NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for STRONG INORGANIC ACID MISTS CONTAINING SULFURIC ACID

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NTP Report on Carcinogens Listing for Strong Inorganic Acid Mists Containing Sulfuric Acid

Carcinogenicity

Occupational exposure to strong inorganic acid mists containing sulfuric acid is *known to be a human carcinogen,* based on studies in humans that indicate a causal relationship between exposure to strong inorganic acid mists containing sulfuric acid and human cancer (reviewed in IARC, 1992).

Occupational exposures to strong inorganic acid mists containing sulfuric acid are specifically associated with laryngeal and lung cancer in humans. Steenland et al. (1988) reported on studies of one U.S. cohort of male workers in pickling operations in the steel industry, which showed excesses of laryngeal cancer after adjusting for smoking and other potential confounding variables [standardized incidence rate ratio (SIR) for laryngeal cancer was 2.30 (95% confidence interval [CI], 1.05-4.36)]. In a ten-year follow-up, Steenland (1997) reported a laryngeal cancer rate ratio of 2.2 (95% CI, 1.2-3.7), consistent with previous findings from this cohort. In a nested case-control study of workers in a U.S. petrochemical plant, Soskolne et al. (1984) found a dose-response for laryngeal cancer risk among workers exposed to moderate (odds ratio [OR] of 4.6; 95% CI, 0.83-25.35) or high levels (OR of 13.4; 95% CI, 2.08-85.99) of sulfuric acid. In a Canadian population based case-control study, after controlling for tobacco and alcohol use and including only the most specific exposure scale, Soskolne et al. (1992) also observed a dose-response for laryngeal cancer risk in workers exposed to sulfuric acid mist, with ORs of 2.52 (95% CI, 0.80-7.91) at the lowest level of exposure and 6.87 (95% CI, 1.00-47.06) at the highest. A report of a similar population based case-control study in Canada by Siemiatycki (1991) suggested an increase in risk for oat-cell carcinoma of the lung (rate ratio [RR] of 2.0; 90% CI, 1.3-2.9). Steenland and Beaumont (1989), reporting on the same U.S. cohort of male workers in pickling operations described by Steenland et al. (1988), found an excess of lung cancer in these workers after adjusting for smoking and other potential confounding variables [standardized mortality ratio (SMR) for lung cancer was 1.36 (95% CI, 0.97-1.84)].

No adequate experimental animal carcinogenicity studies of sulfuric acid or strong inorganic acid mists containing sulfuric acid have been reported in the literature.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

The manufacture of isopropyl alcohol by the strong acid process, which uses sulfuric acid, has been identified by IARC as known to cause an increased incidence of cancer of the paranasal sinuses in workers (reviewed in IARC, 1977).

The carcinogenic activity of sulfuric acid is most likely related to the genotoxicity of low pH environments. Reduced pH environments are known to enhance the depurination rate of DNA and the deamination rate of cytidine (IARC, 1992).

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded; or

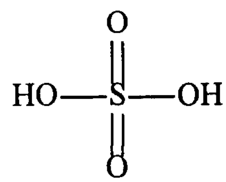
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in previous Reports on Carcinogens as either a known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgement, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL PROPERTIES

Sulfuric Acid
[7664-93-9]



1.1 Chemical Identification

Sulfuric Acid (H_2SO_4, mol. wt. = 98.08) is also called:

- Battery acid
- BOV
- Brown Oil
- Dihydrogen Sulfate
- Dipping acid
- Dithionic acid
- Electrolyte Acid
- Hydrogen sulfate
- Matting acid
- Mattling Acid
- Nordhausen acid (DOT)
- Oil of vitriol
- Sulforic acid
- Sulfuric acid aerosol
- Sulfuric acid, mist
- Sulfuric acid, spent
- Sulphuric acid
- Vitriol
- Vitriol Brown oil
- Vitriolic acid
- Vitriol, oil of

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Clear, colorless	Budavari (1996)
Physical State	Oily liquid	Budavari (1996)
Melting Point, °C	10.36 (anhydrous acid); 3.0 (98%)	Weast and Astle (1980)
Boiling Point, °C	~290; 338 (98.3%)	Budavari (1996); Weast and Astle (1980)
Density at 20 °C	1.84 (96-98% acid)	Budavari (1996); Ludwig (1994)
Dissociation Constant at 25 °C (pKa)	1.92 (Step 2)	Weast and Astle (1980)
Odor	Slightly sulfurous; odorless	Spectrum (1996); Budavari (1996)
Odor Threshold:		
Air	1.0 mg/m^3	Ruth (1986; cited by HSDB, 1997)
Solubility:		
Water at 20 °C	Soluble in cold or hot water with evolution of heat	Weast and Astle (1980)
Organic Solvents	Decomposes in alcohol	
Vapor density (Air = 1)	3.4	Spectrum (1996)
Vapor pressure at 20 °C, mm Hg	0.01	Spectrum (1996)

Commercial sulfuric acid contains 93 to 98% H_2SO_4 and the rest water. Fuming sulfuric acid or oleum contains up to 80% free sulfur trioxide (SO_3) (Budavari, 1996).

Sulfuric acid is very corrosive and desiccates organic matter on contact (Budavari, 1996). Sulfuric acid emits SO_x upon thermal decomposition at $\geq$ 340 °C (Spectrum, 1996; Budavari, 1996).

Liquid sulfuric acid may exist in air as vapor or mist, most often as mist because of sulfuric acid's low volatility and its tendency to react with water. A mist has been defined by Hinds (1985; cited by IARC, 1992) as a liquid aerosol formed by condensation of a vapor or atomization of a liquid.

Sulfuric acid mist has been the most extensively studied of the acid mists. Its human effects depend on many factors such as particle size, water solubility, free hydrogen ion concentration, and presence of other chemicals in the aerosol particle. Acid aerosols as a group have been designated one of six criteria pollutants by the U.S. Environmental Protection Agency because of their increasing presence from various human activities and their potential to cause or aggravate health effects, particularly within the respiratory tract. Sulfuric acid mist may contain aerosol particles up to a few micrometers in diameter; generally, the smaller the particle, the deeper it may penetrate into the lung. Local corrosive effects on skin and mucous epithelia from sulfuric acid mist may occur upon exposure to adequate levels (IARC, 1992).

1.3 Acid Strength

Strong inorganic acids of principal interest for the IARC monograph "Occupational exposures to mists and vapours from sulfuric acid and other strong inorganic acids" are sulfuric acid, hydrochloric acid, nitric acid, and phosphoric acid. The relative strength of inorganic acids is based on the degree of dissociation in water to give hydronium ions (H_3O^+), with the difference between weak and strong acids being several orders of magnitude (IARC, 1992, pp. 41-42).

In some contexts in the literature reviewed, "acid strength" may be related to the concentration of H_2SO_4 in the solution. [The concentrations of H_2SO_4 range from 35.67% to 98.99% in industrial applications described in the IARC monograph as of concern for the generation of strong inorganic acid mists. Additional industries use oleum, concentrated sulfuric acid with free SO_3 concentrations up to 65%. For example, oleum with 40% free SO_3 is used in industrial nitrations and sulfonations (IARC, 1992, pp. 122, 124).] All of these concentrations would give aerosols considered to be strong inorganic acid mists containing sulfuric acid.

2.0 HUMAN EXPOSURE

2.1 Use

Sulfuric acid is a widely used industrial chemical. Manufacture of fertilizers (both phosphate and ammonium sulfate) is the principal use of sulfuric acid. It is used as a reagent in many processes and usually appears in the end products as sulfate waste or spent acid (IARC, 1992).

The breadth of its other industrial uses is discussed in subsection 2.3.2.

2.2 Production, Producers, and Production Volume

Sulfuric acid is the largest volume chemical produced in the United States (Kirschner, 1996). In 1996, the total production volume was 47,677 million tons (43,252 million metric tons [Mg]) (Chem. Eng. News, 1997). As of January 1996, there were 61 companies listed as producers of sulfuric acid (SRI International, 1996), 10 of which produced more than 1.0 million Mg each. The total annual capacity was listed as 48.36 million Mg of sulfuric acid in 1995. The five largest producers listed were IMC-Agrico Co., PCS Phosphate Co., Rhône-Poulenc, Inc., Cargill Fertilizer, Inc., and Magma Metals with the following annual capacities: 8.88 million Mg, 6.286 million Mg, 2.937 million Mg, 2.766 million Mg, and 1.90 million Mg, respectively.

Sulfuric acid is used or produced during various manufacturing processes, during which sulfuric acid mists may be generated. In pickling, for instance, mist may escape from acid tanks when hydrogen bubbles and steam rise from the surface of the solution (IARC, 1992).

Mist may be generated during a process when factors such as evaporative surface area, solution strength, temperature, and pressure combine to effect release or condensation of gases. Concentrations to which workers are exposed depend on proximity to the source and controls of ventilation and containment (IARC, 1992).

2.3 Exposure

2.3.1 Environmental Exposure

Sulfuric acid is found naturally in volcanic locations, especially in volcanic gases (HSDB, 1997). According to the Toxic Chemical Release Inventory for 1995 (TRI95, 1997), the total reported anthropogenic environmental release of sulfuric acid was 26,486,002 lb (13,243 tons; 12,014 Mg).

Ambient air may contain particulate-associated mixtures of sulfuric acid and ammonium sulfates (sulfuric acid partially or completely neutralized by atmospheric ammonia). The relative amounts of sulfuric acid and total sulfates depend on meteorological and chemical parameters. Diammonium sulfate is usually the predominant atmospheric chemical species in the submicrometer particles. The presence of sulfuric acid and sulfates in the atmosphere is believed to be due to oxidation of sulfur dioxide in cloud water and other atmospheric media. The presence of ammonia may be due to anthropogenic pollution such as coke plant emissions. Ambient air concentrations of ammonium sulfates are very low in areas where anthropogenic sulfur dioxide emissions are low or far removed. Sulfuric acid and sulfate aerosol events (periods of distinct acidity) may be due to regional scale atmospheric stagnation episodes or to local sources of sulfur dioxide emissions (Johnson and Kumar, 1988; Burton et al., 1992; Schlesinger and Chen, 1994; Spengler et al., 1996). For example, distinct periods of strong acidity were reported in two eastern U.S. cities, with 24-hour hydrogen ion concentrations exceeding 100 $nmol/m^3$ more than 10 times during summer months and less frequently in winter months [if the hydrogen ion source was only sulfuric acid, the concentration would be expected to be equivalent to 50 nmol/m^3 (0.005 mg/m^3)] (Spengler et al., 1989). Ambient air concentrations of sulfuric acid are an order of magnitude or more lower than concentrations in the occupational settings described in Section 2.3.2 [range in Table 2-1: 0.01-1.7 mg/m^3 (102-17,000 nmol/m^3) with the >16 mg/m^3 outlier excluded].

The Toxic Chemicals Release Inventory for 1995 (TRI95, 1997) includes a total of 1570 facilities reporting environmental releases of sulfuric acid. Among the 835 facilities reporting atmospheric sulfuric acid emissions, 221 facilities reported emissions of up to 200 lb/rep. (reported) yr. The remaining 614 facilities had emissions distributed as follows: > 200 to 2000 lb/rep. yr, 310 facilities; > 2000 to 10,000 lb/rep. yr, 74 facilities; > 10,000 to 50,000 lb/rep. yr, 127 facilities; > 50,000 to 75,000 lb/rep. yr, 28 facilities; > 75,000 to 100,000 lb/rep. yr, 20 facilities; > 100,000 to 150,000 lb/rep. yr, 23 facilities; > 150,000 to 200,000 lb/rep. yr, 10 facilities; and > 200,000 to 1,000,000 lb/rep. yr, 21 facilities. One facility reported an emission of 7,002,800 lb/rep. yr (3,501 tons; 3176 Mg) of sulfuric acid to the air in 1995. The industries reporting releases were pulp and paper mills (SIC 2611 and 2621), petroleum refining (SIC 2911), phosphate fertilizers (SIC 2874), plastics products, not elsewhere classified (SIC 3089), industrial organic chemicals, not elsewhere classified (SIC 2869), and primary copper industries (SIC 3331).

2.3.2 Occupational Exposure

Numerous studies in which occupational exposure to sulfuric acid mist has been examined in industrial processes have been reviewed by IARC (1992). Eight industrial processes were described on pages 42-57 of the monograph: manufacture of isopropyl alcohol, lead batteries, nitric acid, phosphate fertilizers, soap and detergents, synthetic ethanol, and sulfuric acid and pickling and other acid treatments of metals. These and several other industries and processes are listed on page 59 of the monograph.

Workplace exposure measurements have been recorded over several years. As can be seen from Table 2-1, it appears that generally the highest exposures to sulfuric acid mists in the United States have been associated with acid treatment of metals. Numerous studies and activities have been aggregated in this summary table. Values were aggregated without regard to sample type (personal or area). See IARC (1992), pp. 62-68, 71-75, for more details.

Table 2-1. U.S. Workplace Air Concentrations of Strong Inorganic Acid Mists Containing Sulfuric Acid [Summarized from IARC (1992)], mg/m³ (Year of Measurement)

Process/Industry	Reported Means	
	Low	High
Acid treatment of metals:		
Pickling	0.032 (1979)	2.97 (1981)
Cleaning	< 0.01 (1977)	5 (1977)
Etching [Aircraft maintenance (1 study)]	0.062 (1981) (area)	0.067 (1981) (personal)
Electrolytic refining	0.01 (1981)	0.27 (1978[a])
Plating	0.013 (1981)	7.3 (1980)
Anodizing, auto trim (1 study)	<0.01 (1976)	-
Miscellaneous	0.026 (1979)	0.11 (1979)
Phosphate fertilizer manufacture	0.068 (1976)	0.571 (1976)
Lead battery manufacture [Study published in 1961 (year of measurements not reported)]	>16	-
Other lead battery manufacture studies, 1976-1988 (few ranges given)	0.01 (1988)	1.03[b] (1978)
Various other industries:		
Tannery	0.16 (1982)	0.48 (1981)
Corn products, wet milling	1.7 (1988)	-
Paper machine tending (1 study)	0.01 (1981)	
Aircraft maintenance waste treatment plant	<0.015 (1972)	
Volcano observation	-	1.0 (1979)

[a]Same study; [b]No associated range given; ND = not detected

The National Institute of Occupational Health and Safety (NIOSH, 1990) listed results of the National Occupational Exposure Survey (1981-1983), which reported 54,519 plants with potential workplace exposure to sulfuric acid. A total of 775,584 employees, including 173,650 female employees, were potentially exposed to sulfuric acid in the workplace (see **Table 2-2**).

Table 2-2. NIOSH National Occupational Exposure Survey (NOES, 1981-83)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Agricultural Services	1331	5660	2348
Oil and Gas Extraction	396	15957	
General Building Contractors	550	10686	781
Heavy Construction Contractors	397	6768	75
Special Trade Contractors	1857	18559	107
Food and Kindred Products	2714	20199	6060
Tobacco Manufactures	8	56	
Textile Mill Products	670	14283	1886
Apparel and Other Textile Products	154	22765	20760
Lumber and Wood Products	356	5890	170
Furniture and Fixtures	198	1574	284
Paper and Allied Products	1093	26088	2429
Printing and Publishing	6554	52047	13027
Chemicals and Allied Products	2091	66683	8337
Petroleum and Coal Products	525	39541	1020
Rubber and Misc. Plastics Products	323	4069	1084
Leather and Leather Products	173	3681	721
Stone, Clay, and Glass Products	648	9403	498
Primary Metal Industries	1186	25768	628
Fabricated Metal Products	2957	44428	4996
Machinery, Except Electrical	1901	21509	1090
Electric and Electronic Equipment	1454	32790	11594
Transportation Equipment	1059	26749	1264
Instruments and Related Products	783	22232	6454
Miscellaneous Manufacturing Industries	1232	9116	1433
Trucking and Warehousing	981	7850	592
Transportation by Air	919	10709	279
Communication	1311	14955	395
Electric, Gas, and Sanitary Services	1492	40185	1719
Wholesale Trade -Durable Goods	1659	9237	381
Wholesale Trade - Nondurable Goods	2107	7826	474
Automotive Dealers & Service Stations	2374	12735	
Personal Services	1463	16176	13255
Business Services	2972	45401	14434
Auto Repair, Services, and Garages	3755	17789	
Miscellaneous Repair Services	290	290	
Health Services	4412	85263	54829
Museums, Botanical, Zoological Gardens	174	667	246
Total	54519	775584	173650

[a]NIOSH (1990)

Table 8, page 60, of the IARC monograph (IARC, 1992) lists occupations that have potential exposure to strong inorganic acids.

2.4 Regulations and Criteria

EPA regulates sulfuric acid atmospheric emissions under the Clean Air Act regulations concerning Standards of Performance for New Stationary Sources and State Implementation Plans to prevent significant deterioration of air quality; CERCLA (Comprehensive Emergency Response, Compensation, and Liability Act) and EPCRA (Emergency Planning and Community Right-to-Know Act). The specific regulations are described in the Regulations table. EPA regulations pertaining primarily to sulfuric acid in effluents to water, pesticide residues, or solid wastes are not included. FDA regulations on sulfuric acid are not included since they relate to possible ingestion. NIOSH (1974) recommended a $\leq$10-hour time-weighted average (TWA) exposure of 1 mg/m^3. The OSHA permissible exposure limit (PEL) for sulfuric acid in workroom air, the construction industry, and shipyards is 1 mg/m^3 as an 8-hour TWA. ACGIH (1996) also recommended a workroom air threshold exposure limit for sulfuric acid in strong inorganic mists (considered to be a suspected human carcinogen) of 1 mg/m^3 as an 8-hour TWA for a 40-hour work week. In addition, ACGIH recommended a short-term exposure limit (STEL) of 3 mg/m^3. "Worker exposure by all routes should be controlled as low as possible below the TLV."

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 51—PART 51—REQUIREMENTS FOR PREPARATION, ADOPTION, AND SUBMITTAL OF IMPLEMENTATION PLANS. Promulgated: 36 FR 22398, 11/25/71. U.S. Codes: 42 U.S.C. 7401-7671q.	The provisions of this part apply to the administration of air quality maintenance areas under the Clean Air Act. This includes maintenance of national standards, control strategy, prevention of air pollution emergency episodes, ambient air quality surveillance, compliance schedules, protection of visibility and miscellaneous plant content requirements.
	40 CFR 51.160 ff.—Subpart I—Review of New Sources and Modifications. Promulgated: 51 FR 40669, 11/07/86.	A facility may not be constructed or modified that will result in net emissions greater than 7 tons per year of sulfuric acid mist.
	40 CFR 52—PART 52—APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS. Promulgated: 37 FR 10846, 05/31/72.	The provisions of this part set forth the Administrator's approval and disapproval of State plans and the Administrator's promulgation of such plans and portions thereof.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 52.21—Sec. 52.21 Prevention of significant deterioration of air quality. Promulgated: 43 FR 26403, 06/19/78.	State implementation plans (SIPs) with net emissions increase or the potential of a source to emit sulfuric acid mist at a rate that at would exceed 7 tons per year have been disapproved with respect to prevention of significant deterioration of air quality.
	40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 36 FR 24877, 12/23/71. U.S. Codes: 42 U.S.C. 7401, 7411, 7414, 7416, 7429, and 7601,	The provisions of this part apply to the owner/operator of any stationary source which contains an affected facility (a stationary source with an apparatus to which a standard is applicable).
	40 CFR 60.30 ff.—Subpart Cd—Emissions Guidelines and Compliance Times for Sulfuric Acid Production Units.	Sulfuric acid mist shall not exceed 0.25 g/kg of sulfuric acid produced in designated facilities as defined in §60.81(a) of Subpart H. Facilities that control sulfuric dioxide emissions by conversion to sulfuric acid are excluded.
	40 CFR 60.80 ff.—Subpart H—Standards of Performance for Sulfuric Acid Plants.	This subpart sets emission monitoring guidelines and test methods and procedures for any facility producing sulfuric acid by conversion.
	40 CFR 60.83—Sec. 60.83 Standard for acid mist. Promulgated: 39 FR 20794, 06/14/74.	After its performance test, no facility shall discharge any gases into the atmosphere that contain sulfuric acid mist in excess of 0.075 mg/Mg acid produced (0.15 lb/ton). Emission monitoring requirements are set forth in §60.84 and 60.85.
	40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 302.4—Sec. 302.4 Designation of hazardous substances. Promulgated: 54 FR 33449, 08/14/89. Superfund (CERCLA, SARA) reportable quantity (RQ) is 1000 lb (454 kg).	EPA designated as hazardous those substances that when released into the environment may present substantial danger to the public health or welfare or the environment. Notification of EPA is required if the RQ is released to the environment.
	40 CFR 355—PART 355—EMERGENCY PLANNING AND NOTIFICATION. Promulgated: 52 FR 13395, 04/22/87. U.S. Codes: 42 U.S.C. 11002, 11004, and 11048.	The provisions of this part establish the list of extremely hazardous substances, threshold planning quantities, and facility notification responsibilities necessary for the development and implementation of State and local emergency response plans.
	40 CFR 355—Appendix A—The List of Extremely Hazardous Substances and Their Threshold Planning Quantities. Promulgated: 61 FR 20479, 05/07/96.	Sulfuric acid has a reportable quantity and a threshold planning quantity of 1000 lb.
	40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-T0-KNOW.	
	40 CFR 372—Subpart D—Specific Toxic Chemical Listings.	
	40 CFR 372.65—Sec. 372.65 Chemicals and chemical categories to which this part applies. Promulgated: 53 FR 4525, 02/16/88; 53 FR 12748, 04/18/88.	Annual reporting of atmospheric emission of sulfuric acid (acid aerosols including mists, vapors, gas, fog, and other airborne forms of any particle size) has been required since 01/01/87.
NIOSH	1974. Criteria for a Recommended Standard....Occupational Exposure to Sulfuric Acid. Pub. No. 74-128, NTIS No. PB-223098 (NIOSH, 1974).	NIOSH recommends that sulfuric acid be regarded as a pulmonary irritant. Summary of NIOSH recommendation: exposure limit—1 mg/m^3 as a TWA for up to 10 hours.
	06/81. Review and Evaluation of Recent Literature: Occupational Exposure to Sulfuric Acid. Pub. No. 82-104.	
OSHA	29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74. U.S. Code: 29 U.S.C. 653, 655, and 657.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
O S H A	29 CFR 1910.1000 ff.—Appendix Z—Toxic Hazardous Substances. Promulgated: 40 FR 23072, 05/28/75.	PEL for sulfuric acid ≤ 1 mg/m^3 as an 8-hr TWA.
	29 CFR 1915—PART 1915—OCCUPATIONAL SAFETY AND HEALTH STANDARDS FOR SHIPYARD EMPLOYMENT. Promulgated: 47 FR 16986, 04/20/82. U.S. Code: 29 U.S.C. 653, 655, and 657.	
	29 CFR 1915.1000—Sec. 1915.1000 Air Contaminants. Promulgated: 61 FR 31430, 07/01/93.	Exposure of employees in shipyards to inhalation, ingestion, skin absorption, or contact (TLV) with the airborne contaminant sulfuric acid is restricted to 1 mg/m^3 as an 8-hr TWA.
	29 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FR 8577, 02/09/79; 44 FR 20940, 04/06/79.	
	29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.	
	29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts, and mists. Promulgated: 39 FR 22801, 06/24/74.	Exposure of employees in the construction industry to inhalation, ingestion, skin absorption, or contact (TLV) with the airborne contaminant sulfuric acid is restricted to 1 mg/m^3 as an 8-hr TWA.
	29 CFR 1926—Subpart K—Electrical.	
	29 CFR 1926.441—Sec. 1926.441 Batteries and battery charging.	Escape of fumes, gases, or electrolyte spray from batteries of the unsealed type shall be prevented by working in enclosures with outside vents or in well ventilated rooms. Vent caps shall be kept in place to avoid electrolyte spray.

[a]Regulations have been updated through 62 FR 40029, 07/25/97.

3.0 HUMAN STUDIES

3.1 IARC (1992) Review of Sulfuric Acid Epidemiology

Most of the human literature through 1992 has been thoroughly evaluated in the IARC monograph, Volume 54 (1992, pp. 80-96; see Appendix A) and the following summarized studies reviewed therein. Several cohort and case-control studies of occupational exposure to sulfuric acid mists suggest a positive relationship between exposure and the risk of laryngeal or lung cancer. An excess of laryngeal (Steenland et al., 1988) and lung cancer (Steenland and Beaumont, 1989) occurred in a cohort of U.S. steel industry workers in pickling operations. A nested case-control study of workers in a U.S. petrochemical plant found an increased risk of laryngeal cancer among the ethanol production group exposed to strong sulfuric acid (Soskolne et al., 1984). A population-based case-control study of cases in southern Ontario that reported occupational exposure to sulfuric acid also suggested a greater risk of laryngeal cancer (Soskolne et al., 1992). A population-based case control study in Montreal identified significant associations between exposure to "inorganic acid solutions" (mainly solutions of hydrochloric, sulfuric, and nitric acids) and increased risk for oat-cell carcinoma of the lung and cancer of the kidney (Siemiatycki, 1991). Based on these studies, IARC (1992) concluded that there is sufficient evidence that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic to humans.

3.2 Human Studies Published Post-IARC (1992)

Two additional studies evaluated the cancer risk from occupational exposure to sulfuric and other acid mists. These studies are summarized below and in **Table 3-1**.

Coggon et al. (1996) conducted cohort and nested case-control analyses to assess the cancer mortality and aerodigestive cancer incidence in workers at two British lead-acid battery plants and two steel plants between 1950 and 1990. Exposure to sulfuric acid mist was estimated by personnel records and monitoring. Industrial hygiene measurements of sulfuric and hydrochloric acid levels were available after 1970 in the battery plants. Personnel records and a factory-specific job exposure matrix were used to classify workers' exposure. The total cohort included 4401 men and 1356 were classified as never exposed to acid mists, 367 as possibly exposed, and 2678 as definitely exposed. Deaths and cancer incidence were determined by the National Health Service central register. A total of 307 (7%) men were untraced. The mortality experience of the workers was compared to the British national population data. There was no excess of deaths either for all cancers or for any type of cancer, including larynx and lung. The nested case-control compared exposure in cohort men with cancer of the upper aerodigestive tract (oral, pharyngeal, laryngeal) to exposure in controls (5 per case) selected from the cohort, matched on date of birth, factory, and follow-up period for the case. In addition to acid mists, occupational histories for cases and controls were reviewed for potential exposure to asbestos and lead. The authors noted that asbestos and lead did not seem to be important confounding exposures. The standardized mortality ratio for death from all cancers among workers with "definite" exposure to acid mists was 0.92 (confidence interval [CI] = 0.79-1.05). There was a total of 15 cases of upper aerodigestive tract cancer (oral, pharyngeal, laryngeal) and 73 controls in the nested case-control analysis. Seven cases and 23 controls had at least five years' exposure to high levels of sulfuric acid mists (≥ 1 mg/m^3) (odds ratio [OR] = 2.0; 95% CI = 0.4-10). The OR for a high level of maximum exposure to acid mists was 1.3 (95% CI = 0.3-5.7) for 9 cases and 43 controls. The study was limited by a lack of adjustment for potential confounders such as smoking and alcohol consumption, low statistical power for specific cancers such as laryngeal cancer, use of mortality rather than cancer incidence, and a lack of industrial hygiene measurement data in the steel plants before 1970 and in the battery plants. Nonetheless, the study provides some weak support for previous findings.

Steenland (1997) extended the follow-up by 10 years of a previously evaluated cohort of U.S. male steelworkers. The average first year of exposure was 1949 and workers averaged 9.2 years of exposure. Originally 1,156 men were evaluated. The cohort follow-up study identified 14 incident cases of laryngeal cancer among 1,031 workers (89% of the original cohort). Duration of exposure for cases averaged 10.6 years (range 0.5-38.5), and years between first exposure and diagnosis averaged 30.7 years. Expected age- and sex-specific rates of incident cancer were derived from the SEER (Surveillance, Epidemiology, and End Results) program (1970-1994) and three National Cancer Surveys (1938, 1948, 1970). Using personnel records and knowledge of the process, industrial hygienists classified workers into categories reflecting the type of acid exposure; 62% were exposed to only sulfuric acid, 22% to sulfuric and other acids, and 16% only to acids other than sulfuric. A total of 5.6 laryngeal cancers was expected. With the use of population smoking and alcohol use prevalence data, the expected rate of laryngeal cancer was adjusted upward by 14% to 6.4 (rate ratio [RR] = 2.2; CI = 1.2-3.7). An extended analysis revealed no positive trends with increased duration of exposure (2.1 for 5+ yr), potential latency (RR = 2.1 for 20+ years' latency), or for the subgroup of workers (70% of the cohort) with daily contact with sulfuric acid mists (RR = 2.5; CI = 1.7-4.7). The study had the advantage of identifying incident cases with confirmation by medical records, classifying exposure by type of acid exposure, and indirectly adjusting for tobacco and alcohol consumption. The study also excluded any workers who worked at any time in coke ovens, the only known area in steel mills with known respiratory (lung) cancer risk, and measured area concentrations of heavy metals that might cause larynx cancer and found them to be below the limit of detection. Potential misclassification of exposure and confounders are study limitations.

Table 3-1. Recent Human Studies for Strong Inorganic Acid Mists Containing Sulfuric Acid

Design	Study Groups	Exposure Determination	Results	Potential Confounders	Reference
cohort and nested case-control	**Cohort:** 1) cohort - men employed in two battery manufacturing plants and two steel works in Britain; 2) nested case-control - all men in cohort with upper aerodigestive cancer (oral, pharyngeal, laryngeal) **Cases for Nested Case-control analysis**: 15 cases with upper aerodigestive cancer **Controls:** cohort workers without cancer, matched (5:1) on factory, date of birth, and length of case follow-up	**Estimation:** personnel records (type of job); sporadic monitoring at two plants; 2678 men with definite exposure to acid mists (mainly sulfuric acid), 367 with possible exposure, and 1356 never exposed **Duration:** varied, earliest employed since 1950. Through 1988 or 1990.	1) compared cohort mortality with mortality in British population using person-years method 2) compared exposure in cases of upper aerodigestive cancer with age matched controls from the same plant **Standardized Mortality Ratio (SMR) (95% Confidence Interval [CI]):** *among definitely exposed subcohort* 0.92 (0.85 - 0.98) for overall mortality 0.92 (0.79 - 1.05) for all cancers **Case-control analysis:** **Odds Ratio (OR) (95% CI, no. exposed cases/controls):** 2.0 (0.4 - 10, 7/23) for at least five years' high exposure other exposure categories had OR < 2	coincident exposure to other hazardous substances, e.g., hydrochloric acid, asbestos, lead	Coggon et al. (1996)
cohort follow-up	**Exposed:** 1031 men who worked in the U.S. steel industry (3 plants, 1940-1965). Cases of laryngeal cancer identified by questionnaire, death and medical records. **Comparison:** laryngeal cancer rates for ~10% of U.S. population (from U.S. Surveillance, Epidemiology, and End Results [SEER] program, 1970-1994). Rates for other years estimated from 1st-3rd National Cancer Surveys.	**Estimation:** historical (1975-79) personal monitoring for 2/3 plants; sampled areas 2/3 plants; personnel records. All cases classified into categories reflecting type of acid exposure: 62% - sulfuric acid 22% - sulfuric and other acids 16% - only to acids other than sulfuric **Duration:** 9.2 yr average, 1949 average year of first exposure	**Rate Ratio (RR) (95% CI; no. observed/no. expected):** 2.2 (1.2 - 3.7; 14/5.6) for laryngeal cancer through 1994 no positive trends with increased duration of exposure or potential latency	1) smoking 2) alcohol obtained information from questionnaires in original cohort adjusted expected laryngeal cancers upward by 14% (adjustments made by comparing cohort consumption with U.S. population consumption)	Steenland (1997)

4.0 EXPERIMENTAL CARCINOGENESIS

No experimental animal carcinogenicity studies were reported for sulfuric acid in IARC (1992, p. 96; see Appendix A). More recent experimental carcinogenicity studies in animals were not located. Two older animal studies, not cited by IARC (1992), were reviewed by Swenberg and Beauchamp (1997).

Ballou et al. (1978, 1981; cited by Swenberg and Beauchamp, 1997) found no significant increases in neoplasia in 50 male Wistar rats exposed to sulfuric acid aerosols (4 to 156 mg/m^3) on alternate weekdays (6 hours/day) for 2 weeks. However, the reviewers noted the limited value of this study based on the short duration of exposure.

Laskin and Sellakumar (1978; cited by Swenberg and Beauchamp, 1997) reported on initiation-promotion and co-carcinogenesis studies in which no neoplasms of the respiratory tract developed in male Syrian golden hamsters exposed to sulfuric acid mist alone at a concentration of 100 mg/m^3 for 6 hours/day, 5 days/week for the animals' lifespan. Sulfuric acid, following single or multiple intubations of benzo[*a*]pyrene (BaP), was not an effective promoter for BaP-induced respiratory cancer. The reviewers noted that although the study was conducted at a high sulfuric acid concentration, hamsters have a shorter lifespan than desired for carcinogenicity studies.

5.0 GENOTOXICITY

No data were available on the genotoxicity of strong inorganic acid mists containing sulfuric acid. Studies of the genotoxic effects of low pH as reviewed by IARC (1992) are summarized in Appendix A (pp. 102-104) and very briefly below. More recent studies on sulfuric acid mist genotoxicity were not located.

In prokaryotic systems, low pH was positive for gene conversions in *Saccharomyces cerevisiae,* chromosomal aberrations in *Vicia faba* root tips, and mitotic abnormalities in sea urchin embryos. It was negative for the induction of gene mutations in *Salmonella typhimurium, Escherichia coli, Neurospora crassa,* and *S. cerevisiae.*

In mammalian systems *in vitro*, low pH was positive for the induction of gene mutations in mouse lymphoma cells in both the presence and absence of metabolic activation, chromosomal aberrations in Chinese hamster ovary (CHO) cells with and without S9, and morphological transformation in Syrian hamster embryo (SHE) cells. It was negative *in vitro* for the induction of chromosomal aberrations in rat lymphocytes with or without S9 activation.

In humans, 40 workers at a northern Chinese sulfuric acid factory showed a significant increase in the frequency of sister chromatid exchanges, chromosomal aberrations, and micronuclei in their peripheral blood lymphocytes. Sulfur dioxide concentrations in factory air varied from 0.34 to 11.97 mg/m^3 at the time of the investigation but no sulfuric acid concentrations were given. No positive correlation was observed between length of exposure and the frequency of these three endpoints.

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion

The absorption and distribution patterns of sulfuric acid mist are affected by the particle size in the aerosol and by the breathing pattern of the exposed individual (i.e., mouth versus nose breathing). Small particles are able to penetrate more deeply into the lungs (Martonen et al., 1985; Jarabek et al., 1989; U.S. EPA, 1989a; all cited by IARC, 1992), and for all particle sizes, mouth breathing results in a higher dose deposited below the nasopharynx than does nose breathing. Mouth breathing also enhances deposition in the oropharynx, larynx, and upper trachea (Jarabek et al., 1989; cited by IARC, 1992). In addition, diffuse deposition of sulfuric acid mist presents less of a challenge to the pH-buffering system of the lungs than does localized deposition of large particles (Jarabek et al., 1989; Gamble et al., 1984a; both cited by IARC, 1992).

It has been estimated that exposure of lead-acid battery workers to sulfuric acid aerosol with a 5-μm particle size would result in a 90% deposition rate in the extrathoracic portion of the respiratory tract, whereas only 50% of an aerosol with a 2-μm particle size would be deposited in the same region of the lungs (Jarabek et al., 1989; Gamble et al., 1984a; both cited by IARC, 1992).

Amdur et al. (1952; cited by IARC, 1992) calculated that with an average particle size of 1 μm and an exposure concentration of 0.4-1.0 mg/m^3 (0.10-0.25 ppm), 77% of inhaled sulfuric acid would be retained in the airways of exposed human subjects.

Ammonia produced by the respiratory tract is able to partially neutralize the acidity of inhaled acid aerosols, forming ammonium sulfate with sulfuric acid (Utell et al., 1989; Larson et al., 1977; both cited by IARC, 1992). Smaller particles with their greater surface area are more efficiently neutralized than larger particles (Larson et al., 1982; cited by IARC, 1992).

6.2 Pharmacokinetics

No information was found.

6.3 Synergism

There was a significant increase in total lung protein content in rats concurrently exposed for 9 days to 0.2 ppm ozone and sulfuric acid at a concentration of 20 $\mu g/m^3$ (0.0049 ppm), as compared to rats exposed for 9 days to one or the other alone at the same concentrations tested in combination (Last, 1991; cited by Last and Pinkerton, 1997).

Last and Pinkerton (1997), however, found no synergistic (or antagonistic) interactions between ozone and sulfuric acid aerosols in the lungs of rats exposed for 90 days. This study included 3 sets of experiments. In the first experiment, rats were exposed to 0.2 ppm ozone alone, sulfuric acid alone at 150 $\mu g/m^3$ (0.0368 ppm), or both for 23.5 hours/day. In the second experiment, rats were exposed to 0.12 or 0.20 ppm ozone alone, sulfuric acid alone at 100 $\mu g/m^3$ (0.0245 ppm), or both for 23.5 hours/day. In the third experiment, rats were exposed to 0.12 or 2.0 ppm ozone alone, sulfuric acid alone at 20 $\mu g/m^3$ (0.0049 ppm), or both for only 12 hours/day.

7.0 MECHANISMS OF CARCINOGENESIS

The carcinogenic activity of sulfuric acid is most likely related to the genotoxicity of low pH environments in *in vitro* and *in vivo* systems (see Section 5.0). Reduced pH environments are known to enhance the depurination rate of DNA and the deamination rate of cytidine. Deamination of cytidine at CpG sites is thought to be one of the mechanisms responsible for inducing mutations in the *p53* tumor suppressor gene (Swenberg and Beauchamp, 1997).

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 54 (Occupational Exposures to Mist and Vapors from Strong Inorganic Acids; and Other Industrial Chemicals), 1992, Sulfuric Acid and Other Strong Inorganic Acids, pp. 41-130

APPENDIX B

Description of Online Searches for Strong Inorganic Acid Mists Containing Sulfuric Acid

DESCRIPTION OF ONLINE SEARCHES FOR STRONG INORGANIC ACID MISTS CONTAINING SULFURIC ACID

Searches were limited to 1991 [the year before the IARC Monograph (1992), which has an extensive literature review, and the year before the ATSDR (1992) Toxicological Profile] through September 1997.

Online searches for sulfuric acid mist [CASRN 7664-93-9] were performed in databases on the systems of STN International, DIALOG, NLM's TOXNET, and the Chemical Information System from 1991 to date. Toxicology information was sought in EMIC, EMICBACK, TSCATS (epidemiology, chromosomal aberration, genetic toxicity, mutagenicity), the Toxic Chemical Release Inventory 1995 (online availability 1997), and TOXLINE. Occupational safety and health information was obtained from NIOSHTIC. Environmental information was sought in NTIS and Chemical Abstracts which was searched by section code 59 (air). The Chemical Abstracts Service Registry file and SANSS provided chemical identification information.

Regulatory information was obtained from the in-house FESA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FDA), 29 (OSHA), and 40 (EPA).

Review of 1200 life sciences journals for current awareness was done using Current Contents on Diskette®.

APPENDIX C

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Strong Inorganic Acid Mists Containing Sulfuric Acid

NOMINATION
Review based on letter from the United Auto Workers recommending listing in the RoC based on IARC classification of Strong Inorganic Acid Mists Containing Sulfuric Acid as a known human carcinogen (IARC Vol. 54, 1992).

DISCUSSION
Sulfuric acid is used in the manufacture of fertilizers, rayon and other fibers, pigments and colors, explosives, plastics, storage batteries, synthetic detergents, natural and synthetic rubber, pulp and paper, Cellophane, and catalysts. It is the largest volume chemical produced in the United States, and yearly, over 770,000 workers are exposed. Six published epidemiology studies provide sufficient evidence of increased risk of laryngeal and lung cancer in workers exposed to strong inorganic acid mists containing sulfuric acid. There are no adequate animal studies to corroborate observations from epidemiology studies. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known human carcinogen	8 yes/0 no
NTP EC Working Group (RG2)	list as known human carcinogen	7 yes/1 no
NTP Board RoC Subcommittee	list as known human carcinogen	6 yes/0 no

Public Comments Received
A total of 11 public comments were received:
- 10 against listing as a known to be human carcinogen
- 1 providing comments on the content of the background document prepared for the review of this nomination