0.3–10.5 | 1951–62 | Finland | FIOH (1990) |
| Refrigerator manufacturing plant | | | | | USA | Kehoe *et al.* (1932) |
| Charging room | 39 | 60 | 18–181 | 1929–30 | | |
| Distribution and storage of sulfur dioxide | 14 | 73 | 29–147 | 1930 | | |
| Oil refinery and special products plant | | | | | Iran | Anderson (1950) |
| Usually | NR | NR | 0–66 | After 1945 | | |
| Occasionally | NR | NR | 157–262 | 1938–45 | | |
| Silicon carbide plant (furnace area) | | | | 1980 | USA | Smith *et al.* (1984) |
| Personal samples | NR | 2.0[c] TWA | < 0.3–3.9[d] TWA | | | |
| Stationary samples | 1 | 18.9 | | | | |
| Vulcanization of butadiene–styrene rubber | | | | NR | USSR | Volkova & Bagdinov (1969) |
| Range | NR | NR | 0.3–19 | | | |
| Usual range | NR | NR | 1–2 | | | |
| Food production | | | | 1952 | Finland | FIOH (1990) |
| Dosing of apple purée to a kettle | 1 | 199 | | | | |
| Cooking of marmalade | 1 | 16.2 | | | | |
| Beverage industry (sterilization of alcohol with sulfur dioxide gas) | 5 | 7.7 | 2.4–17.8 | 1958 | Finland | FIOH (1990) |
| Textile mill (finishing of bleached wool with hydrosulfite) | 1 | 3.7 | | 1954 | Finland | FIOH (1990) |

**Table 9 (contd)**

| Industry, operation | No. of samples | Concentration of sulfur dioxide ($mg/m^3$)[a] | | Year of measurement | Country | Reference |
|---|---|---|---|---|---|---|
| | | Mean | Range | | | |
| Power plants | | | | | | |
| Boiler rooms | NR | < 1.3 | NR | NR | Finland | Kangas (1991) |
| Boiler room, leakage | NR | NR | 6.6–26.2 | | | |
| Flame cutting of oil kettles | 4 | NR | 21–65.5 | | | |
| Close to diesel engines | 4 | < 2.6 | NR | NR | Finland | Kangas (1991) |
| Nine photographic laboratories | 29 | < 2.6 | NR | NR | Finland | Kangas (1991) |
| Glass, porcelain and ceramic products plants, close to furnaces | 13 | < 2.6 | NR–44 | NR | Finland | Kangas (1991) |
| Brick manufacturing plants, burning of bricks | 27 | < 2.6 | NR–10 | NR | Finland | Kangas (1991) |
| Mineral fibre plants, close to furnaces | 9 | < 2.6 | NR | NR | Finland | Kangas (1991) |
| Paper mill, bleaching | 6 | 0.4 | ND–1.8 | 1963 | Finland | FIOH (1990) |
| Paper mill | | | | NR | Finland | IARC (1981) |
| Beating/refining | NR | 0.2 | | | | |
| Wet end of paper machine | NR | 0.01 | | | | |
| Two paper mills, recovery plant | | | | | India | Gautam *et al.* (1979) |
| | 2 | 2.4 | 1.1–3.6 | 1971 | | |
| | 3 | 0.5 | Trace–0.8 | 1976–77 | | |
| Fire fighting at 14 sites during fires | 26 | 6.0 | 0–109 | 1986 | USA | Brandt-Rauf *et al.* (1988) |

ND, not detected; NR, not reported

[a]Measurements based on long-term sampling and given as the average concentration over about one working day or longer are indicated as TWA (time-weighted average concentration).

[b]Median

[c]Mean of means

[d]Range of means

**Table 10. Occupational exposure limits and guidelines for sulfur dioxide**

| Country | Year | Concentration ($mg/m^3$) | Interpretation[a] |
|---|---|---|---|
| Australia | 1990 | 5 | TWA |
| | | 10 | STEL |
| Austria | 1982 | 5 | TWA |
| Belgium | 1990 | 5.2 | TWA |
| | | 13 | STEL |
| Brazil | 1978 | 10 | TWA |
| Bulgaria | 1984 | 10 | TWA |
| Chile | 1983 | 4 | TWA |
| China | 1981 | 13 | TWA |
| Czechoslovakia | 1990 | 5 | TWA |
| | | 10 | STEL |
| Denmark | 1990 | 5 | TWA |
| Finland | 1990 | 5 | TWA |
| | | 13 | STEL |
| France | 1990 | 5 | TWA |
| | | 10 | STEL |
| Germany | 1990 | 5[b] | TWA |
| Hungary | 1990 | 3[b] | TWA |
| | | 6[b] | STEL |
| India | 1983 | 13 | TWA |
| Indonesia | 1978 | 13 | TWA |
| Japan | 1983 | 13 | TWA |
| Mexico | 1983 | 13 | TWA |
| Netherlands | 1986 | 13 | TWA |
| Norway | 1990 | 5 | TWA |
| Poland | 1984 | 10 | TWA |
| Republic of Korea | 1983 | 5 | TWA |
| | | 10 | STEL |
| Romania | 1975 | 10 | TWA |
| | | 15 | Ceiling |
| Sweden | 1990 | 5 | TWA |
| | | 13 | Ceiling |
| Switzerland | 1990 | 5 | TWA |
| | | 10 | STEL |
| United Kingdom | 1990 | 5 | TWA |
| | | 13 | STEL |
| USA | | | |
| ACGIH | 1990 | 5.2 | TWA |
| | | 13 | STEL |
| OSHA | 1989 | 5 | TWA |
| | | 10 | STEL |
| USSR | 1990 | 10[b] | STEL |

**Table 10 (contd)**

| Country | Year | Concentration ($mg/m^3$) | Interpretation[a] |
|---|---|---|---|
| Venezuela | 1978 | 13 | TWA |
| | | 13 | Ceiling |
| Yugoslavia | 1971 | 10 | TWA |

From Arbeidsinspectie (1986); Cook (1987); US Occupational Safety and Health Administration (OSHA) (1989); American Conference of Governmental Industrial Hygienists (ACGIH) (1990); Direktoratet for Arbeidstilsynet (1990); International Labour Office (1991)

[a]TWA, 8-h time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

[b]Skin notation

The Commission of the European Communities (1980) established limit values for sulfur dioxide (to become law on 1 April 1993) and for associated suspended particles, as follows. The annual median value should be no more than 80 $\mu g/m^3$ in the presence of $> 40$ $\mu g/m^3$ suspended particulates, or 120 $\mu g/m^3$ in association with $\geq 40$ $\mu g/m^3$ particulates. The median value in winter (1 October–31 March) should not exceed 130 $\mu g/m^3$ with $> 60$ $\mu g/m^3$ particulates and 180 $\mu g/m^3$ with $\leq 60$ $\mu g/m^3$ particulates. The 98th percentile of all daily mean values taken throughout the year should not exceed 250 $\mu g/m^3$ sulfur dioxide in the presence of $> 150$ $\mu g/m^3$ particulates and no more than 350 $\mu g/m^3$ with $\leq 150$ $\mu g/m^3$ particulates.

The US national primary air quality standard for sulfur dioxide, set by the US Environmental Protection Agency, is 80 $\mu g/m^3$ (0.03 ppm) calculated as an annual arithmetic mean and 365 $\mu g/m^3$ (0.14 ppm) computed as a maximal 24-h concentration that is not to be exceeded more than once per year. Secondary standards, which protect the public from any known or anticipated adverse effects, allow 0.02 ppm (0.05 $mg/m^3$) as an annual arithmetic mean, 0.10 ppm (0.26 $mg/m^3$) as a 24-h maximum not to be exceeded more than once per year and 0.50 ppm (1.3 $mg/m^3$) as a 3-h maximum not to be exceeded more than once per year (Weil, 1983).

The US Environmental Protection Agency (1989) established sulfur dioxide emission standards for primary copper smelters, primary zinc smelters and primary lead smelters in which discharge of any gases that contain sulfur dioxide in excess of 0.065% by volume is prohibited. Sulfur dioxide emission standards also have been established for sulfuric acid plants: discharge into the atmosphere of gases that contain sulfur dioxide in excess of 2 kg/tonne of acid produced is prohibited, the production being expressed as 100% $H_2SO_4$. Stationary gas turbines are prohibited from discharging into the atmosphere gases that contain sulfur dioxide in excess of 0.015% by volume, at 15% oxygen and on a dry basis.

The standard for emissions of sulfur dioxide from municipal refuse-fired plants in the Federal Republic of Germany in 1981 was 34 ppm (90 $mg/m^3$) (Skizim, 1982).

The US Food and Drug Administration (1989) established that sulfur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite and potassium metabisulfite are generally

recognized as safe as chemical preservatives for foods, except that they must not be used in meats or in food recognized as a source of vitamin $B_1$, or on raw or fresh fruits and vegetables.

## 2. Studies of Cancer in Humans

Exposure to sulfur dioxide occurs in different occupational environments (see Section 1); however, the epidemiological studies that have specifically addressed cancer risks in relation to exposure to sulfur dioxide have been conducted primarily in smelter workers and in pulp and paper workers. These occupational groups are treated separately in view of the substantial differences in the exposure environments.

No epidemiological study was found on cancer risks in relation to exposure to sulfites, bisulfites or metabisulfites.

### 2.1 Smelting of nonferrous metals

A series of studies of both cohort and case–control design addressed cancer risks among workers at the Anaconda copper smelter in Montana, USA (Lubin *et al.*, 1981; Welch *et al.*, 1982; Lee-Feldstein, 1983). The studies focused mainly on exposure to arsenic (see IARC, 1987). Mortality was followed in 1938–77 for a cohort of 8045 white men who had been employed for 12 months or more before 1956 (Lee-Feldstein, 1983). Work areas were rated on a relative scale with respect to the level of sulfur dioxide (and arsenic). A total of 3522 workers died during the follow-up period, and 816 (10.1%) were lost. A total of 302 respiratory cancer deaths were seen, corresponding to standardized mortality ratios (SMR) of 2.09 [95% confidence interval (CI), 1.59–2.58] for men in the light exposure category for sulfur dioxide, 2.97 [2.00–3.95] for medium exposure and 3.17 [2.07–4.27] for heavy sulfur dioxide exposure in comparison with regional rates. The highest risks were seen in workers with high or medium exposure to both arsenic and sulfur dioxide, suggesting a positive interaction between the two exposures. Multivariate modelling (Lubin *et al.*, 1981) suggested that respiratory cancer risks associated with work in the areas of medium and heavy sulfur dioxide exposure were not significantly increased when medium or heavy exposure to arsenic was controlled for. The authors noted that it was difficult to separate the effects of the two exposures since they often occurred together.

A follow-up of mortality through 1977 of a sample of 1800 men in the same cohort also included information on smoking habits for 81.6% of the sample (Welch *et al.*, 1982). Telephone interviews or mailed questionnaires were used to obtain information on smoking from cases or next-of-kin. Although results were not reported on smoking habits in relation to sulfur dioxide exposure, few differences in smoking habits were reported between men in the different arsenic exposure categories; since arsenic and sulfur dioxide exposures were correlated, the finding suggests that smoking was not a confounder in relation to sulfur dioxide.

Another US copper smelter that has been investigated in many epidemiological studies was located in Tacoma, WA (USA). The studies also focused primarily on arsenic exposure; only one of them included data on risks in relation to exposure to sulfur dioxide (Enterline & Marsh, 1982). The mortality of 2802 men who had worked for one year or more at the smelter

during the period 1940–64 was followed through to 1976. Only 1.8% could not be traced, and death certificates were obtained for 95.6% of deceased individuals. An overall SMR of 1.98 [95% CI, 1.60–2.36] was observed for cancer of the respiratory system in comparison with Washington State rates; no significant excess risk was seen for cancers at other sites. Two departments at the smelter (the cottrell area and the arsenic department) had high (> 0.5 $mg/m^3$) arsenic levels during 1938–47 but differed in sulfur dioxide concentrations. The levels of sulfur dioxide were reported to be 5–20 ppm (13–52 $mg/m^3$) in the cottrell area, where dust is eliminated by electrical precipitation, but very low in the arsenic department. For workers who had ever worked in the cottrell area, the SMR was 3.51 [95% CI, 1.75–6.27]; and for those who had ever worked in the arsenic department (and never at the cottrell), the SMR was 3.17 [1.97–4.36], suggesting that sulfur dioxide exposure did not play an important role in the respiratory cancer excess at the smelter.

A third copper smelter in the USA that has been investigated was located in Salt Lake City, Utah (Rencher *et al.*, 1977). An attempt was made to include all deaths among the smelter workers occurring in 1959–69. [No detailed description of the cohort studied was given, and consequently the completeness of follow-up cannot be assessed.] Lung cancer constituted 7.0% of the deaths among the smelter workers compared with 2.7% for the state. A cumulative exposure index was computed for arsenic, sulfur dioxide and some other agents for each deceased worker from work histories and from estimated levels in different work areas. The workers who died of lung cancer had significantly higher indices of exposure to arsenic, lead and sulfur dioxide than workers who died of non-respiratory causes.

A combined analysis was performed on the mortality experience in 1949–80 of a cohort of 6078 white male workers who had been employed for at least three years between 1946 and 1976 at one or more of eight US copper smelters, including the Utah smelter described above (Enterline *et al.*, 1987). Vital status was unknown for 1.6% at the end of follow-up; death certificates could be located for 94.1% of those known to be dead. Workers were assigned into different exposure categories on the basis of estimated levels of arsenic, sulfur dioxide and some other agents by job and year. Smoking histories were obtained through telephone interviews with the study subjects or next-of-kin for 76% of the lung cancer cases and for 85% of a 5% sample of the remaining members of the cohort. The relative risk for lung cancer increased with duration of exposure to sulfur dioxide at peak levels of 12 ppm (32 $mg/m^3$) and higher ($p$ for trend, 0.03), without adjusting for exposure to arsenic and smoking. Exposure to sulfur dioxide at a level of more than 6 ppm (16 $mg/m^3$) did not, however, have a significant, independent effect in a logistic regression model that included age, arsenic, smoking and interaction terms.

A series of epidemiological studies was also performed at a smelter in northern Sweden which produces copper and other non-ferrous metals, mainly from arsenic-rich sulfide ores (Pershagen *et al.*, 1977). Although increased rates were reported of cancers at a few sites, only lung cancer has been investigated in relation to sulfur dioxide exposure. A case–control study nested in a cohort of 3958 smelter workers, who had been employed for at least three months in 1928–66 and who were followed through to 1977, included 76 lung cancer cases and 152 age-matched, deceased controls (Pershagen *et al.*, 1981). Assessment of exposure to arsenic and sulfur dioxide was based on estimations of levels in different departments; workers in the roaster department were most heavily exposed to both compounds. Few measurements were

made, but, in 1954, sulfur dioxide concentrations of 15–300 mg/m$^3$ were reported in the departments with the highest levels. Information on smoking was obtained from next-of-kin of all study subjects. The relative risks for lung cancer were 6.5 for smokers in the 'high sulfur dioxide' departments, 14.7 for those in 'high arsenic' departments and 22.0 for workers in roaster departments, compared to nonsmoking workers with lowest exposure, indicating that arsenic is more important than sulfur dioxide in determining excess risk. [The Working Group noted that confidence intervals could not be estimated from the data presented.]

In a follow-up of mortality in the same cohort through 1981, 106 cases of lung cancer were identified; all but 0.4% of the workers were traced (Järup *et al.*, 1989). Cumulative exposures to arsenic and sulfur dioxide were calculated on the basis of the work histories of each worker, and exposure levels during different time periods were estimated. The overall SMR for lung cancer was 3.72 (95% CI, 3.04–4.50). A positive dose–response relationship was found between cumulative exposure to arsenic and lung cancer risk ($p < 0.001$); no dose–response relationship was found for exposure to sulfur dioxide.

Lung cancer mortality was followed through 1982 in a cohort of 4393 men who had been employed for a minimum of one year in 1943–70 at a zinc–lead–cadmium smelter in the United Kingdom (Ades & Kazantzis, 1988). Only 0.7% of the cohort could not be traced; 182 men had died of lung cancer. Exposure to cadmium, zinc, sulfur dioxide, arsenic, lead and dust was assessed from job histories and from estimates of air concentrations in different work places, partly based on measurements and biological monitoring. The overall SMR for lung cancer was 1.25 (95% CI, 1.07–1.44) relative to regional rates. Although there were suggestions of increased relative risks with cumulative exposure for each of the factors under study, only the risks associated with exposures to arsenic and lead reached statistical significance ($p < 0.025$ and $p < 0.01$, respectively). The indices of cumulative exposure to sulfur dioxide, arsenic and lead were highly correlated.

### 2.2 Pulp and paper manufacture

Cancer risks in the pulp and paper industry have been evaluated previously (IARC, 1981, 1987). Here, only studies that specifically addressed exposures to sulfur dioxide or the sulfite process are addressed.

In a proportionate mortality analysis, the recorded causes of death of 2113 US and Canadian members of the Pulp, Sulfite and Paper Mill Workers' Union who died during 1935–64 were compared with corresponding US mortality rates (Milham & Demers, 1984). The proportionate mortality ratio (PMR) was increased ($p < 0.05$) for cancer of the stomach (PMR, 2.18; 33 deaths) and for lymphosarcoma and reticulum-cell sarcoma (PMR, 2.69; 7 deaths) in sulfite workers, when those who had also worked in the sulfate process were excluded. The PMR for lung cancer was 0.85 (21 deaths; $p > 0.05$).

Mortality in a cohort of 3572 men who had been employed for at least one year between 1945 and 1955 in one or more of five US pulp and paper mills in the states of Washington, Oregon and California was followed until 1977 (Robinson *et al.*, 1986). Death certificates could not be retrieved for 1% of the deceased, and 1% was lost to follow-up. In a subcohort of 1779 sulfite process workers, cancer mortality was less frequent (SMR, 0.79; 90% CI, 0.66–0.95; 88 deaths) in comparison with national rates. For stomach cancer, lung cancer and lymphosarcoma and reticulosarcoma, the SMRs were 1.49 (90% CI, 0.83–2.46; 11 deaths),

0.81 (0.57–1.13; 26 deaths) and 1.33 (0.45–3.05; 4 deaths), respectively. After a 20-year latency, the SMR for stomach cancer was 1.76 [0.81–3.35], based on nine deaths.

Mortality was analysed until 1985 among 883 white men who had participated in a medical survey in 1961 and had worked for at least one year for a paper company in New Hampshire, USA (Henneberger *et al.*, 1989). One percent was lost to follow-up, and 2.5% of the death certificates could not be traced. A total of 36 deaths from cancer were observed among 297 sulfite pulp mill workers, which corresponds to an SMR of 1.20 (95% CI, 0.84–1.66) in relation to national rates. The SMR for lung cancer was 1.13 (0.56–2.02, 11 deaths); one case each occurred of stomach cancer and leukaemia, compared with 1.4 and 1.1 expected, respectively; for cancer of the pancreas, the SMR was 3.05 (0.98–7.12, 5 deaths), and all five cases occurred after a latency of at least 20 years (mean latency, 51 years). The SMR for lung cancer was higher among workers with at least 20 years of latency and at least 20 years of duration of employment (SMR, 1.86 [95% CI, 0.74–3.80], 7 cases).

Cancer incidence was studied through 1980 in a cohort of 3545 workers who had been employed for at least one year in 1945–61 in one of three pulp and paper mills in south-eastern Finland (Jäppinen *et al.*, 1987). Only 0.4% were lost to follow-up. Among the 248 men who had worked in the sulfite mill, there were 33 cases of cancer, corresponding to a standardized incidence ratio of 1.05 (95% CI, 0.72–1.47) compared with regional rates. The ratios were 1.29 (0.47–2.81; 6 cases) for cancer of the stomach and 0.90 (0.41–1.71; 9 cases) for cancer of the lung. One case of leukaemia was observed, with 0.7 expected.

### 2.3 Other industries

Occupational risk factors for cancers of the brain, kidney and lung were investigated in a series of case–control studies in a region of the USA where a large chemical plant was located (Bond *et al.*, 1983, 1985, 1986). Industrial hygienists established chemical and physical agent-specific exposure profiles for the subjects employed at the plant on the basis of work histories and job functions. The plant produced many products, however, and the exposure environment included sulfur dioxide, chlorine, hydrogen chloride, carbon tetrachloride and heat.

In a study in four Texas counties in 1949–79, 28 former employees of the plant who had died of primary intracranial neoplasms were identified (Bond *et al.*, 1983). One control group was matched on age and year of death and included 110 former employees who had died of causes other than cancer; the other control group consisted of 111 men matched on year and duration of employment, selected from a 5% random sample of people who had ever been employed at the plant. Odds ratios of 2.02 (90% CI, 0.99–4.11) and 1.19 (0.58–2.43) were reported for exposure to sulfur dioxide (11 cases) in relation to the first and second control groups, respectively. When the analysis was restricted to the 16 glioblastomas, an odds ratio of 1.40 (0.6–3.4; 7 cases) was seen in comparison with the second control group. No significant increase in risk was observed in subgroups with more than 20 years of service or first employment before 1945.

In another study, 26 former employees of the plant were identified who had died of renal cancer in 1958–80 in five nearby counties (Bond *et al.*, 1985). Two matched control groups, selected according to the same criteria as in the previous study, comprised 92 and 98 men who had worked at the plant. The odds ratios for exposure to sulfur dioxide (five cases) were

0.31 (90% CI, 0.13–0.73) and 0.31 (0.13–0.76) in relation to the first and second control groups, respectively. The deficit was closely linked to a significantly decreased risk among workers who had been engaged in magnesium production and who were classified as having been exposed to sulfur dioxide.

A case–control study nested in a cohort of 19 608 men who had worked for at least one year between 1940 and 1980 at the same plant covered 308 who had died of lung cancer and an equal number of controls in each of two control groups of dead workers, matched on race, year of birth and year of hire (Bond *et al.*, 1986). Controls in the second group had each survived at least as long as the corresponding case. Information on potential confounding factors, including smoking, was obtained by telephone interviews with the study subjects or next-of-kin. Interviews were completed for 81.9% of 896 subjects—mostly with next-of-kin for cases and for the first control group and with the subjects themselves for the second control group. Workers who had been exposed to sulfur dioxide had an odds ratio of 1.40 (95% CI, 1.04–1.89; 126 cases) when the two control groups were considered together. When allowing for 15 years of latency, the odds ratio was 1.27 (95% CI, 0.93–1.73), based on 108 cases. In a multivariate analysis, with adjustment for cigarette use, vitamin A consumption, hot working conditions and socioeconomic status, the odds ratios for lung cancer were 0.48 (95% CI, 0.15–1.54) for low exposure to sulfur dioxide, 1.69 (0.88–3.22) for moderate exposure and 1.45 (0.67–3.17) for high exposure, as compared to the first control group ($p$ for trend, 0.003). No trend was found in comparison with the second control group ($p$ for trend, 0.32). Similar odds ratios were noted in relation to duration of exposure to heat.

A population-based case–control study carried out in Montréal (Siemiatycki, 1991), described in detail on p. 95, also examined exposure to sulfur dioxide (15% of the population). The only notable finding was an odds ratio of 1.5 for stomach cancer, restricted to the French-Canadian subset of the study population (30 exposed cases; 90% CI, 1.0–2.1), which increased to 3.5 with substantial exposure (4 cases; 90% CI, 1.3–9.2). Corresponding odds ratios for the whole population were 1.3 (90% CI, 0.9–1.7) for any exposure and 2.2 (0.9–5.6) for substantial exposure, based on 42 cases. The odds ratio for lung cancer was 1.0 (138 exposed cases; 90% CI, 0.8–1.3) for any exposure and 0.7 (8 cases; 90% CI, 0.3–1.6) for substantial exposure.

## 3. Studies of Cancer in Animals

### 3.1 Inhalation

*Mouse*: An experimental group of 35 male and 30 female LX mice and a control group of 41 males and 39 females, three months old, were exposed to 0 or 500 ppm [1310 mg/m$^3$] **sulfur dioxide** [purity unspecified] for 5 min per day on five days a week for life. Only mice that survived for 300 days or more were considered in the results [average survival time not shown], since lung tumours were not seen before that time. Female mice exposed to sulfur dioxide had an increased incidence of lung tumours: 13/30 adenomas and carcinomas *versus* 5/30 in controls, [$p$ = 0.02; Peto's incidental test]; 4/30 lung carcinomas *versus* none in the controls. The incidence of lung neoplasias was higher in treated males (15/28 *versus* 11/35 in controls), but the difference was not significant; lung carcinomas occurred with equal frequency in treated and control males (2/28 and 2/35) (Peacock & Spence, 1967).

### 3.2 Oral administration

#### 3.2.1 *Mouse*

Three groups of 50 male and 50 female ICR/ICL mice, aged eight weeks at the start of the experiment, were given 0, 1 or 2% **potassium metabisulfite** [purity unspecified] in distilled water as drinking-water *ad libitum* for 104 weeks. At least 94% of the mice in each group survived beyond 26 weeks. The incidences of various types of tumours were similar in the control and experimental groups: total tumour incidences were 14/99, 14/96 and 16/94 in the three groups, respectively (Tanaka *et al.*, 1979). [The Working Group noted that data on survival were incomplete.]

#### 3.2.2 *Rat*

Six groups of 20 male and 20 female weanling Wistar rats were fed 0, 0.125, 0.25, 0.5, 1 or 2% **sodium metabisulfite** (95–99% pure [impurities unspecified]) in the diet for 104 weeks. More than 50% of controls and about 75% of each experimental group survived until the termination of experiment [average survival time unspecified]. Groups of five females and five males of the $F_1$ generation were fed the same concentrations in the diet for 104 weeks. Data on tumour incidence are given for the $F_0$ and $F_1$ generations combined. The incidences of thyroid and pituitary tumours were increased in treated males, but no dose–response relationship was observed. The authors reported that the incidences of these tumours in the concurrent controls were exceptionally low compared to those in historical controls and that the incidences found in treated animals represent the numbers normally found in this strain of rat (Til *et al.*, 1972).

### 3.3 Administration with known carcinogens

The Working Group was aware of studies in mice and hamsters involving combined administration of a carcinogen and mixtures of sulfur dioxide and nitrogen dioxide (Pott & Stöber, 1983; Heinrich *et al.*, 1989). These were not included in this monograph because the effect of sulfur dioxide alone could not be evaluated.

#### 3.3.1 *Rat*

Six groups of rats [age, sex and strain unspecified] were exposed on five days per week for life to: Group 1, clean air (15 animals); Group 2, 10 ppm [26 mg/m$^3$] **sulfur dioxide** for 6 h per day (15 animals); Group 3, 10 mg/m$^3$ benzo[*a*]pyrene for 1 h per day (30 animals); Group 4, 10 ppm sulfur dioxide for 6 h per day plus 10 mg/m$^3$ benzo[*a*]pyrene for 1 h per day (30 animals); Group 5, 4 ppm [10.5 mg/m$^3$] sulfur dioxide plus 10 mg/m$^3$ benzo[*a*]pyrene for 1 h per day (45 animals); and Group 6, 10 ppm sulfur dioxide for 6 h per day followed by 4 ppm sulfur dioxide plus 10 mg/m$^3$ benzo[*a*]pyrene for 1 h per day (46 animals) [experimental time and survival not specified]. The following incidences of lung carcinomas were observed: Group 1, 0/15; Group 2, 0/15; Group 3, 1/30; Group 4, 2/30; Group 5, 4/45; and Group 6, 9/46 [no statistical analysis reported] (Laskin *et al.*, 1976). [The Working Group noted the incomplete reporting of the experiment, in particular, the lack of data on survival and the lack of clarity concerning hyperplastic changes in both control and treated animals.]

Seven groups of male Sprague-Dawley CD rats, aged nine weeks at the start of the experiment, were exposed by: Group 1, inhalation to clean air (46 animals); Group 2, inhala-

tion to clean air plus intratracheal instillation of gelatin vehicle (0.05%) once weekly in weeks 4–19 (26 animals); Group 3, inhalation to 10 ppm [26 mg/m$^3$] **sulfur dioxide** for 6 h per day on five days a week for 21 weeks (20 animals); Group 4, inhalation to 30 ppm [79 mg/m$^3$] sulfur dioxide (20 animals) for 6 h per day on five days a week for 21 weeks; Group 5, inhalation to clean air plus intratracheal instillation of 1 mg benzo[*a*]pyrene once weekly in weeks 4–19 (74 animals); Group 6, inhalation to 10 ppm sulfur dioxide for 6 h per day on five days per week for 21 weeks plus 1 mg benzo[*a*]pyrene once weekly in weeks 4–19 (74 animals); and Group 7, inhalation to 30 ppm sulfur dioxide for 6 h per day on five days per week for 21 weeks plus intratracheal instillation of 1 mg benzo[*a*]pyrene once weekly in weeks 4–19 (74 animals). The experiment was terminated at 105 weeks [mean survival time unspecified]. The three groups treated with benz[*a*]pyrene had lower survival than other groups and a high incidence of squamous-cell carcinoma of the lung that was not enhanced by inhalation of sulfur dioxide: the incidences of squamous-cell carcinoma in groups 1–7 were 0/43, 0/26, 0/20, 0/18, 65/72, 65/72 and 69/74. Sulfur dioxide did not influence time to appearance of tumours. The authors noted that the high incidence of tumours in the group given benzo[*a*]pyrene alone precluded detection of a significant enhancing effect of sulfur dioxide on the incidence of benzo[*a*]pyrene-induced lung tumours (Gunnison *et al.*, 1988).

Groups of male Wistar rats, seven weeks of age, were treated as follows: Group 1 (10 animals) served as untreated controls; Group 2 (30 animals) was given *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in the drinking-water at 100 mg/l *ad libitum* for eight weeks; Group 3 (10 animals) was given tap water for eight weeks followed by 1% **potassium metabisulfite** in the drinking-water for 32 weeks; Group 4 (19 animals) was treated as Group 2 but was then given 1% potassium metabisulfite in the drinking-water for 32 weeks. All surviving animals were killed at 40 weeks [survival unspecified]. The incidence of adenocarcinoma of the gastric pylorus was 0/10, 1/30, 0/10 and 5/19 ($p < 0.05$, Fisher test) in the four groups, respectively (Takahashi *et al.*, 1986).

### 3.3.2 *Hamster*

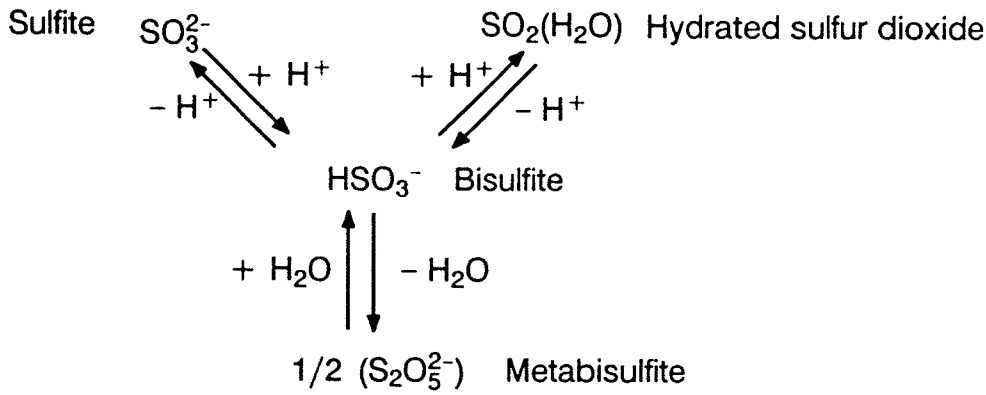
In a study reported as a short communication, four groups of male Syrian golden hamsters [number of animals and age at start unspecified] were exposed for 104 weeks by nose inhalation only to: Group 1, 2 mg/m$^3$ benzo[*a*]pyrene; Group 2, 2 mg/m$^3$ benzo[*a*]-pyrene plus 172 ppm [450 mg/m$^3$] **sulfur dioxide**; Group 3, 10 mg/m$^3$ benzo[*a*]pyrene; Group 4, 10 mg/m$^3$ benzo[*a*]pyrene plus 172 ppm sulfur dioxide [dosing schedule unspecified]. The mean survival times were: Group 1, 60 weeks; Group 2, 60 weeks; Group 3, 57 weeks; and Group 4, 45 weeks [no data on controls were given]. The authors stated, without presenting numerical data, that exposure to benzo[*a*]pyrene alone induced a few neoplastic alterations and that the addition of sulfur dioxide resulted in more tumours in the upper respiratory tract within a shorter time (Pauluhn *et al.*, 1985). [The Working Group noted the inadequate reporting.]

## 4. Other Relevant Data

### 4.1 Absorption, distribution, metabolism and excretion

Sulfur dioxide in aqueous solution is rapidly hydrated to sulfurous acid, which itself quickly dissociates to bisulfite and sulfite (Figure 1). The species that dominates among these rapidly interconvertible hydration products depends primarily upon pH but also on ionic strength and temperature (Gunnison & Jacobsen, 1987). At pH close to 7, the ratio of $HSO_3^-$ to $SO_2$ concentrations is greater than 100 000:1. Therefore, sulfur dioxide is transported through aqueous systems at neutral pH almost totally in its hydrated form. Because of this rapid hydration, the interactions of sulfur dioxide with biological molecules in an aqueous medium are probably those of sulfite and bisulfite. Two alternative reaction pathways have been suggested, however, on the basis of observations *in vitro*: Eickenroht *et al.* (1975) suggested that sulfur dioxide itself acts directly as an electron receptor; Mottley *et al.* (1985) demonstrated anaerobic production of the $SO_2$ anion radical from sulfite by rat liver microsomes.

**Figure 1. Interconversion of oxysulfur[IV] compounds**




From Fazio & Warner (1990)

Except where specified to the contrary, the term 'sulfite' is used below to indicate the various rapidly interconvertible hydration products of sulfur dioxide.

#### 4.1.1 *Humans*

Sulfur dioxide is a highly water-soluble gas and is thus rapidly absorbed in the moist upper respiratory tract. With quiet breathing through the nose, negligible quantities of sulfur dioxide reach the nasopharynx; deeper airway penetration can occur with oral inhalation, particularly when maximal deep breaths are taken, as in exercise. The fractional penetration increases at higher sulfur dioxide concentrations (Kleinman, 1984). Sulfur dioxide can also penetrate the airways by absorption on inhalable particulates, and especially deliquescent materials.

Plasma levels of *S*-sulfonates in humans exposed continuously under controlled conditions to sulfur dioxide at 0.3–6.0 ppm [0.8–15.7 mg/m$^3$] for up to 120 h were correlated

positively with atmospheric levels of sulfur dioxide (Gunnison & Palmes, 1974). Human sulfite oxidase may have a protective effect in that it prevents sulfite from reacting with biological molecules by oxidizing it to sulfate (Gunnison & Jacobsen, 1987).

#### 4.1.2 *Experimental systems*

The covalent reactions of sulfur dioxide and sulfite with cellular protein and non-protein sulfhydryl compounds have been reviewed (Menzel *et al.*, 1986). A central reaction is addition across disulfide bonds to form *S*-sulfonates (Gunnison & Benton, 1971). Sulfite can react with DNA (see Section 4.4.2).

Diffusion of sulfur dioxide, its solubility in aqueous solution and its irreversible reaction in tissue all appear to be linear processes in excised porcine trachea (Ben-Jebria *et al.*, 1990).

When dogs inhaled $^{35}$S-sulfur dioxide through the nose and mouth, little of the label reached the lower airways; when the labelled sulfur dioxide was inhaled through a tracheostomy, however, it was absorbed rapidly through the lungs and trachea and radiolabel was found in all organs (Balchum *et al.*, 1960). Inhaled $^{35}$S-sulfur dioxide was excreted primarily in the urine as sulfate by dogs (Yokoyama *et al.*, 1971).

Once absorbed, sulfur dioxide appears to be metabolized rapidly to sulfate by the widely distributed enzyme sulfite oxidase. After it has been oxidized to sulfate, it becomes part of the large sulfate pool within the body. Tejnorová (1978) reported relatively large differences in sulfite oxidase activity among five species: rats had the highest levels and rabbits the lowest. An inverse correlation was shown between enzyme activity and sensitivity to bisulfite toxicity. These results reflect species differences in rate of *S*-sulfonate formation (Gunnison & Palmes, 1978).

Ingested radiolabelled sulfite was reported to be excreted almost entirely in the urine of monkeys within 24 h, but no free sulfite was detected in rat urine. Seven days after dosing, mice retained < 1% and rats, 2% of the radiolabel (Gibson & Strong, 1973). In rabbits, sulfite was cleared predominantly by metabolism to sulfate (Gunnison & Palmes, 1976).

### 4.2 Toxic effects

#### 4.2.1 *Humans*

Charan *et al.* (1979) reported acute accidental exposure of five subjects to very high concentrations of sulfur dioxide. The two with the highest exposure died immediately; histological examination of the lungs revealed acute pulmonary oedema and alveolar haemorrhage. Two of the survivors showed airway obstruction, which was irreversible in one and was mild in the other individual 116 days after the exposure. Pulmonary oedema, followed by the development of 'bronchiolitis obliterans', an obstructive, irreversible lung disease, was described in a nonsmoking man who was exposed accidentally to a high concentration of sulfur dioxide for 15–20 min when a canister of this compound ruptured beneath him (Woodford *et al.*, 1979). Two nonsmoking miners exposed to high concentrations of sulfur dioxide after a mine explosion also developed severe airway obstruction (Rabinovitch *et al.*, 1989).

Workplace standards (see Table 10) have been set to prevent local irritation of mucous membranes of the nose, throat and eyes (WHO, 1979).

The prevalence of chronic bronchitis was significantly increased over that in controls in workers exposed to sulfur dioxide while working in a sulfite pulp factory in Sweden. During the three years before the study was performed, more than 50% of the daily mean values for sulfur dioxide in the sulfite pulp mill were above 14 mg/m$^3$ (5 ppm), with occasional peak exposures up to 140 mg/m$^3$. The mean annual concentration of sulfur dioxide in the surrounding community was 6.5–40 μg/m$^3$ (Stjernberg *et al.*, 1986).

In healthy individuals exposed to sulfur dioxide at levels below 1 ppm (2.6 mg/m$^3$), increased airway resistance is generally not observed; however, when young adult asthmatics were exposed while exercising to sulfur dioxide through a mouthpiece, increased airway resistance was reported with levels as low as 0.25 ppm [0.7 mg/m$^3$] (Sheppard *et al.*, 1981). The effects were much less with unencumbered breathing (Linn *et al.*, 1983). Bronchoconstriction due to sulfur dioxide appears to be mediated by a parasympathetic reflex reaction (Nadel *et al.*, 1965).

Bronchoalveolar lavage of 12 healthy, nonsmoking subjects 24 h after exposure for 20 min to 4 or 8 ppm [10.5 or 21 mg/m$^3$] sulfur dioxide showed increased alveolar macrophage lysosomal activity; at the higher level, the numbers of macrophages and lymphocytes in the lavage fluid were increased. No effect on lung function was observed (Sandström *et al.*, 1989a,b).

Many studies have linked sulfur dioxide levels in the general environment to a variety of adverse health consequences, including acute and chronic bronchitis, respiratory tract infections and mortality, particularly among people with pre-existing lung or heart disease. Sulfur dioxide is, however, only one component of gas–aerosol complexes including sulfate particulates of various toxicities (see p. 141). It has been suggested (WHO, 1987) that sulfur dioxide is not the most potent, direct cause of these effects but is a good surrogate for the components responsible for effects, as it is the most easily measured and is the atmospheric precursor of sulfuric acid and acid sulfates.

Ingestion of sulfites has been postulated to be a cause of rapid, acute allergic reactions, including fatal anaphylactic-like responses (Settipane, 1984). A sulfite-sensitive subpopulation of asthmatics has been postulated to exist who have a relative deficiency of sulfite oxidase (Stevenson & Simon, 1984). The possibility that sulfur dioxide may be generated from sulfite in the low pH of the stomach has been considered as a mechanism of sulfite sensitivity (Simon, 1986). Skin reactions have been noted rarely which have been suggested to result from allergy to inhaled sulfur dioxide (Pirilä *et al.*, 1963).

### 4.2.2 *Experimental systems*

The extensive work of Amdur (1959, 1974) clearly demonstrated the bronchoconstrictive effects of sulfur dioxide in guinea-pigs. Cessation of tracheal ciliary activity was observed in rabbits that inhaled sulfur dioxide at concentrations above 200 ppm [524 mg/m$^3$] (Dalhamn & Strandberg, 1961). Only a relatively negligible amount of sulfur dioxide reached the trachea after nose inhalation, as 90–95% had been absorbed in the nasal cavities.

Increased bronchial hyperresponsiveness to acetylcholine has been observed in dogs following exposure to sulfur dioxide at 1 ppm [2.6 mg/m$^3$] (Islam *et al.*, 1972).

Addition of sodium metabisulfite to the diet of rats at 0.5–8% for 10 days to 2 years induced hyperplastic and inflammatory changes in the forestomach and haemorrhagic

microerosions, necrosis of epithelial cells, cellular inflammatory infiltration and atypical glandular hyperplasia in the glandular stomach (Feron & Wensvoort, 1972). Addition of this compound to the diet of groups of 20 male and 20 female rats at doses of 0.125–8% resulted in consumption levels of 0.098–1.91%. The no-effect level was established to be 0.44% over 48 weeks. At higher levels, several animals had mild inflammatory and hyperplastic changes to the gastric mucosa (Til *et al.*, 1972). These findings support the conclusion that dietary potassium metabisulfite promotes the carcinogenic activity of *N*-methyl-*N'*-nitro-*N*-nitroso-guanidine in rat stomach, as reported by Takahashi *et al.* (1986) (see p. 164).

### 4.3 Reproductive and developmental effects

#### 4.3.1 *Humans*

A variety of environmental exposures involving sulfur dioxide have been related to human reproductive effects (Nordström *et al.*, 1978a,b, 1979a,b; Hemminki & Niemi, 1982; Sakai, 1984; Monteleone-Neto *et al.*, 1985). In none of these papers could a clear relationship be determined between sulfur dioxide concentrations and reproductive outcomes.

#### 4.3.2 *Experimental systems*

*(a) Sulfur dioxide*

Groups of 10 female albino rats (weighing 165–185 g) were exposed for 12 h per day for three months to 0, 0.159 or 4.97 mg/m$^3$ sulfur dioxide (Shalamberidze & Tsereteli, 1971). An additional group was exposed to 2.52 mg/m$^3$ sulfur dioxide in combination with 1.20 mg/m$^3$ nitrogen dioxide. Oestrous cyclicity was determined for 24 days prior to exposure, during exposure and during a recovery period. Females with a normal oestrous cycle were tested for fertility. The ovaries, uterus and pituitary, thyroid and adrenal glands from four rats per group were examined by histopathology at the end of exposure. It was reported that the higher exposure level prolonged the interoestrual period (dioestrus) and the oestrus and that these females had fewer monthly oestrous cycles. Cycle length returned to normal within seven months after exposure. Circulatory changes were found in the ovaries and uteri of females in the high exposure group. In a second experiment, decreased litter sizes were found in similarly exposed groups of seven females. [The Working Group noted that it is not clear when the females were mated within the exposure period.] Body weights of the offspring were reduced at least through postnatal day 12 in these groups.

Groups of 40 or 32 CF-1 mice were exposed for 7 h per day to filtered air or to sulfur dioxide (purity, 99.98%) at 25 ppm [66 mg/m$^3$] on days 6–15 of gestation, and groups of 20 New Zealand white rabbits were exposed to filtered air or sulfur dioxide at 70 ppm [183 mg/m$^3$] on days 6–18 of gestation. In both species, less food was consumed during the first few days of exposure to sulfur dioxide; no other significant effect was seen in the dams. In mice, fetal weight was reduced by 5% by exposure to sulfur dioxide; ossification of the sternebrae and occipital was retarded [data not shown], but the incidence of malformations was not significantly increased. In rabbits, the incidence of a few minor skeletal variants was significantly increased [data not shown] in the group exposed to sulfur dioxide (Murray *et al.*, 1979).

Groups of 13–17 CD-1 mice were exposed to sulfur dioxide at 0, 32, 65, 125 or 250 ppm [0, 84, 170, 328 or 655 mg/m$^3$] on days 7–17 of gestation [presumably for 24 h]; pregnancy

outcome was evaluated on day 18. No dose-related effect was seen on the dams, on fetal viability or on fetal morphology. Fetuses in the 65- and 125-ppm groups were smaller than controls; however, fetuses in the high-dose group weighed more than the controls (Singh, 1982). Additional females [numbers not stated] were exposed to sulfur dioxide at 0, 32 or 65 ppm on days 7–18 [presumably for 24 h] of gestation, and offspring were examined after birth for growth, viability and neurological development. Birth weight was reported to be significantly decreased at 65 ppm. The time required for the righting reflex on postnatal day 1 and negative geotaxic behaviour on postnatal day 10 were significantly increased at both exposure levels (Singh, 1989).

(*b*) *Sulfite*

Groups of 10–12 Wistar rats received 0, 0.32, 0.63, 1.25, 2.5 or 5.0% sodium sulfite heptahydrate (guaranteed grade) in the diet on days 8–20 of gestation. The average daily intakes in the exposed groups were 0.3, 1.1, 2.1 and 3.3 g/kg bw. Pregnancy outcome was examined on day 20. An additional four females that received 0.32 or 5.0% sodium sulfite heptahydrate on days 8–20 of gestation were allowed to give birth, and the growth and viability of the neonates was determined. The authors stated that food intake was low in the 0.32, 0.63 and 5.0% groups; maternal body weight gain during pregnancy was reduced in the 5.0% group. Fetal body weights were reduced in all treated groups but there was little evidence of a dose–response relationship. No external, skeletal or visceral malformation was observed in any group; fetal skeletal variations were not significantly affected by treatment. In the few litters examined postnatally, no effect was reported on viability or growth [weight data analysed on an individual basis] (Itami *et al.*, 1989).

An $LD_{50}$ of 1.04 mg/egg was obtained when sodium sulfite was injected into the air cell of 0-h single-comb white Leghorn chickens. No teratogenic effect was observed (Verrett *et al.*, 1980).

(*c*) *Bisulfite*

Adult male Swiss mice were exposed by intraperitoneal injection to sodium bisulfite either at up to 1000 mg/kg bw acutely or for up to 40 times 400 mg/kg bw over a 56-day period. Dose-related mortality was observed at more than 700 mg/kg bw, but no effect on testicular histology was noted in survivors (Bhattacharjee *et al.*, 1980).

Pregnancy outcome was evaluated in groups of 14–29 female Wistar rats made deficient (1–2% of control level) in hepatic sulfite oxidase activity. A low-molybdenum diet and drinking-water with a high sodium tungstate level allowed systemic exposure to endogenous sulfite; administration of drinking-water supplemented with 25 or 50 mM sulfite (as sodium metabisulfite) beginning on day 21 of tungsten administration further increased sulfite exposure. Appropriate control groups were included in the design. Breeding began 42 days after initiation of treatment; fetuses were examined on day 21 of gestation. The authors paid particular attention to the induction of anophthalmia, the incidence of which was elevated in litters of sulfite oxidase-deficient rats in a pilot study. Controls given molybdenum gained less weight during pregnancy. The concentration of protein *S*-sulfonate in the aorta (an index of exposure to sulfite) was markedly elevated in the treated groups, but there was no significant effect on embryonic viability, fetal weight or fetal morphology (Dulak *et al.*, 1984).

(*d*) *Metabisulfite*

Groups of 13 female and five or six male, newly weaned rats [strain unspecified] received drinking-water containing sodium metabisulfite at doses equivalent to 0, 375 or 750 ppm sulfur dioxide [0, 983 or 1965 mg/m$^3$]. These animals produced two $F_1$ litters after 11 weeks of treatment; the $F_{1a}$ litters in turn produced an $F_2$ generation. Weights of females in the $F_{1b}$ and $F_2$ generations were lower than those of controls, but no effect was reported on fertility, general health, organ weight or histology (Lockett & Natoff, 1960).

In a multigeneration study, groups of 20 male and 20 female Wistar received diets (enriched with 50 ppm (mg/kg) thiamine and stored at –18 °C prior to feeding) containing 0, 0.125, 0.25, 0.5, 1.0 or 2.0% sodium metabisulfite (purity, 95–99%) beginning at weaning. $F_0$ rats were mated within their treatment group at 21 and 34 weeks. $F_{1a}$ rats were mated to produce $F_{2a}$ and $F_{2b}$ litters at 12 and 30 weeks of age, and $F_{2a}$ rats were mated at weeks 14 and 22 to produce an $F_3$ litter. The authors reported a marginal reduction in body weight gain in $F_1$ and $F_2$ generation rats given 2% metabisulfite. Litter size at birth was reduced only in the $F_{2a}$ generation in groups that had received more than 0.25% metabisulfite (Til *et al.*, 1972).

Groups of 18, 18, 13 and 20 Wistar rats received 0, 0.1, 1 and 10% potassium metabisulfite in the diet on days 7–14 of pregnancy. One-third of the control, low- and high-dose dams were allowed to deliver litters for evaluation of postnatal growth and viability; the remaining 12–13 females were examined for pregnancy outcome on day 20 of gestation. Dam body weight gain and fetal body weights were reduced in the group given 10%, as were neonatal survival and the survival rate of offspring on day 4 after birth. The incidences of several skeletal variations were elevated in the treated groups, but no significant difference was noted (Ema *et al.*, 1985).

A group of 40 male and 40 female Wistar rats, 28–32 days old, were given 1.2 g/l potassium metabisulfite (equivalent to about 700 mg/l of sulfur dioxide) in the drinking-water for about 20 months. A similar, untreated group served as controls. At nine months of age, 22 females from the control and 21 females from the treated group were mated; in the second generation, 23 control and 20 treated females were mated. In both generations, weaned young mice were given the same regimen as their parents. A 20% reduction ($p < 0.05$) in litter size was reported in the first generation of treated rats; a similar but not significant reduction in litter size was reported in the second generation. There were fewer males than females (21%) in the litter of the second generation than in controls (53%) ($p < 0.01$) (Cluzan *et al.*, 1965).

**4.4 Genetic and related effects** (see also Table 11 and Appendices 1 and 2)

4.4.1 *Humans*

Significant increases in the frequencies of sister chromatid exchange, micronuclei and chromosomal aberrations were observed in cultured lymphocytes from 40 workers exposed in a sulfuric acid factory in Taiyuan City, northern China, as described on p. 102. The workers were exposed to a variety of agents, including sulfur dioxide (Meng & Zhang, 1990a,b).

The frequency of chromosomal aberrations in cultured lymphocytes from seven workers exposed to sulfur dioxide in a sulfite pulp mill in Sweden was compared with that of 15 controls (Nordenson *et al.*, 1980). The exposed subjects had been employed for > 15 years at

the mill, and one was a smoker. The controls were healthy men from Umeå, Sweden, five of whom were smokers. The mean numbers of breaks/100 cells were 3.72 ± 1.31 (standard deviation) for the sulfur dioxide-exposed workers and 0.66 ± 0.81 for the controls, analysed on the basis of individual values ($t = 5.79$; $p < 0.001$). The frequency of gaps was also increased in the exposed workers ($p < 0.01$). [The Working Group noted the lack of detail about the control subjects, in particular, about exposure conditions and other exposures.]

The frequencies of chromosomal aberrations and sister chromatid exchange in cultured lymphocytes from eight male workers exposed to sulfur dioxide in a light metal foundry in Scandinavia were compared with those of eight controls (Sorsa *et al.*, 1982). The controls were male clerical workers with an average age of 46.4; five of them were smokers. The exposed subjects were men with an average age of 47.9 and average length of employment of 19.5 years; three of them were smokers. Their average daily exposures to sulfur dioxide were estimated to vary between 0.2 and 3.0 ppm [0.52 and 7.9 mg/m$^3$], with individual mean time-weighted average exposures of 1.0 ± 0.85 (standard deviation) ppm [2.62 ± 2.23 mg/m$^3$]. The mean numbers of aberrations per 100 cells, excluding gaps, were 2.0 ± 1.3 in the exposed group and 2.25 ± 1.5 in the control group, and the mean numbers of sister chromatid exchanges per cell were 8.9 ± 0.9 in the exposed and 9.2 ± 1.8 in the control group. Thus, neither the low average level of sulfur dioxide to which the workers were exposed nor smoking had any effect on either parameter.

4.4.2 *Experimental systems*

At high concentations (1 M), bisulfite deaminates cytosine to uracil in isolated DNA, the reaction rate being optimal between pH 5 and 6. If this reaction occurs in cells, there would be resulting cytosine-to-thymidine transition mutations. Lower concentrations of bisulfite can catalyse transaminations, which lead to protein–nucleic acid cross-linking and DNA damage as a result of bisulfite-generated radicals (Shapiro, 1977).

Bisulfite at very high concentrations induced clear plaque mutations in lambda phage but failed to induce mutations in T4 phage. In *Escherichia coli*, reverse mutations were induced at a number of loci containing cytosine–guanine bases (Mukai *et al.*, 1970); however, no mutation was induced in the *lacI* gene of repair-competent *E. coli*, which may also involve transitions of cytosine–guanine bases (Kunz & Glickman, 1983).

Bisulfite was mutagenic only to those strains of *Salmonella typhimurium* that contain the *his* G46 (base-pair substitution-sensitive) and *his* D6610 (frameshift-sensitive) mutations. These mutations occur preferentially under acidic conditions and at much lower concentrations of bisulfite than those required for addition to cystosine, which leads to deamination.

In *Saccharomyces cerevisiae*, bisulfite did not induce gene conversion, but sulfur dioxide and bisulfite induced mutation.

Sulfur dioxide and sulfite induced chromosomal aberrations in *Tradescantia paludosa* and *Vicia faba* and micronuclei in *T. paludosa*. Bisulfite induced chlorophyll mutations in *Hordeum vulgare*.

Bisulfite treatment did not affect DNA repair synthesis in Syrian hamster embryo (SHE) cells. It did not induce mutations at either the $Na^+/K^+$ ATPase or *hprt* locus in cultured Chinese hamster V79 or SHE cells. Sister chromatid exchange was induced in Chinese

**Table 11. Genetic and related effects of sulfur dioxide, sodium bisulfite and metabisulfite**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| BPF, Phage lambda, clear plaque mutation | + | 0 | 192000.0000, pH 5.6 | Hayatsu & Miura (1970) |
| BPF, Phage lambda, clear plaque mutation | (+) | 0 | 64000.0000, pH 5 | Hayatsu (1977) |
| BPR, Bacteriophage T4, reverse mutation | - | 0 | 57600.0000, pH 5 | Ripley & Drake (1984) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | - | 0 | 64000.0000, pH 5.9 | Münzner (1980) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | - | 0 | 6400.0000 | Pagano & Zeiger (1987) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | - | 0 | 64000.0000, pH 5.9 | Münzner (1980) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | - | 0 | 12800.0000 | Pagano & Zeiger (1987) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | - | 0 | 64000.0000, pH 5.9 | Münzner (1980) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | - | 0 | 64000.0000, pH 5.9 | Münzner (1980) |
| SA9, *Salmonella typhimurium* G46, reverse mutation | + | 0 | 64000.0000, pH 5.9 | Münzner (1980) |
| SA9, *Salmonella typhimurium* G46, reverse mutation | + | 0 | 32000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* G46, reverse mutation | (+) | 0 | 5120.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA92, reverse mutation (G46) | + | 0 | 64000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* TA92, reverse mutation (G46) | (+) | 0 | 6400.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA1950, reverse mutation | + | 0 | 64000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* TA2410, reverse mutation | + | 0 | 64000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* TS24, reverse mutation | + | 0 | 64000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* GW19, reverse mutation | + | 0 | 64000.0000, pH 5.2 | De Giovanni-Donnelly (1985) |
| SA9, *Salmonella typhimurium* SB2802, reverse mutation (G46) | + | 0 | 2560.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TR3243, reverse mutation (D6610) | + | 0 | 6400.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA88, reverse mutation (D6610) | (+) | 0 | 3840.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA110, reverse mutation (D6610) | (+) | 0 | 2560.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA90, reverse mutation (D6610) | - | 0 | 6400.0000 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* TA97, reverse mutation (D6610) | + | 0 | 640.0000, pH 5 | Pagano & Zeiger (1987) |
| SA9, *Salmonella typhimurium* D3052, reverse mutation | - | 0 | 38400.0000, pH 5 | Pagano & Zeiger (1987) |

**Table 11 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SAS, *Salmonella typhimurium* C3076, reverse mutation | - | 0 | 19200.0000, pH 5 | Pagano & Zeiger (1987) |
| SAS, *Salmonella typhimurium* TA97, reverse mutation | - | 0 | 5120.0000, pH 7.0 | Pagano *et al.* (1990) |
| SAS, *Salmonella typhimurium* TA97, reverse mutation | + | 0 | 5120.0000, pH 5.0 | Pagano *et al.* (1990) |
| ECK, *Escherichia coli* K12 (4 strains), reverse mutations (TA target) | - | 0 | 64000.0000, pH 5.2 | Mukai *et al.* (1970) |
| ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation, *trp* locus | - | 0 | 64000.0000 | Mallon & Rossman (1981) |
| EC2, *Escherichia coli* WP2, reverse mutation, *trp* locus | - | 0 | 64000.0000 | Mallon & Rossman (1981) |
| EC2, *Escherichia coli* WP2 *pol*A, reverse mutation, *trp* locus | - | 0 | 64000.0000 | Mallon & Rossman (1981) |
| EC2, *Escherichia coli* WP2 *lex*A, reverse mutation, *trp* locus | - | 0 | 64000.0000 | Mallon & Rossman (1981) |
| EC2, *Escherichia coli* WP2 *rec*A, reverse mutation, *trp* locus | - | 0 | 64000.0000 | Mallon & Rossman (1981) |
| ECR, *Escherichia coli* K15 (9 strains) (TA or deletion targets) | - | 0 | 64000.0000, pH 5.2 | Mukai *et al.* (1970) |
| ECR, *Escherichia coli* K15 (13 strains) (CG targets) | + | 0 | 64000.0000, pH 5.2 | Mukai *et al.* (1970) |
| ECR, *Escherichia coli* LacI, reverse mutation | - | 0 | 64000.0000, pH 5.2 | Kunz & Glickman (1983) |
| SCG, *Saccharomyces cerevisiae* BZ34, gene conversion | - | 0 | 6400.0000 | Murthy *et al.* (1983) |
| SCR, *Saccharomyces cerevisiae*, reverse mutation, *ad* locus | + | 0 | 128.0000, pH 3.6 | Dorange & Dupuy (1972) |
| SCR, *Saccharomyces cerevisiae*, petite mutations, strains 626 & 5215 | + | 0 | 60.0000, pH 3 | Guerra *et al.* (1981) |
| HSM, *Hordeum vulgare*, chlorophyll mutations | + | 0 | 450.0000 | Kak & Kaul (1979) |
| TSI, *Tradescantia paludosa*, micronuclei | + | 0 | 1.0000, 2–6 h | Ma *et al.* (1984) |
| TSC, *Tradescantia paludosa*, chromosomal aberrations | + | 0 | 0.0002 | Ma *et al.* (1973) |
| VFC, *Vicia faba*, chromosomal aberrations | + | 0 | 60.0000 | Njagi & Gopalan (1982) |
| RIA, DNA repair synthesis, Syrian hamster embryo cells | - | 0 | 3200.0000, pH 7 | Doniger *et al.* (1982) |
| G9H, Gene mutation, Chinese hamster V79 cells, *hprt* locus | - | 0 | 640.0000 | Mallon & Rossman (1981) |
| GIA, Gene mutation, Chinese hamster V79 cells, $Na^+/K^+$ ATPase locus | - | 0 | 1280.0000 | Mallon & Rossman (1981) |
| GIA, Gene mutation, Syrian hamster embryo cells, *hprt* locus | - | 0 | 1300.0000 | Tsutsui & Barrett (1990) |
| GIA, Gene mutation, Syrian hamster embryo cells, $Na^+/K^+$ ATPase locus | - | 0 | 1300.0000 | Tsutsui & Barrett (1990) |
| SIC, Sister chromatid exchange, Chinese hamster ovary cells | + | 0 | 6.0000 | MacRae & Stich (1979) |
| SIS, Sister chromatid exchange, Syrian hamster embryo cells | + | 0 | 30.0000 | Tsutsui & Barrett (1990) |
| CIS, Chromosomal aberrations, Syrian hamster embryo cells | - | 0 | 325.0000 | Tsutsui & Barrett (1990) |
| TCS, Cell transformation, Syrian hamster embryo cells, focus assay | + | 0 | 325.0000 | DiPaolo *et al.* (1981) |

**Table 11 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| TCS, Cell transformation, Syrian hamster embryo cells, focus assay (confirmation by s.c. injection into *nu/nu* mice) | + | 0 | 1280.0000 | Wirth *et al.* (1986) |
| TCS, Cell transformation, Syrian hamster embryo cells, focus assay | + | 0 | 30.0000 | Tsutsui & Barrett (1990) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | + | 0 | 25.0000 | Beckman & Nordenson (1986) |
| CHL, Chromosomal aberrations, human lymphocytes *in vitro* | + | 0 | 25.0000 | Beckman & Nordenson (1986) |
| SVA, Sister chromatid exchange, NMRI mouse bone marrow *in vivo* | - | 0 | 660.0000, × 1 oral | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, NMRI mouse bone marrow *in vivo* | - | 0 | 50.0000, × 12 s.c., over 3.7 h | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, sulfite oxidase-deficient NMRI mouse bone marrow *in vivo* | - | 0 | 165.0000, × 1 oral | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, sulfite oxidase-deficient NMRI mouse bone marrow *in vivo* | - | 0 | 50.0000, × 8 s.c., over 2.3 h | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, Chinese hamster bone marrow *in vivo* | - | 0 | 660.0000, × 1 oral | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, Chinese hamster bone marrow *in vivo* | - | 0 | 50.0000, × 12 s.c., over 3.7 h | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, sulfite oxidase-deficient Chinese hamster bone marrow *in vivo* | - | 0 | 330.0000, × 1 oral | Renner & Wever (1983) |
| SVA, Sister chromatid exchange, sulfite oxidase-deficient Chinese hamster bone marrow *in vivo* | - | 0 | 50.0000, × 8 s.c., over 2.3 h | Renner & Wever (1983) |
| MVM, Micronuclei, NMRI mouse bone marrow *in vivo* | - | 0 | 660.0000, × 2 oral | Renner & Wever (1983) |
| MVM, Micronuclei, sulfite oxidase-deficient NMRI mouse bone marrow | - | 0 | 165.0000, × 2 oral | Renner & Wever (1983) |
| MVC, Micronuclei, Chinese hamster bone marrow *in vivo* | - | 0 | 660.0000, × 2 oral | Renner & Wever (1983) |
| MVC, Micronucleus, sulfite oxidase-deficient Chinese hamster bone marrow *in vivo* | - | 0 | 330.0000, × 2 oral | Renner & Wever (1983) |
| CBA, Chromosomal aberrations, NMRI mouse bone marrow *in vivo* | - | 0 | 660.0000, × 2 oral | Renner & Wever (1983) |

**Table 11 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| CBA, Chromosomal aberrations, sulfite oxidase-deficient NMRI mouse bone marrow *in vivo* | – | 0 | 165.0000, × 2 oral | Renner & Wever (1983) |
| CBA, Chromosomal aberrations, Chinese hamster bone marrow *in vivo* | – | 0 | 660.0000, × 2 oral | Renner & Wever (1983) |
| CBA, Chromosomal aberrations, sulfite oxidase-deficient Chinese hamster bone marrow *in vivo* | – | 0 | 330.0000, × 2 oral | Renner & Wever (1983) |

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, µg/ml; in-vivo tests, mg/kg bw; standardized to sulfur dioxide

hamster ovary and SHE cells, but chromosomal aberrations were not induced in SHE cells. Sulfur dioxide induced morphological transformation of SHE cells, but there was no synergism with ultra-violet light in the transformation process (DiPaolo *et al.*, 1981), such as was observed in V79 cells (Mallon & Rossman, 1981). Transformation occurred under conditions in which no change to DNA was observed, but consistent, qualitative polypeptide changes and quantitative changes were detected in these cells (Wirth *et al.*, 1986). In a single study, sulfur dioxide induced sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro*.

After oral or parenteral administration, sodium metabisulfite did not induce bone-marrow cytogenetic damage in either hamsters or mice.

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Sulfur dioxide is produced commercially by burning sulfur or various sulfides or by recovering it from flue gases or non-ferrous metal smelting gases. Large quantities are used as intermediates in the manufacture of sulfuric acid and sulfite pulp. It is also used in agriculture and in the food and beverage industries as, among other things, a biocide and a preservative. Sulfite pulp workers have been exposed to fluctuating levels of sulfur dioxide, often exceeding 10 ppm (26 mg/m$^3$), but levels have decreased with modernization of facilities and processes. In metal industries, the roasting of ores and the combustion of various sulfur-containing fuels have resulted in mean exposures to sulfur dioxide in the range of 1–10 ppm (2.6–26 mg/m$^3$) in copper smelters, but at about 1 ppm (2.6 mg/m$^3$) or less in other facilities. Mean levels exceeding 1 ppm (2.6 mg/m$^3$) have also been reported in the manufacture of sulfuric acid and of superphosphate fertilizers, as well as at certain fire sites during fire fighting. Levels of sulfur dioxide in ambient air do not usually exceed 0.05 ppm (0.1 mg/m$^3$), except in some urban areas.

Sodium sulfite is used mainly in the pulp industry. Both sodium and potassium meta-bisulfure are used in food processing, chemical industries, water treatment, photoprocessing and the textile industry. Levels of occupational exposure have not been reported.

### 5.2 Human carcinogenicity data

In four US and one Swedish cohort studies of copper smelters, increased lung cancer risks were observed in relation to exposure to arsenic, but no independent effect of sulfur dioxide was seen.

One proportionate mortality study from the USA and Canada, as well as two US and one Finnish cohort studies, analysed cancer risks among sulfite pulp mill workers. Three of them suggested an increase in risk for stomach cancer; however, potential confounding factors were not adequately controlled. Lung cancer risks were not elevated in any of these studies.

In case–control studies performed at a chemical facility in Texas with a complex exposure environment, increased risks for lung cancer and brain tumours were indicated in workers with high exposure to sulfur dioxide; however, the findings using two different control groups were not consistent.

A population-based case–control study from Canada suggested an increased risk for stomach cancer in men exposed to sulfur dioxide, but no excess was indicated for lung cancer.

No epidemiological studiy was available on cancer risks associated with exposure to sulfites, bisulfites or metabisulfites.

### 5.3 Carcinogenicity in experimental animals

*Sulfur dioxide* was tested for carcinogenicity in one study in mice by inhalation exposure. A significant increase in the incidence of lung tumours was observed in females.

*Sulfur dioxide* was tested for enhancement of carcinogenicity when administered with benzo[*a*]pyrene in two studies in rats and in one study in hamsters. One incompletely reported study found an increase in the incidence of lung tumours in rats exposed to sulfur dioxide in conjunction with benzo[*a*]pyrene. The other study in rats suffered from limitations owing to the high incidence of lung tumours in controls given benzo[*a*]pyrene. The study in hamsters was inadequately reported.

*Potassium metabisulfite* was tested for carcinogenicity in one study in mice by oral administration in the drinking-water and *sodium metabisulfite* in one study in rats by oral administration in the diet. No increase in tumour incidence was observed in mice, and there was no indication of a dose-related increase in tumour incidence in rats, but both studies had some inadequacies in reporting of data.

*Potassium metabisulfite* was tested for enhancement of carcinogenicity in one study in rats. It significantly increased the incidence of gastric adenocarcinoma after initiation with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

No data were available on the carcinogenicity in experimental animals of sulfites or bisulfites.

### 5.4 Other relevant data

At high concentrations, sulfur dioxide irritates the upper airways and can induce acute and chronic bronchitis. At lower levels (less than 0.25 ppm [0.65 mg/m$^3$]), no effect of sulfur dioxide is seen on the airways of sensitive individuals in the general population who take exercise, presumably since this relatively hygroscopic gas is removed by the nose and mouth.

Conflicting results for the induction of chromosomal aberrations in lymphocytes were obtained in two studies of workers exposed to sulfur dioxide, among other agents. In a single study, no increase was reported in the frequency of sister chromatid exchange in lymphocytes of exposed workers.

Sulfur dioxide and its aqueous forms did not induce sister chromatid exchange, chromosomal aberrations or micronucleus formation in bone marrow of mice or Chinese hamsters. In a single study, sister chromatid exchange and chromosomal aberrations were induced in human lymphocytes. In cultured mammalian cells, bisulfite induced transformation and sister chromatid exchange but not gene mutation, chromosomal aberrations or DNA repair synthesis. In plants, chromosomal aberrations, micronuclei and gene mutation were induced. Sulfur dioxide and bisulfite induced gene mutation but not gene conversion in yeast. Mutations were induced in bacteria and phage.

Bisulfite solutions at high concentrations caused deamination of cytosine in DNA *in vitro*.

### 5.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity in humans of sulfur dioxide, sulfites, bisulfites and metabisulfites.

There is *limited evidence* for the carcinogenicity in experimental animals of sulfur dioxide.

There is *inadequate evidence* for the carcinogenicity in experimental animals of sulfites, bisulfites and metabisulfites.

**Overall evaluation**

Sulfur dioxide, sulfites, bisulfites and metabisulfites *are not classifiable as to their carcinogenicity to humans (Group 3).*

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

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