Sulfites: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Sulfurous acid, monosodium salt	7631-90-5
Disulfurous acid, sodium salt (1:2)	7681-57-4
Disulfurous acid, disodium salt	7757-74-6
Sulfurous acid, disodium salt	7757-83-7
Sulfurous acid, dipotassium salt	10117-38-1
Sulfurous acid, monoammonium salt	10192-30-0
Sulfurous acid, diammonium salt	10196-04-0
Disulfurous acid, dipotassium salt	16731-55-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of eight chemicals consists of inorganic sulfites or sulfurous acid salts. The chemicals in this group contain sulfur in oxidation state IV and include sulfites, bisulfites, disulfites and metabisulfites. These chemicals have been grouped together for assessment due to their similarity in chemical properties, uses (such as antioxidant and antimicrobial) and toxicological profile.

Sulfites in aqueous solutions involve complex equilibria among the different species of sulfur oxidation state IV. The composition of their mixture in solutions depends on the pH and temperature. Sulfur dioxide may be produced from sulfites at low pH. At a pH closer to 7, the concentration ratio of bisulfite (HSO_3^-) to sulfur dioxide (SO_2) is very high (Gunnison and Jacobsen, 1987).

Sulfites occur naturally in some foods and beverages as a result of fermentation (e.g. in beer and wine). A small percentage of the population (up to 1 %) is sensitive to sulfites (FDA, cited in Grotheer et al., 2005), as sulfur dioxide may be generated from sulfites in the stomach at low pH (Simon, 1986). The sensitivity to sulfur dioxide can cause a wide range of reactions in humans ranging from mild to severe dermatological, pulmonary, gastrointestinal, or cardiovascular symptoms (Grotheer et al., 2005).

Import, Manufacture and Use

Australian

Two chemicals in this group are listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume less than 100000 tonnes. These are:

- sodium metabisulfite (Cas No. 7681-57-4); and
- sodium sulfite (Cas No. 7757-83-7).

The following industrial uses were reported for these two chemicals under previous mandatory and/or voluntary calls for information.

The chemicals have reported cosmetic use including as preservatives.

The chemicals have reported domestic use including:

- as cleaning/washing agents; and
- in additives.

The chemicals have reported commercial use including:

- as pH-regulating agents;
- in leather and textiles processing;
- in photographic processing;
- as electroplating, reducing and tanning agents; and
- as bleaching and colouring agents.

The chemicals have reported site-limited use including:

- in the production of other chemical;
- in mining and metal extraction;
- in pulp, paper and board processing; and
- as flotation agents in water treatment.

These two chemicals also have non-industrial uses in food and beverage processing as antioxidants and enzyme inhibitors.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances in preparations in Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The majority of chemicals in this group have the following reported cosmetic use as:

- preservatives (up to 0.2 % as free SO_2);
- oxidative hair dye products (up to 0.67 % as free SO_2);
- hair waving/straightening products (up to 6.7 % as free SO_2);
- self-tanning products (up to 0.45 % as free SO_2); and
- antioxidants and reducing agents.

The majority of chemicals in this group have reported domestic use including:

- as cleaning/washing agents; and
- in additives.

The chemicals have reported commercial use including:

- in the leather and textile industry; and
- in the photo processing industry.

The majority of chemicals in this group have reported site-limited use including:

- in producing other chemicals and detergents;
- as an oxygen scavenger in petroleum technology;
- manufacturing explosives;
- as antioxidant/flotation agents in water treatment; and
- in pulp, paper and board processing.

Restrictions

Australian

No known restrictions have been identified for industrial uses.

The Complementary Medicines Evaluation Committee (CMEC) noted the literature review prepared by the Therapeutic Goods Administration (TGA) (CMEC, 2004) on the safety of sulfites in medicines and stated that there is not sufficient evidence to determine a level of exposure to sulfites in medicines which is without risk to sensitive individuals. Therefore, all medicines containing sulfites should be labelled in accordance with the requirements of the Therapeutic Goods Order 69.

The group acceptable daily intake (ADI) for sulfites (confirmed in 1998 by the Joint FAO/WHO Expert Committee on Food Additives—JECFA) is 0–0.7 mg/kg bw/day (FSANZ, 2012).

Under the Food Standards Code, sulfites added to food and/or beverages must be declared on the label in the ingredients list, when present at 10 mg/kg or more (FSANZ, 2012).

International

EU Health and Consumers Cosmetic restrictions on concentrations (Annex III/99 and VI/9 lists of substances and preservatives) for the use of inorganic sulfites and hydrogen sulfites (applying for all chemicals in this group except for CAS No. 7757-74-6) are:

- as preservatives—up to 0.2 % (as free SO_2);
- oxidative hair dye products—up to 0.67 % (as free SO_2);
- hair waving/straightening products—up to 6.7 % (as free SO_2);
- self-tanning products for the face—up to 0.45 % (as free SO_2); and
- certain self-tanning products—up to 0.40 % (as free SO_2).

New Zealand Cosmetic Products Group Standard Schedule 5 (maximum authorised concentration of sulfites in the finished cosmetic products) and Schedule 7 (preservatives that cosmetic products may contain with restrictions) have imposed concentration limits similar to the EU.

The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex VI Part 1: List of preservatives allowed for use in cosmetic products for inorganic sulfites and hydrogensulfites (of oxidation state IV) is 0.2 % (as free SO_2).

In the Substances Listed in EU Directives: Plastics in contact with food—Specific Migration Limit (Total) [SML(T)] for sodium bisulfite is 10 mg/kg (30) (as free SO_2).

Existing Worker Health and Safety Controls

Hazard Classification

Two chemicals in this group are classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Sodium bisulfite (CAS No. 7631-90-5):

Xn; R22 (acute toxicity)

Xi; R31 (contact with acid liberates toxic gas)

Sodium metabisulfite (CAS No. 7681-57-4):

Xn; R22 (acute toxicity)

Xi; R41 (serious eye damage)

Xi; R31 (contact with acid liberates toxic gas)

Exposure Standards

Australian

Two chemicals in this group (sodium bisulfite, CAS No. 7631-90-5 and sodium metabisulfite, CAS No. 7681-57-4) have an exposure standard of 5 mg/m^3 time weighted average (TWA).

No exposure standards are available for the other chemicals in this group.

The exposure standard for sulfur dioxide of 5.2 mg/m^3 (2 ppm) (TWA) is also relevent to uses of these chemicals that may generate sulfur dioxide.

International

The following exposure standards are identified for all chemicals in this group (Galleria Chemica):

An exposure limit (OEL, TWA, STEL, PEL or STV) of 5–10 mg/m^3 in different countries such as USA, United Kingdom, Canada, Ireland, Spain, Norway and Switzerland.

Health Hazard Information

Toxicokinetics

Sulfites generated in the human body (endogenous sulfites) can be oxidised by a mitochondrial enzyme sulfite oxidase, to sulfates that are mainly excreted in the urine. Endogenous sulfites can also be metabolised to thiosulfates by enzymatic reaction with 3-mercaptopyruvate or to S-sulfonates by nonenzymatic reaction with biological chemicals containing disulfide bonds. These metabolites were detected at very low concentrations in human and rat urine (CIR, 2003).

Sulfites that are ingested, inhaled or injected (exogenous sulfites) are metabolised by sulfite oxidase to sulfates. Oral and intravenous studies in dogs, rats, rabbits and monkeys showed rapid metabolic clearance and less than 10 % of the administered dose was excreted unmetabolised in the urine (CIR, 2003).

In rats, the liver can metabolise a fraction of dosed sulfite; the rest passes through the organ and enters the systemic circulation. Hepatic sulfite oxidase activity studies showed that the rat liver contains 10 to 20 times more sulfite oxidase activity than the human liver (CIR, 2003).

Sulfite may damage DNA chains by a reaction involving free radicals. However, mammalian tissues are largely protected against hazards from sulfite by its oxidation to the relatively non toxic sulfate (OECD, 2001).

Acute Toxicity

Oral

Sodium metabisulfite (CAS No. 7681-57-4) and sodium bisulfite (CAS No. 7631-90-5) are classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The data available support this classification for these two chemicals.

Based on the data available (for four chemicals in this group), all chemicals in this group should be classified for acute oral toxicity.

The LD50 for sodium metabisulfite is 1131 mg/kg bw in female rats and 1903 mg/kg bw in male rats (ChemIDplus).

Sodium bisulfite has an LD50 of 2000 mg/kg bw in rats (ChemIDplus).

The LD50 in rats for potassium metabisulfite (CAS No. 16731-55-8) was reported as 1040 mg/kg bw or 1800 mg/kg bw, in two different studies (GRAS, 1972 cited in CIR, 2003).

Sodium sulfite (CAS No. 7757-83-7) has an oral LD50 >2000 mg/kg bw in rats (3560 mg/kg bw for females and 3930 mg/kg bw for males). However, the mouse or rabbit oral LD50 is <2000 mg/kg bw (820 mg/kg bw for the mouse and 600–700 mg/kg bw for rabbits) (WHO, 1974).

No oral LD50 data are available for sodium metabisulfite (CAS No. 7757-74-6), potassium sulfite (CAS No. 10117-38-1), ammonium bisulfite (CAS No. 10192-30-0) or ammonium sulfite (CAS No. 10196-04-0).

Dermal

Based on the limited data available, sulfites are considered to be of low acute dermal toxicity.

The LD50 for sodium metabisulfite in rats is >2000 mg/kg bw. Sulfites exhibit low acute toxicity in animal tests (US EPA, 2007).

No acute dermal toxicity data for the other chemicals in this group are available.

Inhalation

Based on the limited data available, no conclusion can be made on the acute inhalation toxicity of the chemicals in this group.

No 4-hour LC50 values are available for any of the chemicals in this group. However, one non-guideline acute inhalation toxicity study that used an aerosol containing ammonium sulfite (CAS No. 10196-04-0) and ammonium sulfate in guinea pigs indicated an LC50 >0.4 mg/L/1 hour (Rothenberg et al., 1986 cited in CIR, 2003).

A group of guinea pigs was exposed (whole body) for one hour to 0.204, 0.395 or 1.152 mg/m^3 of sodium sulfite (CAS No. 7757-83-7) aerosols with a mass median aerodynamic diameter (MMAD) of 0.36 µm. The chemical caused dose-related changes in the lung capacity parameters (bronchoconstriction) with a lowest observed adverse effect concentration (LOAEC) of 0.204 mg/m^3 (Chen et al., 1987 cited in CIR, 2003).

Two chemicals in this group, sodium bisulfite (CAS No. 7631-90-5) and sodium metabisulfite (CAS No. 7681-57-4**)** are classified as hazardous with the risk phrase 'Contact with acid liberates toxic gas' (Xi; R31) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). Based on the rationale that sulfites, in contact with acids, liberate the toxic gas sulfur dioxide (SO_2) (CIPC, 2008), the other chemicals in this group should also be classified with the same risk phrase.

Observation in humans

Ingesting sulfites may cause irritation of the human stomach, due to liberation of SO_2, producing sulfurous acid (HSDB). In some asthmatic individuals, adverse reactions such as bronchospasm, angioedema (swelling of the dermis), urticaria, nausea, abdominal cramping and/or diarrhoea were reported following ingestion of food containing sulfites (Grotheer et al., 2005).

Corrosion / Irritation

Respiratory Irritation

No data are available on respiratory tract irritation from a single exposure.

A 3-day repeated dose study indicated irritation of the tracheal epithelium in rats from exposure to sodium sulfite (CAS No. 7757-83-7) aerosols at 15 mg/m^3 (CIR, 2003).

Skin Irritation

Based on the data available, the chemicals in this group are not considered to be skin irritants.

In acute dermal irritation studies (OECD TG 404) with sodium sulfite, sodium bisulfite and potassium sulfite, no skin irritation was observed in albino rabbits (SCCNFP, 2003).

In a skin irritation test (OECD TG 404) that used the Draize scale for scoring, sodium metabisulfite did not produce any skin irritation in albino rabbits (OECD, 2001).

Eye Irritation

Sodium metabisulfite (CAS No. 7681-57-4) is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in HSIS (Safe Work Australia). The available data for this chemical support this classification.

Based on the data available, the chemicals in this group should be classified with the same risk phrase.

In an acute eye irritation test (OECD TG 405) on rabbits with sodium metabisulfite, a small area of mild corneal opacity, transient moderate congestion of the iris and mild conjunctivitis were observed in the treated eyes. The corneal opacity was reversible and the cornea was normal within 14 days of exposure, but mild conjunctival irritation persisted. The chemical was therefore considered to be irritating to the eyes (CIR, 2003).

In acute eye irritation studies (OECD TG 405) with sodium sulfite and sodium bisulfite in rabbits, slight to severe effects in the cornea and the iris in most of the exposed animals persisted during the observation periods (eight and 15 days, respectively). Slight to moderate conjunctival effects (erythema and oedema) were also observed up to the end of the observation periods. Due to the persistency of eye effects, especially of increased corneal opacity, both chemicals were considered as severe eye irritants (SCCNFP, 2003).

Sensitisation

Respiratory Sensitisation

No data are available for the chemicals in this group.

Skin Sensitisation

Based on the available data, the chemicals in this group are not likely to be skin sensitisers.

Sodium metabisulfite (CAS No. 7681-57-4) was tested in 10 guinea pigs for dermal sensitisation. The chemical did not show any skin sensitisation properties and was considered not to be a skin sensitiser (OECD, 2001).

No skin sensitisation data are available for the other chemicals in this group.

A Cosmetic Ingredient Review (CIR) report (2003) indicated that dermal penetration of sulfites is unlikely to occur due to the ionic nature of these chemicals. Sulfites (including sulfite, bisulfite and metabisulfite), which are used widely in cosmetic products, are rarely contact allergens and were not found to be potent primary sensitisers (CIR, 2003).

Observation in humans

Based on the available data, sulfites are not likely to be skin or respiratory sensitisers in humans generally, except in some sensitive individuals (~1 % of the population according to the FDA, cited in Grotheer et al., 2005).

It was stated that 50 of 2894 patients were sensitised to sodium metabisulfite (CAS No. 7681-57-4), potassium metabisulfite (CAS No. 16731-55-8) and sodium bisulfite (CAS No. 7631-90-5). Only two patients were sensitised to sodium sulfite (CAS No. 7757-83-7) (Vena et al., 1994). Angelini et al., (1997) reported that only 14 of 980 eczematous patients were positive in a patch test with sodium metabisulfite. The data available did not meet the criteria for classification of sulfites as skin sensitisers according to the Approved Criteria (NICNAS, 2005).

Sodium metabisulfite is unlikely to induce respiratory sensitisation in humans, but may enhance symptoms of asthma in sensitive individuals. Humans exposed to this chemical may experience effects such as urticaria (vascular reaction of the skin), oedema, rhinitis (inflammation of the nasal mucosa), and nasal congestion (OECD, 2001).

Ingestion of sulfites was reported to cause rapid acute allergic reactions such as anaphylactic responses, especially to asthmatic people who have a deficiency of sulfite oxidase enzyme (IARC, 1997).

The US Food and Drug Administration (FDA, cited in Grotheer et al., 2005) estimated that up to 1 % of the population is sensitive to sulfites. This sensitivity can cause a wide range of reactions ranging from mild to severe dermatological, pulmonary, gastrointestinal, or cardiovascular symptoms (Grotheer et al., 2005).

Repeated Dose Toxicity

Oral

Based on the data available for sodium metabisulfite, the chemicals in this group are not considered to cause serious damage to health by repeated oral exposure.

In an 8-week study, SD rats (normal and sulfite oxidase enzyme—which oxidises sulfite to sulfate—deficient) were exposed to sodium metabisulfite (CAS No. 7681-57-4) or a mixture containing sodium metabisulfite and acetaldehyde hydroxysulfonate, in drinking water at doses of 0, 7, 70 or 175 mg/kg bw/day (as SO_2). A no observed effect level (NOEL) for sodium metabisulfite was established as 70 mg/kg bw/day (as SO_2) for all treated rats (normal and enzyme deficient), based on severe gastric lesions, significant body weight reduction and increased urine excretion with sulfites observed at the highest dose. The NOEL for the mixture was 7 mg/kg bw/day (as SO_2) for enzyme-deficient rats, based on severe gastric and hepatic lesions at higher doses. At necropsy, lung oedema was observed in sodium metabisulfite treated, enzyme-deficient rats (Hui et al., 1989 cited in CIR, 2003).

No data are available for the other chemicals in this group.

Dermal

No data are available for the chemicals in this group.

Inhalation

Based on the limited data available for sodium metabisulfite, the chemicals in this group are not considered to cause serious damage to health through repeated inhalation exposure.

Groups of six rats (Sprague Dawley) were exposed to sodium sulfite (CAS No: 7757-83-7) aerosols with a particle size of approximately 1 µm at concentrations of 0.1, 1, 5 or 15 mg/m^3 for three days. Mild pulmonary oedema at 5 mg/m^3 and irritation of the tracheal epithelium at 15 mg/m^3 were observed (CIR, 2003).

In a repeated dose study, eight dogs (beagle) were exposed to 1 mg/m^3 of sodium metabisulfite (CAS No: 7681-57-4) aerosols with a mass median aerodynamic diameter (MMAD) of 0.63 µm for 290 days. Severe epithelial changes were observed with hyperplastic foci in the respiratory region of the nasal cavity. An increase in the nonciliated cell numbers in the membranous portion of the trachea of the animals was also observed. No other effects were reported (CIR, 2003).

Genotoxicity

Based on the data available, the chemicals in this group are not considered to be genotoxic.

Sodium sulfite (CAS No. 7757-83-7) gave negative results in bacterial reverse mutation tests (OECD TG 471) with or without metabolic activation (SCCNFP, 2003) and did not interfere with mitotic division of oocytes in mice (CIR, 2003). Therefore, sodium sulfite was reported as non genotoxic (CIR, 2003).

A mixture of sodium bisulfite (CAS No. 7631-90-5) and sodium sulfite (1:3) was tested at concentrations of 0.05–1 mmol/L in human peripheral lymphocytes. Positive results were obtained for chromosomal aberrations: micronucleus formation, and sister chromatid exchange (WHO, 1999). In an in vitro unscheduled DNA synthesis test with rat hepatocytes (OECD TG 486), and in an in vivo micronucleus test (OECD TG 474), sodium bisulfite (CAS No. 7631-90-5) did not show any evidence of mutagenicity (SCCNFP, 2003). Sodium bisulfite gave both positive and negative results in the mutagenicity testing. The positive results in *Salmonella typhimurium* strains containing his-G46 and his-D6610 mutations, and in some *E.coli* strains were suggested to be due to the presence of sulfurous acid under acidic conditions. At a neutral pH and lower concentrations, sodium bisulfite was not mutagenic to these strains. However, sodium bisulfite alone gave negative results in all in vivo studies with mammalian systems (rats and mice) (CIR, 2003).

Sodium metabisulfite (CAS No. 7681-57-4) was reported to show equivocal results in some in vitro tests, but showed negative results in vivo (OECD, 2001). CIR (2003) reported sodium metabisulfite and potassium metabisulfite (CAS No. 16731-55-8) as non genotoxic.

Potassium sulfite (CAS No. 10117-38-1) gave negative results in bacterial reverse mutation tests (OECD TG 471) with or without metabolic activation (SCCNFP, 2003).

Carcinogenicity

Based on the data available, the chemicals in this group are not considered to be carcinogenic.

Based on a 104-week repeated dose toxicity study in rats, with up to 2 % sodium bisulfite in the diet, sodium bisulfite is not considered carcinogenic to rats (OECD, 2001).

Sodium metabisulfite and potassium metabisulfite were not carcinogenic in rats (Wistar) or mice (ICR/ICL), when tested by oral administration with up to 2 % concentration for 104 weeks. There was no increase in tumour incidence compared to the historical controls (IARC, 1997).

Potassium metabisulfite (1 %) was also tested in rats (Wistar) for enhancement of carcinogenicity. The chemical was administered in drinking water for 32 weeks, after initiation with N-methyl-N'-nitro-N-nitrosoguanidine (100 mg/L in drinking water for eight weeks). An increase in the incidence of gastric adenocarcinoma was observed. The incidences of adenocarcinomas of the gastric pylorus were 0/10 (untreated animals), 1/30 (animals treated with only N-methyl-N'-nitro-N-nitrosoguanidine), 0/10 (animals treated with only 1 % potassium metabisulfite) and 5/19 (animals treated with N-methyl-N'-nitro-N-nitrosoguanidine and 1 % potassium metabisulfite) (IARC, 1997). IARC concluded that potassium metabisulfite is not carcinogenic to rats but enhances carcinogenicity.

As there is a lack of evidence for carcinogenicity in laboratory animals exposed to sulfites, bisulfites and metabisulfites, IARC reported that sulfites, bisulfites and metabisulfites are not classifiable as to their carcinogenicity to humans (Group 3) (WHO, IARC, 1997; SCCNFP, 2003).

Reproductive and Developmental Toxicity

Based on the data available, the chemicals in this group are not considered to cause reproductive or developmental toxicity.

In a multigeneration reproductive study, a group of rats (Wistar) was orally administered sodium metabisulfite (CAS No. 7681-57-4) in the diet at up to 2 % (actual doses; 0, 48, 105, 217, 454 and 942 mg/kg bw/day) for 104 weeks. No effects were observed on reproductive performance in any generation and no histopathological effects on gonads were observed. The no observed adverse effect level (NOAEL) for reproductive toxicity was 2 % (942 mg/kg bw/day) (OECD, 2001).

Pregnant rats (Wistar) were exposed by gavage to sodium bisulfite (CAS No. 7631-90-5) at 0, 1, 5, 24, or 110 mg/kg bw/day on days 6–15 of gestation. The NOAEL for maternal toxicity or embryo foetotoxicity was 110 mg/kg bw/day. A NOAEL of 123 mg/kg bw/day was established in a study with pregnant rabbits (Dutch belted) exposed to sodium metabisulfite (CAS No. 7681-57-4) at 0, 1.23, 5.71, 26.5 or 123 mg/kg bw/day on days 6–18 of gestation. In both these studies, there were no treatment related effects reported on nidation (nesting behaviour), maternal or foetal survival. The number of abnormalities in soft or skeletal tissues of the treated groups were similar to controls (OECD, 2001).

Groups of 20 pregnant rats (Wistar) were exposed by oral gavage to potassium metabisulfite (CAS No. 16731-55-8) at 0, 1.55, 7.19, 33.4 or 155 mg/kg bw/day on days 6–15 of gestation. Another study exposed pregnant mice (CD-1) to the chemical at 0, 1.25, 5.47, 26.9 or 125 mg/kg bw/day on days 6–15 of gestation. In both studies, potassium metabisulfite had no adverse effect on reproduction; the NOAELs for maternal toxicity were 155 and 125 mg/kg bw/day for rats and mice, respectively.

In a reproductive and developmental toxicity study, groups of 12 pregnant rats (Wistar) were dosed with sodium sulfite heptahydrate in the diet at concentrations of 0, 0.32, 0.63, 1.25, 2.5 or 5 % (up to 3300 mg/kg bw) on days 8–20 of gestation. The chemical was considered to produce signs of foetal toxicity at very high doses, but is not considered teratogenic.

The following effects were reported:

- maternal toxicity at 5 % (decreased feed consumption and body weight gain);
- significant reduction in foetal body weights ($p < 0.05$) in all pups, except in female pups in the the 2.5 % group;
- foetal skeletal variations (not statistically significant) such as lumbar rib, hypoplastic rib and delayed ossifications in all treated groups, except at 1.25 %; and
- renal pelvis and lateral ventricle dilation in foetuses (no dose response).

No evidence of growth retardation or other signs of toxicity were observed in 3-week old offspring (IARC, 1997; CIR, 2003).

Risk Characterisation

Critical Health Effects

The main critical effects to human health are severe eye irritation and acute oral toxicity. The chemicals in this group will liberate toxic gas when in contact with acid and therefore may cause effects in individuals with a high acid content in the stomach.

A small percentage of the population (up to 1 %) are sensitive to sulfites (FDA, cited in Grotheer et al., 2005). Those who have asthma are most at risk to sulfite sensitivity and other forms of sulfite reactions. This sensitivity can cause a wide range of allergic reactions ranging from mild to severe.

Public Risk Characterisation

The general public may be exposed to the chemical through oral, dermal and inhalation routes when using cosmetic/domestic products containing these chemicals.

Currently, there are no restrictions in Australia on using these chemicals in cosmetics or domestic products. New Zealand and the European Union (EU) have restricted the use of these chemicals in cosmetics. The EU also has restrictions on using sodium bisulfite (CAS No. 7631-90-5) in plastics with food contact use.

In the absence of any regulatory controls for cosmetic/domestic use of these chemicals, the characterised critical health effects (such as severe eye irritation and liberating toxic gas when in contact with acid) have the potential to pose an unreasonable risk under the uses identified. The risks could be mitigated by implementing concentration limits for certain uses to reduce exposure.

Sensitivity to sulfites is more likely to be related to exposure via food and beverages than to circumstances related to industrial use.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from the chemicals in this group is considered high if adequate control measures to minimise occupational exposure to the chemicals are not implemented.

The chemicals should be appropriately classified and labelled to ensure that a person conducting a business, or an employee at a workplace, has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of these chemicals in cosmetics and/or domestic products be managed through changes to poisons scheduling; and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of these chemicals is considered to be sufficient, provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the concentrations of these chemicals in cosmetics/personal care products and domestic products be restricted in concentrations similar to those recommended by the EU. Exemptions to scheduling may be applicable at low concentrations.

Consideration should be given to the following:

- severe eye irritation effects;
- acute oral toxicity; and
- the posibility of liberating toxic gas when the chemical is in contact with acids.

Sensitivity to sulfites that causes allergic reactions in a small percentage of the population should also be considered.

The Scientific Committee on Cosmetic products and Non Food Products (SCCNFP) concluded that sulfites (as free SO_2) do not pose any unacceptable risk to human health when used in cosmetic formulations at the intended use concentrations (up to 0.67 % in oxidative hair dye products, up to 6.7 % in hair waving/straightening products, up to 0.45 % in self tanning products for the face and up to 0.40 % in self tanning products for the body) (SCCNFP, 2003). These maximum use concentrations were estimated by calculating margins of safety for exposure, using NOAELs and safety factors (e.g. 10 % of topically applied sulfites become bioavailable without prior conversion to sulfate) (SCCNFP, 2003).

Work Health and Safety

The chemicals in this group are recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This assessment does not consider classification of physical hazards and environmental hazards.

Based on the hazard data/classifications available for some chemicals in this group (sodium bisulfite, CAS No. 7631-90-5 and sodium metabisulfite, CAS No. 7681-57-4), all the chemicals in this group should be classified as hazardous with the following risk phrases.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Contact with acids liberates toxic gas (R31)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals in this group should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storage, handling and using a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks by automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not be solely relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of hazardous chemical are prepared; and
- managing risks arising from storage, handling and use of a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of physical hazards of the chemical has not been undertaken as part of this assessment.

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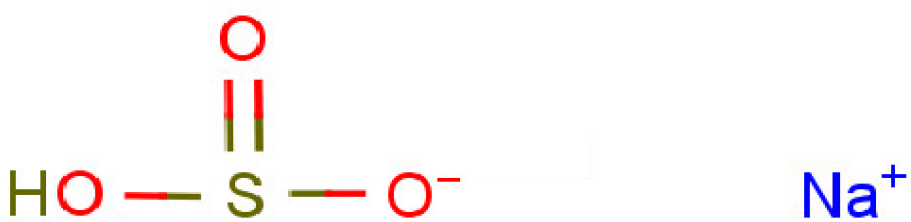
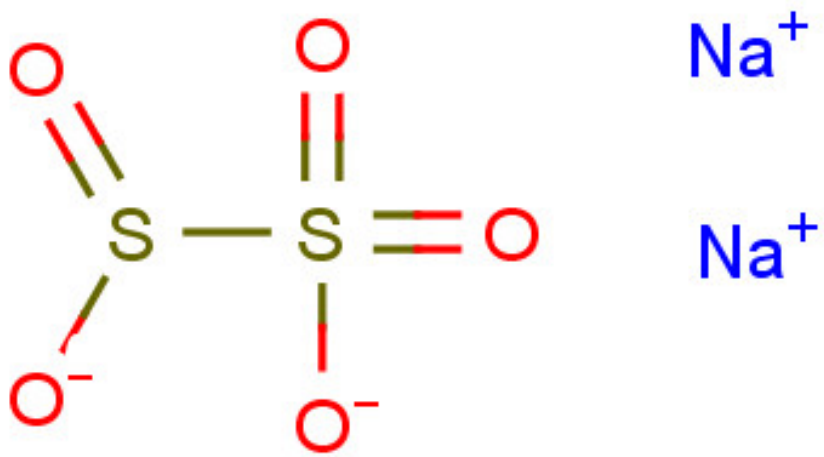
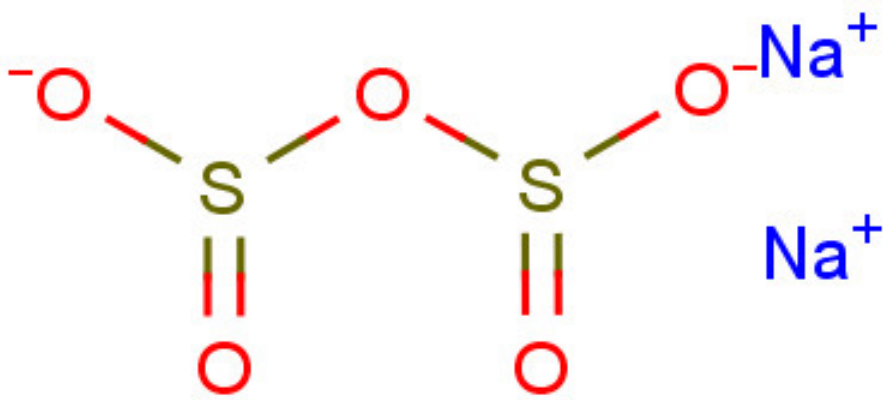
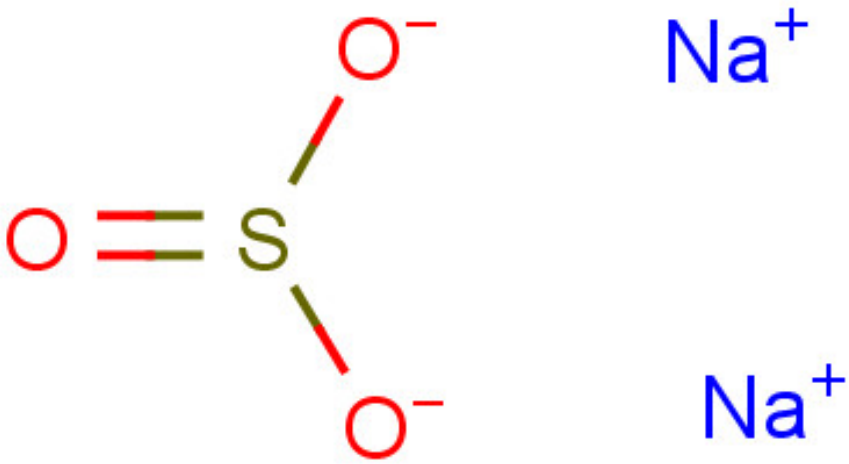
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Sulfurous acid, monosodium salt** Sodium bisulfite Sulfurous acid, sodium salt (1:1) Sodium hydrogen sulfite Sodium acid sulfite Monosodium sulfite
CAS Number	7631-90-5
Structural Formula	
Molecular Formula	H2O3S.Na
Molecular Weight	104.06

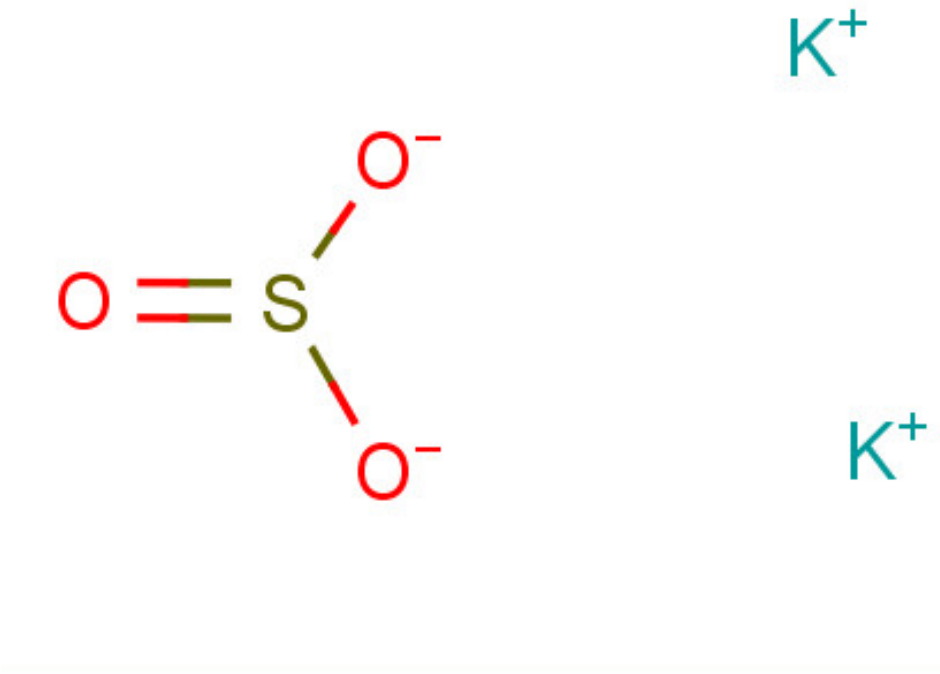
Chemical Name in the Inventory and Synonyms	**Disulfurous acid, sodium salt (1:2)** Sodium metabisulfite Disulfurous acid, sodium salt (1:2) Disodium disulfite Sodium pyrosulfite Sodium disulfite
CAS Number	7681-57-4
Structural Formula	
Molecular Formula	H2O5S2.2Na
Molecular Weight	190.11

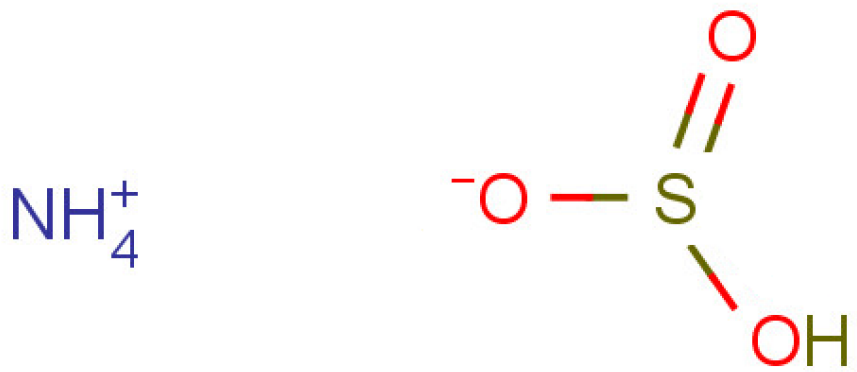
Chemical Name in the Inventory and Synonyms	**Disulfurous acid, disodium salt** Disulfurous acid, disodium salt 7757-74-6 Sodium metabisulfite Disodium pentaoxodisulfite Disodium pyrosulfite Pyrosulfurous acid, disodium salt
CAS Number	7757-74-6
Structural Formula	

	
Molecular Formula	H2O5S2.2Na
Molecular Weight	190.11

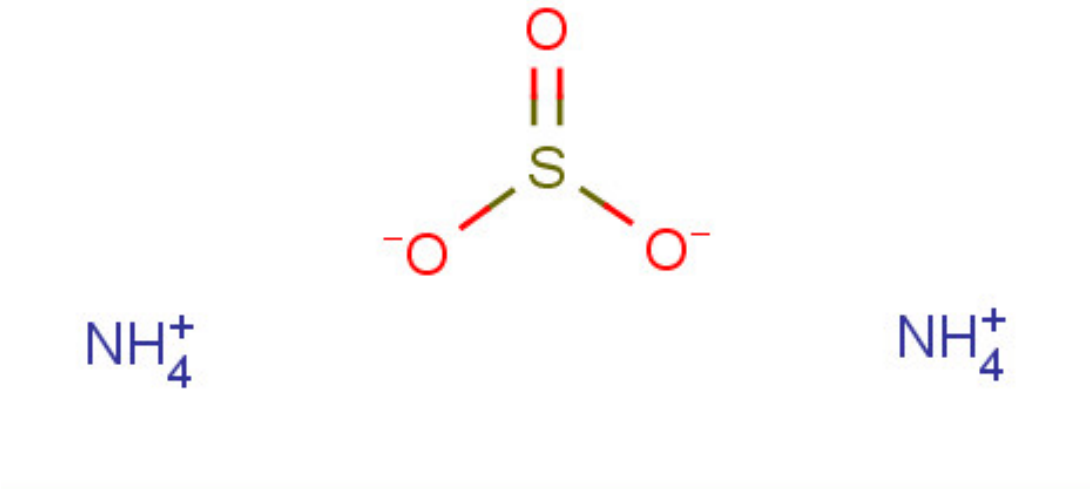
Chemical Name in the Inventory and Synonyms	**Sulfurous acid, disodium salt** Sodium sulfite Sodium sulfite Sulfurous acid, sodium salt (1:2) Disodium sulfite
CAS Number	7757-83-7
Structural Formula	
Molecular Formula	H2O3S.2Na
Molecular Weight	126.04

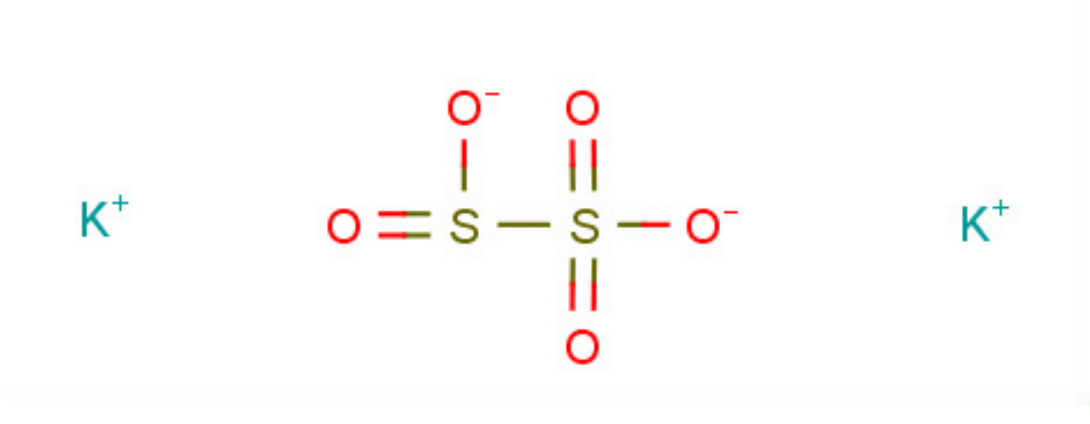
Chemical Name in the Inventory and Synonyms	**Sulfurous acid, dipotassium salt** Potassium sulfite

	Dipotassium sulfite Sulfurous acid, potassium salt
CAS Number	10117-38-1
Structural Formula	
Molecular Formula	H2O3S.2K
Molecular Weight	158.26

Chemical Name in the Inventory and Synonyms	**Sulfurous acid, monoammonium salt** Ammonium bisulfite Ammonium acid sulfite Ammonium hydrogen sulfite Monoammonium sulfite
CAS Number	10192-30-0
Structural Formula	
Molecular Formula	H3N.H2O3S

Molecular Weight	99.11

Chemical Name in the Inventory and Synonyms	**Sulfurous acid, diammonium salt** Ammonium sulfite Diammonium sulfite Diammonium sulfonate Sulfurous acid, ammonium salt (1:2) Ammonium hydrogen sulfite
CAS Number	10196-04-0
Structural Formula	
Molecular Formula	H3N.1/2H2O3S
Molecular Weight	116.14

Chemical Name in the Inventory and Synonyms	**Disulfurous acid, dipotassium salt** Potassium metabisulfite Potassium pyrosulfite Potassium disulfite Disulfurous acid, potassium salt (1:2) Dipotassium disulfite
CAS Number	16731-55-8
Structural Formula	
Molecular Formula	H2O5S2.2K
Molecular Weight	222.32

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