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Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals

Summary of Data Reported and Evaluation

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OCCUPATIONAL EXPOSURES TO MISTS AND VAPOURS FROM SULFURIC ACID AND OTHER STRONG INORGANIC ACIDS (Group 1)

For definition of Groups, see Preamble Evaluation.

VOL.: 54 (1992) (p. 41)

Sulfuric acid
CAS No.: 7664-93-9

Sulfur trioxide
CAS No.: 7446-11-9

Oleum
CAS No.: 8014-95-7

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Strong inorganic acids may be present in the work environment as mists, vapours or gases. The most prevalent acids are sulfuric, hydrochloric, nitric and phosphoric acids, which may be present in a wide variety of industries, including the extraction, fabrication and finishing of metal, fertilizer production, battery manufacture and various segments of the petroleum, chemical and petrochemical industries. Millions of workers worldwide are estimated to be potentially exposed to these acids.

Sulfuric acid is the most widely used of the strong inorganic acids. Average exposures to sulfuric acid mists in pickling, electroplating and other acid treatment of metals are frequently above 0.5 mg/m^3, while lower levels are usually found in the manufacture of lead-acid batteries and in phosphate fertilizer production. Exposure to sulfuric acid also occurs during its manufacture and during the production of isopropanol, synthetic ethanol and detergents. Hydrochloric acid is used in industries that involve acid treatment of metals, where occupational exposure levels to hydrochloric acid mists and gas are frequently above 1 mg/m^3. Exposures to hydrochloric acid may also occur during its synthesis and use in various industrial processes. Pickling and other acid treatments of metal may entail occupational exposures to nitric and phosphoric acids, but these occur less frequently than exposures to sulfuric and hydrochloric acids. Exposure to nitric acid also occurs during its manufacture and exposure to phosphoric acid in phosphate fertilizer production.

5.2 Human carcinogenicity data

An early study of isopropanol manufacture in the USA using the strong-acid process demonstrated an excess of nasal sinus cancer. Studies of one US cohort of workers in pickling operations within the steel industry showed excesses of laryngeal and lung cancer after smoking and other potentialconfounding variables had been controlled for. A Swedish study of a cohort of workers in steel pickling also showed an excess risk for laryngeal cancer. A nested case-control study of workers in a US petrochemical plant showed an elevated risk for laryngeal cancer among workers exposed to sulfuric acid. Of two population-based case-control studies in Canada, one of laryngeal cancer showed an increased risk for exposure to sulfuric acid, and one of lung cancer suggested an excess risk; the latter also suggested a risk associated with exposure to mixed inorganic acids. In all these studies, sulfuric acid mists were the commonest exposure, and positive exposure-response relationships were seen in two of the studies.

Additional supporting evidence was provided by one cohort study in the soap manufacturing industry in Italy,

which showed an increased risk for laryngeal cancer. Studies of three US cohorts and one Swedish cohort in the phosphate fertilizer manufacturing industry showed excess lung cancer, but there was potential confounding from exposure to radon decay products in some cohorts.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Acid mists containing particles with a diameter of up to a few micrometers will be deposited in both the upper and lower airways. They are irritating to mucous epithelia, they cause dental erosion, and they produce acute effects in the lungs (symptoms and changes in pulmonary function). Asthmatics appear to be at particular risk for pulmonary effects.

Significant increases in the incidences of sister chromatid exchange, micronucleus formation and chromosomal aberrations in peripheral lymphocytes were observed in a single study of workers engaged in the manufacture of sulfuric acid.

The studies reviewed examined the effects of pH values < 7 specifically. In cultured mammalian cells at pH 6.7 or below, cell transformation, gene mutation and chromosomal aberrations were induced. Mitotic abnormalities were induced in sea urchins and clastogenic effects in plants. Gene conversion was induced in yeast cells. No point mutation was observed in fungi, yeast or bacteria. Acid pH caused depurination of isolated DNA.

5.5 Evaluation

There is *sufficient evidence* that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic.

Overall evaluation

Occupational exposure to strong-inorganic-acid mists containing sulfuric acid is *carcinogenic to humans (Group 1)*.

Synonyms for sulfuric acid

- Battery acid
- BOV
- Dihydrogen sulfate
- Dipping acid
- Electrolyte acid
- Hydrogen sulfate
- Matting acid
- Mattling acid
- Nordhausen acid
- Oil of vitriol
- Sulphuric acid
- Vitriol brown oil

Synonyms for sulfur trioxide

- Sulfan
- Sulfuric anhydride

- Sulfuric oxide
- Sulfur oxide (SO_3)
- Sulphur trioxide

Synonyms for oleum

- Fuming sulfuric acid
- Sulfuric acid fuming
- Sulfuric acid mixture with sulfur trioxide

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SULFUR DIOXIDE AND SOME SULFITES, BISULFITES AND METABISULFITES (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 54 (1992) (p. 131)

Sulfur dioxide
CAS No.: 7446-09-5

Sodium sulfite
CAS No.: 7757-83-7

Sodium bisulfite
CAS No.: 7631-90-5

Sodium metabisulfite
CAS No.: 7681-57-4

Potassium metabisulfite
CAS No.: 16731-55-8

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 metabisulfure 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

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)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms for Sulfur dioxide

- Sulfurous acid anhydride
- Sulfurous anhydride
- Sulfurous oxide
- Sulfur oxide [SO_2]
- Sulphur dioxide
- Sulfur superoxide

Synonyms for Sodium sulfite

- Anhydrous sodium sulfite
- Disodium sulfite
- Sodium sulphite
- Sulfurous acid, disodium salt

Synonyms for Sodium bisulfite

- Hydrogen sulfite sodium
- Monosodium sulfite
- Sodium acid sulfite
- Sodium bisulphite
- Sodium hydrogen sulfite
- Sodium sulfite [$NaHSO_3$]
- Sulfurous acid, monosodium salt

Synonyms for Sodium metabisulfite

- Disodium disulfite
- Disodium metabisulfite
- Disodium pyrosulfite
- Disulfurous acid, disodium salt
- Pyrosulfurous acid, disodium salt
- Sodium disulfite

- Sodium metabisulphite
- Sodium pyrosulfite

Synonyms for Potassium metabisulfite

- Dipotassium disulfite
- Dipotassium metabisulfite
- Dipotassium pyrosulfite
- Disulfurous acid, dipotassium salt
- Potassium disulfite
- Potassium metabisulfite
- Potassium pyrosulfite
- Pyrosulfurous acid, dipotassium salt

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HYDROCHLORIC ACID
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 54 (1992) (p. 189)
CAS No.: 7647-01-0

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Hydrochloric acid is one of the most widely used industrial chemicals. It is used in pickling and cleaning steel and other metals, in the production of many inorganic and organic chemicals, in food processing, in cleaning industrial equipment, in extraction of metals and for numerous other purposes.

Hydrochloric acid may occur in workroom air as a gas or mist. The mean concentration of hydrochloric acid during pickling, electroplating and other acid treatment of metals has been reported to range from < 0.1 to 12 mg/m^3. Mean levels exceeding 1 mg/m^3 may also occur in the manufacture of sodium sulfite, calcium chloride and hydrochloric acid, in offset printing shops, in zirconium and hafnium extraction, and during some textile processing and laboratory work.

Hydrochloric acid levels in ambient air usually do not exceed 0.01 mg/m^3.

5.2 Human carcinogenicity data

One US study of steel-pickling workers showed an excess risk for cancer of the lung in workers exposed primarily to hydrochloric acid. An increased risk for laryngeal cancer was observed in the same cohort; however, no analysis was performed of workers exposed to hydrochloric acid. None of three US industry-based case-control studies suggested an association between exposure to hydrogen chloride and cancers of the lung, brain or kidney. In one Canadian population-based case-control study, an increased risk for oat-cell carcinoma was suggested in workers exposed to hydrochloric acid; however, no excess risk was observed for other histological types of lung cancer.

5.3 Animal carcinogenicity data

In one lifetime study in male rats exposed by inhalation at one dose level, hydrogen chloride did not produce a treatment-related increase in the incidence of tumours. Hydrogen chloride was tested at one dose level in combination with formaldehyde by inhalation exposure in the same long-term experiment in male rats. Hydrogen chloride did not influence the nasal carcinogenicity of formaldehyde when mixed with it upon entry into the inhalation chamber. When the two compounds were premixed before entry into the inhalation chamber, an increased incidence of nasal tumours was observed over that seen in animals treated with the combination mixed on entry or with formaldehyde alone.

5.4 Other relevant data

In single studies, hydrochloric acid induced mutation and chromosomal aberrations in mammalian cells; it also induced chromosomal aberrations in insects and in plants. Hydrochloric acid did not induce mutation in bacteria.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of hydrochloric acid.

There is *inadequate evidence* for the carcinogenicity in experimental animals of hydrochloric acid.

Overall evaluation

Hydrochloric acid is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Anhydrous hydrochloric acid
- Chlorohydric acid
- Hydrochloric acid gas
- Hydrogen chloride
- Muriatic acid

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DIETHYL SULFATE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 54 (1992) (p. 213)

CAS No.: 64-67-5
Chem. Abstr. Name: Sulfuric acid, diethyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Diethyl sulfate is manufactured from ethylene and sulfuric acid. It is used principally as an intermediate (ethylating agent) in the manufacture of dyes, pigments and textile chemicals, and as a finishing agent in textile production. It is an obligatory intermediate in the indirect hydration (strong acid) process for the preparation of synthetic ethanol from ethylene.

No data were available on levels of occupational exposure to diethyl sulfate.

5.2 Human carcinogenicity data

One cohort study at a US isopropanol and ethanol manufacturing plant revealed an increased risk for laryngeal cancer. A subsequent case-control study nested in an expanded cohort at this plant indicated that the increased risk was related to exposure to sulfuric acid; the risk persisted even after exclusion of workers in the ethanol and isopropanol units. A cohort study from two US plants producing ethanol and isopropanol suggested an increased risk for cancers of the larynx, buccal cavity and pharynx, but not of the lung, in strong-acid workers. An association between estimated exposure to diethyl sulfate and risk for brain tumour was suggested in a study of workers at a US petrochemical plant.

No measurement of exposure diethyl sulfate was available for the industrial processes investigated in the epidemiological studies. It is therefore difficult to assess the contribution of diethyl sulfate to the increased cancer risks. Furthermore, exposure to mists and vapours from strong inorganic acids, primarily sulfuric acid, may play a role in increasing these risks.

5.3 Animal carcinogenicity data

Diethyl sulfate was tested for carcinogenicity by oral and subcutaneous administration in one strain of rats. After subcutaneous administration, a high incidence of malignant tumours occurred at the injection site. Following oral gavage of diethyl sulfate, forestomach tumours were observed. A low incidence of malignant tumours of the nervous system was observed in the same strain of rats after prenatal exposure.

5.4 Other relevant data

Diethyl sulfate induced specific locus mutations in mouse germ-line cells. It was clastogenic in mice and newts, induced DNA damage in mice and rats and ethylated DNA in mice. Diethyl sulfate induced chromosomal aberrations and micronucleus formation in cultured human lymphocytes. It induced alkali-labile sites in cultured human leukocytes in one study. In cultured mammalian cells, diethyl sulfate induced chromosomal aberrations, micronucleus formation, sister chromatid exchange, forward mutation and DNA single-strand breaks; it also induced unscheduled DNA synthesis in primary cultures of rat hepatocytes. In single studies, diethyl sulfate did not induce aneuploidy or reciprocal translocation in *Drosophila melanogaster* but did induce sex-linked

recessive lethal mutations and genetic crossing-over. In plant cells, diethyl sulfate induced chromosomal aberrations, mutation and unscheduled DNA synthesis. It induced reverse mutation and mitotic recombination in yeast. Diethyl sulfate induced mutation and DNA damage in bacteria.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of diethyl sulfate.

There is *sufficient evidence* for the carcinogenicity in experimental animals of diethyl sulfate.

Diethyl sulfate is a strong alkylating agent which ethylates DNA. As a result, it is genotoxic in virtually all test systems examined including induction of potent effects in somatic and germ cells of mammals exposed *in vivo*.

Overall evaluation

Diethyl sulfate is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 4 (1974) (p. 277); Suppl. 7 (1987) (p. 198)

Subsequent evaluation: Vol. 71 (1999)

Synonyms

- Diethyl sulphate
- Diethyl tetraoxosulfate
- DS
- Ethyl sulfate
- Sulfuric acid, diethyl ester

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DIISOPROPYL SULFATE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 54 (1992) (p. 229)

CAS No.: 2973-10-6
Chem. Abstr. Name: Sulfuric acid, bis(1-methylethyl)ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Diisopropyl sulfate is an intermediate in the indirect hydration (strong- or weak-acid) process for the preparation of isopropanol from propylene. It has no other known industrial use.

No data were available on levels of occupational exposure to diisopropyl sulfate.

5.2 Human carcinogenicity data

An early US cohort study of isopropanol manufacture using the strong-acid process in a petrochemical plant demonstrated an excess risk for nasal sinus cancer. An increased risk for cancer of the buccal cavity and pharynx was suggested in a cohort of workers at an isopropanol unit in the USA. A cohort study at an isopropanol plant in the United Kingdom indicated an increased risk for nasal cancer (based on one case only) and for brain tumours.

One cohort study at a US isopropanol and ethanol manufacturing plant revealed an increased risk for laryngeal cancer. A subsequent case-control study nested in an expanded cohort at this plant indicated that the increased risk was related to exposure to sulfuric acid; the risk persisted even after exclusion of workers in the ethanol and isopropanol units. A cohort study from a US plant producing ethanol and isopropanol suggested an increased risk for cancers of the larynx, buccal cavity and pharynx, but not of the lung, in strong-acid workers.

No measurement of exposure to diisopropyl sulfate was available for the industrial processes investigated in the epidemiological studies. It is therefore difficult to assess the contribution of diisopropyl sulfate to the increased cancer risks. Furthermore, exposure to mists and vapours from strong inorganic acids, primarily sulfuric acid, probably plays a role.

5.3 Animal carcinogenicity data

Diisopropyl sulfate was tested for carcinogenicity by subcutaneous injection in one strain of rats and by skin application in one strain of mice. It produced local sarcomas in rats skin papillomas and carcinomas in mice. In a screening study in two strains of mice, an increased incidence of lung adenomas was observed following subcutaneous injection.

5.4 Other relevant data

No data were available to the Working Group.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of diisopropyl sulfate.

There is *sufficient evidence* for the carcinogenicity in experimental animals of diisopropyl sulfate.

Overall evaluation

Diisopropyl sulfate is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Subsequent evaluation: Vol. 71 (1999)

Synonyms

- Di-isopropylsulphate
- Diisopropylsulfate
- Diisopropyl tetraoxosulfate
- DIPS
- Isopropyl sulfate
- Sulfuric acid, diisopropyl ester

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