FOREWORD INTRODUCTION

SULFURIC ACID

CAS N°: 7664-93-9

SIDS Initial Assessment Report for 11th SIAM

(Orlando, Florida, 23-26 January, 2001)

Chemical Name : Sulfuric acid

CAS no: 7664-93-9

Sponsor Country : France

National SIDS Contact Point in Sponsor Country:

Mme. Laurence Musset
Bureau des substances et préparations
Ministère de l'environnement
20 avenue de Ségur
75302 Paris 07 SP
France

History: The national peer review consisted of a presentation and critical discussion at a national panel of experts in toxicology and ecotoxicology from administration, university and industry and nominated by the ministry of environment. In parallel, a review was performed by the national institute on environmental and industrial risk (INERIS) by request from the ministry of environment. For this particular substance, only the verification of the most relevant underlying study reports or publications was performed.

Testing completed : none

Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7664-93-9
Chemical Name	Sulfuric acid
Structural Formula	H_2SO_4

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The LC50 values for sulfuric acid aerosol observed in acute inhalation studies conducted in different species are low and are most likely due to the corrosive/irritant effect of this chemical. For guinea pigs, the LC50 (8 hours; particle size approximately 1μm) ranges from 0.018 to 0.050 mg/l, depending on the age of the animals. Depending on the duration of exposure, the LC50 ranges from 0.37 to 0.42 mg/l in rats, 0.6 to 0.85 mg/l in mice and 1.47 to 1.61 mg/l in rabbits. Only one acute oral toxicity study was available. This study indicated an LD50 of 2140 mg/kg in the rat.

Sulfuric acid is corrosive to the skin, eyes and mucous membranes. 10% solutions of sulfuric acid appear not to be irritating to the skin in difference species. Conflicting results (not irritating or severely irritating) are observed in eye irritation studies using 10% sulfuric acid, depending on the protocol used (OECD/EU or US). Sulfuric acid is not considered as an allergen by skin contact in humans.

In numerous repeated inhalation studies with sulfuric acid aerosol, toxicity was confined to changes in the structure and function of the respiratory tract, suggesting that it has a local effect and no systemic effects. The observed changes are related to the irritant properties of sulfuric acid and are most likely due to the H+ ion. In a 28-day inhalation study in the rat exposed to sulfuric acid aerosol, minimal squamous metaplasia was observed in the laryngeal epithelium following exposure to the lowest concentration used (0.3 mg/m3). This effect was fully reversible. Exposure to 1.38 mg/m3 caused more severe metaplasia accompanied by cell proliferation.

Sulfuric acid has been shown to be without effect in genetic toxicity studies *in vitro* (bacterial test). It has been shown to cause chromosomal aberrations in a non-bacterial test *in vitro*. The chromosomal effects are well known to be a consequence of reduced pH, being seen using any strong acid. There are no *in-vivo* mutagenicity studies available.

No carcinogenic effect was observed in carcinogenicity studies conducted by inhalation with sulfuric acid aerosol using 3 different animal species. Small increases in tumor incidence were reported in rats and mice after chronic gastric intubation or intratracheal instillation of sulfuric acid solution, but no clear conclusion can be drawn from these studies.

Several epidemiological studies have suggested a relationship between exposure to inorganic acid mists containing sulfuric acid and an increased incidence of laryngeal cancer. IARC has concluded that "occupational exposure to strong inorganic mists containing sulfuric acid is carcinogenic for humans (Group

1).” Concerns have been raised that confounding factors could not be fully excluded.

Because sulfuric acid is a direct-acting toxicant, and because it is unlikely to reach the reproductive organs, reproductive effects in mammals are not likely to occur following exposure to sulfuric acid by any route. In a developmental toxicity/teratogenicity study conducted by inhalation with sulfuric acid aerosol, the NOAEL for maternal toxicity appears to be 20 mg/m3 in mice and rabbits. No evidence of foetotoxicity or teratogenicity was seen in either species.

Environment

Sulfuric acid is a strong mineral acid that dissociates readily in water to sulfate ions and hydrated protons, and is totally miscible with water. Its pKa is 1.92 at 25 °C. At pH 3.92, for example, the dissociation is 99 %, and sulfate ion concentration is 1.2 x 10^{-4} moles = 11.5 mg/l. So at environmentally relevant concentrations, sulfuric acid is practically totally dissociated, sulfate is at natural concentrations and any possible effects are due to acidification. This total ionisation will imply also that sulfuric acid, itself, will not adsorb on particulate matters or surfaces and will not accumulate in living tissues.

The NOECs selected were obtained on a natural (cold water) lake artificially contaminated by the controlled addition of sulfuric acid:

- NOEC in phytoplankton community structure = pH 5.6 = 0.13 mg/l sulfuric acid
- NOEC in zooplankton population repartition = pH 5.6 = 0.13 mg/l sulfuric acid.
- NOEC in fish population recruitment = pH 5.93 = 0.058 mg/l sulfuric acid

There is only one validated NOEC available for warm water fish (*Jordanella floridae*), 0.025 mg/l, which is derived from the LOEC/2.

Exposure

Estimated worldwide production of sulfuric acid is 160 million ton/year. The main uses are non dispersive (industrial uses). In some countries, sulfuric acid is approved for agricultural use. The occurrence of sulfuric acid in the environment comes mainly from the hydrolysis of sulfur oxides produced by combustion processes (natural and anthropogenic), wet deposition, generally as a mixture with nitrogen oxides and nitric acid and not from the manufacturing and use of the acid. The emissions to the aquatic environment generally occur from manufacturing industrial locations after neutralisation and are mainly in the form of sulfate ions. Alternatively, following manufacturing and use, it can enter the terrestrial environment as stable gypsum (calcium sulfate).

NATURE OF FURTHER WORK RECOMMENDED

Environment: the collection of information about exposure during agricultural use should be considered.

Health: the collection of information about occupational exposure to sulfuric acid mist should be considered due to the carcinogenic potential.

FULL SIDS SUMMARY

CAS N° 7664-93-9		SPECIES	PROTOCOL	RESULTS
PHYSICO-CHEMICAL				
2.1	Melting point			10.4-10.5 °C (sulfuric acid 100 %) 3 °C (sulfuric acid 98 %) -32 °C (sulfuric acid 93 %) -38 °C (sulfuric acid 78 %) -44 °C (sulfuric acid 74 %) -64 °C (sulfuric acid 65 %)
2.2	Boiling point			290 °C at 1013 hPa (sulfuric acid 100 %) 310-335 °C at 1013 hPa (sulfuric acid 98 %)
2.3	Density			1.835 at 20 °C (sulfuric acid 93-100 %)
2.4	Vapour pressure			< 0.001 hPa at 20 °C 0.004 hPa at 50 °C 1.3 hPa at 145.8 °C
2.5	Partition coefficient			Not relevant for ionisable compounds
2.6	Water solubility			Miscible pKa = 1.92
2.7	Density			1.835 at 20 °C (sulfuric acid 93-100 %)
2.11	Oxidising properties			Powerful acidic oxidizer which can cause ignition or explosion in contact with many materials.
2.12	Additional remarks			Vigorous reaction when water added to sulfuric acid.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.2	Stability in water			Strong acid : dissociates in water to sulfate and hydrated proton
3.3.1	Transport between environmental compartments			Very mobile in soil. Mobility increases with the dilution in water. Wet acidic deposition on soils are 75 % sulfuric acid
ECOTOXICOLOGY				
4.1	Acute/prolonged toxicity to fish	*Lepomis macrochirus* *Brachydanio rerio*	pH decreasing each 96 hours ISO 7346/1	LC50 96h = 16-28 mg/l (pH 3.25 to 3.5) LC50 24h = 82 mg/l
4.2	Acute toxicity to aquatic invertebrates	*Daphnia magna*	ISO 6341	EC50 24h = 29 mg/l
4.3	Toxicity to aquatic plants e.g. algae	Epilimnetic phytoplankton in a natural lake	Phytoplankton community structure study	NOEC = 0.13 mg/l (pH 5.6)

4.4	Toxicity to micro-organisms e.g. bacteria	*Pseudomonas fluorescens* Protozoan community	Test solutions neutralized Substrate colonization	EC0 = 6900 mg/l NOEC = pH 6.61 (from original pH 8.36)
4.5.1	Chronic toxicity to fish	*Salvelinus fontinalis* *Salvelinus fontinalis* *Salvelinus fontinalis* *Jordanella floridae* Lake fish populations	Embryo survival and time hatching Weight of young fish 26 °C, fry growth Population decrease, recruitment	NOEC = 0.31 mg/l (pH 5.2) NOEC = 0.15 mg/l (pH 5.5) NOEC = 0.13 mg/l (pH 5.56) LOEC 20 % = pH 6.0 = 0.049 mg/, NOEC = LOEC/2 = 0.025 mg/l NOEC = 0.058 mg/l (pH 5.93)
4.5.2	Chronic toxicity to aquatic invertebrates	*Tanytarsus dissimilis* Lake zooplankton population	Reproduction Population repartition	NOEC = 0.15 mg/l(pH 5.5) NOEC = 0.13 mg/l (pH 5.59)
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other	LD50 = 2140 mg/kg
5.1.2	Acute Inhalation Toxicity	Guinea pig Guinea pig Guinea pig Rat Rat Rat Mouse Mouse Mouse Rabbit	Other Other Other Other Other Other Other Other Other Other	LC50 = 0.030 mg/1/8h (particle size: 0.8 µ) LC50 > 0.109 mg/1/8h (particle size:0.4 µ) LC0 (old animal) = 0.020 mg/1/8h LC50 (old animal) = 0.050 mg/1/8h LC0 (young animal) = 0.008 mg/1/8h LC50 (young animal) = 0.018 mg/1/8h LC100= 0.087 mg/1/2.75 LC50 = 0.375 mg/1/4h LC50 = 0.425 mg/1/8h LC0 = 0.461 mg/1/7h LC100 = 0.699 mg/1/7h LC0 = 0.718 mg/1/3.5h LC100 = 1.470 mg/1/3.5h LC50 = 0.510 mg/1/2h LC50 = 0.850 mg/1/4h LC50 = 0.600 mg/1/8h LC0 = 0.461 mg/1/7h LC40 = 0.699 mg/1/7h LC50 = 0.320 mg/1/2h LC0 = 0.699 mg/1/7h LC50 = 1.610 mg/1/7h

				LC0 = 0.718 mg/1/3.5h LC50 = 1.470 mg/1/3.5h
5.2.1	Skin irritation/corrosion	Rabbit, Guinea-pig, Human	FDA, FSHA, Federal Register V37, 1972	Not irritating
		Rabbit, Human	CFR, DOT 1986 (rabbit) and 1988 (human) + Hill top Chamber	Not irritating
5.2.2	Eye irritation/Corrosion	Rabbit	OECD TG 405	Sulfuric acid 10%: not irritating
		Rabbit	Directive 79/831/EEC, Annex V, part B	Sulfuric acid 10%: not irritating
		Rabbit	US, FHSA (CFR, 1979) and NAS 1138 Committee (1977)	Sulfuric acid 10% (0.01 ml): slightly irritating Sulfuric acid 10% (0.05 ml): severely irritating Sulfuric acid 10% (0.1 ml): severely irritating
		Rabbit	US.FHSA Fed. Reg. Vol 38 (187) Part II and 16 CFR 1500.42 (1973) and Draize method (1944)	Sulfuric acid 10%: severe irritant Sulfuric acid 5%: moderate irritant
5.4	Repeated Dose Toxicity by Inhalation	Rat (réf. 74)	OECD TG 412	a NOEL/NOAEL can not be identified
		Rat (réf. 106)	Other	NOEL/NOAEL not indicated
		Rat (réf. 111)	Other	NOEL/NOAEL not indicated
		Rat (réf. 26)	Other	NOEL/NOAEL not indicated
		Rat (réf. 25)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 111)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 26)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 25)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 184)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 168)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 2)	Other	NOEL/NOAEL not indicated
		Guinea pig (réf. 3)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 165)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 64)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 63)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 155)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 160)	Other	NOEL/NOAEL not indicated

	Repeated Dose Toxicity by Inhalation (continued)	Rabbit (réf. 154)	Other	NOEL/NOAEL not indicated
		Rabbit réf. 156)	Other	NOEL/NOAEL not indicated
		Rabbit (réf. 167)	Other	NOEL/NOAEL not indicated
		Monkey (réf. 2)	Other	NOEL/NOAEL not indicated
		Monkey (réf. 3)	Other	NOEL/NOAEL not indicated
		Mouse (réf. 168)	Other	NOEL/NOAEL not indicated
		Hamster (réf. 105)	Other	NOEL/NOAEL not indicated
		Dog (réf. 110)	Other	NOEL/NOAEL not indicated
5.5	GENETIC TOXICITY *IN VITRO*			
A.	Bacterial test (Gene mutation)	*S. typhimurium*	Other	- (with metabolic activation) - (without metabolic activation)
		E. coli	Other	- (without metabolic activation)
B.	Non-bacterial *In Vitro* test (Chromosomal aberrations)	Developing embryos of Sphaerechinus granularis and Paracentrotus lividus	Other	+ (without metabolic activation)
		Chinese hamster Ovary (CHO) K1 cells	Other	+ (with metabolic activation) + (without metabolic activation
5.7	Carcinogenicity	Rat (réf. 187)	Other	Local and weak carcinogen, (gastric intubation)
		Rat (réf. 187)	Other	Local and weak carcinogen, (intratracheal instillation)
		Mouse (réf. 187)	Other	Local and weak carcinogen, (gastric intubation)
		Hamster (réf. 105)	Other	No evidence of carcinogenic potential (inhalation, mist)
		Rat (réf. 55)	Other	No carcinogenic effect, (inhalation, mist)
		Guinea pig (réf. 54)	Other	No carcinogenic effect (inhalation, mist)
5.9	Developmental toxicity / Teratogenicity	Mouse	Similar to OECD TG 414 (inhalation)	NOAEL maternal = 20 mg/m3 NOEL teratogenicity = 20 mg/m3
		Rabbit	Similar to OECD TG 414 (inhalation)	NOAEL maternal = 20 mg/m3 NOEL teratogenicity = 20 mg/m3
5.10	Other data	49 articles/reviews included in the IUCLID dossier for additional information		
5.11	Experience with human exposure	50 articles/epidemiological studies included in the IUCLID dossier		

SIDS Initial Assessment Report

1. IDENTITY

Name (OECD) : Sulfuric acid

CAS number : 7664-93-9

Molecular formula : H_2SO_4

Molecular weight : 98

Other names : Dihydrogen sulphate
Oil of vitriol

Sulfuric acid is a colourless and odourless viscous liquid crystallising at 3 to 10 °C depending on its water content (from 0 to 2 %). Water content is generally up to 8 %. Other impurities (sulfur dioxide, nitrogen compounds and heavy metals) are < 0.1 %. Its density is 1.834 to 1.836 at 20 °C

Sulfuric acid is a strong mineral acid that dissociates readily in water to sulfate ions and hydrated protons, and is totally miscible with water. Its pKa is 1.92 at 25 °C. So at pH 3.92, for example, the dissociation is 99 %, and the sulfate ion concentration is 1.2×10^{-4} moles = 11.5 mg/l. So at environmentally relevant concentrations, sulfuric acid is practically totally dissociated, sulfate is at natural concentrations, and possible effects are due to acidification.

This total ionisation also implies that sulfuric acid will not adsorb on particulate matters or surfaces and will not accumulate in living tissues.

The dissolution/dissociation in water is strongly exothermic, so a vigorous reaction occurs when water is added to sulfuric acid. It is a powerful acidic oxidizer which can cause ignition or explosion in contact with many materials.

Sulfuric acid has a low vapour pressure (< 0.001 hPa at 20 °C). However mists and aerosols can be formed in some industrial applications.

2. GENERAL INFORMATION ON EXPOSURE

Estimated world-wide production of sulfuric acid is 160 million tonnes/year. The continental repartition is 40 million tonnes/year in Europe, 60 in America and 60 in Asia-Pacific. The production in the sponsor country (France) was 2.05 million tonnes / year in 1999.

The main uses are non dispersive :

- 32 % for phosphoric acid and fertilisers production
- 58 % as basic chemical for chemical synthesis, pigment, oil industries
- 2 % for metal extraction, refining and processing of metals
- 0.8 % batteries
- about 7 % for other industrial uses (pulp and paper …)

A very minor agricultural use (about 0.025 %) is as desiccant for potato crops.

In the workplace, sulfuric acid can exist as an acid mist. This situation can occur because sulfur trioxide generates very dense sulfuric acid mists with atmospheric humidity. However, this occurs only in the event of accidental leakage of sulfur trioxide, and is not a result of normal activity.

Other sulfuric acid uses that are important sources of sulfuric acid mists in the workplace are:
- car and industrial batteries loading
- metal sheets cleaning for surface treatment
- electro-chemical production of zinc and copper : sulfuric acid is driven off as fine droplets by evolved hydrogen.
- Loading and discharging of sulfuric acid

Occupational exposure limit values for different countries are presented in Annex I. For most of the countries (e.g. USA, France, Japan, Finland) the limit value for an 8 hour-exposure is 1 mg/m3 except for Germany : MAK value, 8 hours : 0.1 mg/m3.

Sulfuric acid occurrence in the environment mainly comes from hydrolysis of sulfur oxides produced by combustion processes (natural and anthropogenic) wet deposition, generally as mixture with nitrogen oxides and nitric acid and not from manufacturing. The emissions to the aquatic environment generally occur from manufacturing industrial locations after neutralisation and are mainly in the form of sulfate ions. Alternatively, following manufacturing and use, it can enter the terrestrial environment as stable gypsum (calcium sulfate).

Sulfuric acid use in agriculture as desiccant for potato crops is reported in UK (Food and Environment Protection Act, 1985, Part III, Control of Pesticides Regulations 1986, Evaluation of Fully Approved or Provisionally Approved Products, Evaluation on Sulphuric Acid, April 1998). In 1992, 90 685 ha of potato crops were treated with 77% w/w sulfuric acid. Doses ranged from 112 l/ha to 335 l/ha, which means a total consumption of about 40 000 t sulfuric acid in this agricultural use.

3. ENVIRONMENT

3.2. Effects on the aquatic environment

Preliminary remarks

Quality criteria: The principal quality criteria for acceptance of data are that the test procedure should be well described (with reference to an official guideline) and that the toxicant concentrations must be measured with an adequate analytical method.

Four situations can be distinguished and are summarised in the following table according to criteria defined in IUCLID system.

Table: Quality criteria for acceptance of ecotoxicity data

Case	Detailed description of the test	Accordance with scientific guidelines	Measured concentration	Conclusion: reliability level
I	+	+	+	[1] : valid without restriction

II	±	±	±	[2] : valid with restrictions; to be considered with care
III	insufficient or -	-	-	[3] : invalid
IV	the information to give an adequate opinion is not available			[4] : not assignable

Publications were assigned validity 4 when they could not be checked directly. Validity 3 was assigned systematically when no clear description was given of the test substance. This approach is important for sulfuric acid, as sources for sulfuric acid production can be recovery from many processes leading to various impurities.

Analytical monitoring reported in the IUCLID file refers to pH measurements. At concentrations reported in publications and study reports, the toxicity has been assumed to be due to acidity only, because at these low concentrations, sulfate quantities added are below most of natural medium concentrations. So the sulfuric acid environmental risk assessment is in fact acidity risk assessment.

3.2.1 Aquatic effects

3.2.1.1. Effects in fish

The acute toxicity of sulfuric acid in fish has been reported in 10 different publications, leading to 8 LC50 values in 24, 48 or 96 hours duration. Only two references were assigned validity 2 : one study performed according to the international standard ISO7346/1, in a 24 hours static test in *Brachydanio rerio*, not under GLP, giving an LC50 24 hours of 82 mg/l. The other one was obtained in a study where *Lepomis macrochirus* were exposed successively 96 hours to each pH tested (from pH 7.5 original water to pH 5.0, 4.5, 3.5, 3.25 and 3.0. However the LC50 48 hours was retained as a worst case one and measured as being from pH 3.25 to pH 3.5, which gives a value of 16 to 28 mg/l sulfuric acid. No LC50 was found lower than *Lepomis macrochirus* one in all publications assigned validity 3 or 4.

The chronic toxicity of sulfuric acid in fish was assessed in 6 publications reporting laboratory tests. 5 validity 2 NOEC values were derived, 3 of them being in the same range: NOECs for embryo survival and time for hatching of *Salvelinus fontinalis* (pH 5.2 and pH 5.5 giving substance concentrations 0.31 mg/l and 0.15 mg/l), and a NOEC for weight of young *Salvelinus fontinalis* produced in 10 month (pH 5.56, giving 0.13 mg/l). The fourth NOEC is far lower, being derived from a LOEC on fry growth of *Jordanella floridae* in 45 days of pH 6.0 (0.049 mg/l) giving 20 % inhibition, which, divided by 2 can give a NOEC of 0.025 mg/l.

The difference between *Salvelinus fontinalis* and *Jordanella floridae* is their optimal temperature : *Salvelinus* is a cold water fish (Brook trout), and *Jordanella* a warm water fish. The difference in physiology could explain the difference in sensitivity.

Table of validated fish toxicity results

		SPECIES	PROTOCOL	RESULTS
4.1	Acute/prolonged toxicity to fish	*Lepomis macrochirus* *Brachydanio rerio*	pH decreasing each 96 hours ISO 7346/1	LC50 96h = 16-28 mg/l (pH 3.25 to 3.5) LC50 24h = 82 mg/l
4.5.1	Chronic toxicity to fish	*Salvelinus fontinalis* *Salvelinus fontinalis* *Salvelinus fontinalis* *Jordanella floridae* Lake fish populations	Embryo survival and time hatching Weight of young fish 26 °C, fry growth Population decrease, recruitment	NOEC = 0.31 mg/l (pH 5.2) NOEC = 0.15 mg/l (pH 5.5) NOEC = 0.13 mg/l (pH 5.56) LOEC 20 % = pH 6.0 = 0.049 mg/, NOEC = LOEC/2 = 0.025 mg/l NOEC = 0.058 mg/l (pH 5.93)

Remark : the original results as published are underlined. Other values were calculated.

3.2.1.2. Effects in invertebrates

The acute toxicity of sulfuric acid in aquatic invertebrates is reported in 8 different publications, leading to 7 LC 50 values in 24, 48 or 96 hours duration. Only one reference describing a *Daphnia magna* test in 24 hours was assigned validity 2. This test was performed according to the international standard ISO 6341, and gave a LC50 24 hours of 29 mg/l. It is the lowest LC50 published.

The chronic toxicity in invertebrates was assessed in 4 publications, one only giving a validity 2 result. It is a laboratory test in the midge *Tanytarsus dissimilis* giving a NOEC 35 days on reproduction success of pH 5.5 (0.15 mg/l).

3.2.1.3. Effects in aquatic plants / algae

No standard algae growth inhibition study could be found. Nevertheless a NOEC in phytoplankton is available from field studies with data on *Chlorella mucosa* (chlorophyte), *Dinobryon sertularia*, *Mallomonas* sp., *Stichogloea* sp., *Uroglena* sp. (chrysophycean species), *Asterionella ralfsii* (diatom), *Gymnodinium* sp., *Peridinium inconspicuum* (dinoflagellates) *Chroococus minutus*, *Merismopedia* sp. (cyanophyte) (see chapter 3.2.1.4).

3.2.1.4 Studies on an experimentally acidified lake

The effect of sulfuric acid addition for several years (1976 to 1983) in a natural (cold water) Canadian “Lake 223” was assessed in aquatic species populations. From an initial level of about 6.7, the pH was lowered at a pH rate of about 0.5 pH units a year (6.49 – 6.13 - 5.93 – 5.64 – 5.59) until it reached an average pH 5.1 and was held there for 3 years. This lake was one of the lakes of “ELA” (Experimental Lake Area) in Canada, where a set of natural lakes was selected as representative for a natural non-polluted environment.

Fish population was analysed during these years. A NOEC for the most sensitive fish species, fathead minnow (*Pimephales promelas*) and slimy sculpin (*Cottus cognatus*) recruitment was pH 5.93, giving 0.058 mg/l. This NOEC in recruitment integrates not only reproductive success, but also prey/predator relationships (presence/lack of suitable food as smaller fish, invertebrates or

aquatic plants/algae, presence/lack of predators for smaller fish). Moreover it integrates effects of successive one-year exposures to pH 6.49 and 6.13, which models a progressive acidification by sulfuric acid deposition.

The zooplankton community study was also analysed by identifying the species and counting the organisms. A NOEC for population repartition (from copepod to cladoceran dominance) was pH 5.59 (0.13 mg/l). This NOEC integrates not only reproductive success, but also prey/predator relationships (presence/lack of suitable food as smaller invertebrates or aquatic plants/algae, presence/lack of fish predators). Here also it integrates effects of successive one-year exposures to pH 6.49, 6.13, 5.93 and 5.64.

The phytoplankton community structure was also studied, giving a NOEC of pH 5.6 (0.13 mg/l) (chlorophyte increase and species shift to large inedible *Gymnodium* sp.). This NOEC integrates not only algae growth rate, but also consumption by invertebrates and fish, and also effects of successive one year exposures to pH 6.49, 6.13, 5.93.

3.2.1.5 Toxicity in micro-organisms

A multispecies-microcosm test was performed : the structure and function of naturally derived periphytic communities on polyurethane foam artificial substrates were monitored. The artificial substrates were suspended at 1m depth in a man-made outdoor ponds. After 21 days substrates were collected. pH was set in different ponds to 8.34-7.61-6.90-6.61-5.34-3.33. The control pond was pH 8.36.

Significant effects on protozoan species richness were observed in this test at a pH = 5.33. Therefore the NOEC for species richness was 6.61. In this experiment, the sulfuric acid concentration calculation is more problematic, because the initial pH in the ponds is far from neutrality, and alkaline (pH 8.36). So the assumption that pH is only the result of sulfuric acid dilution in water, which was an approximation in pH 6.7 Canadian Lake 223 experiments, is here completely false. Ignoring the buffering capacity of the pond water, it is therefore impossible to derive a NOEC as sulfuric acid mg/l.

Discussion

It is remarkable that sensitivity to pH is not universal among species and related ecosystems : for example at pH 6.0, *Jordanella floridae* fry growth already begins to be inhibited.

Some interesting examples are also salamanders : *Ambystoma jeffersonianum* eggs have hatching success > 90 % only at pH 6 at 10 °C, and at pH 5 to 6 at 5 °C. Eggs do not hatch successfully above pH 6. And *Ambystoma maculatum* eggs hatch only from pH 7 to 9.

The sulfuric acid hazard assessment is in fact hazard assessment of acidity. All the observations made and the results derived would be the same for any strong acid, provided the anion has no toxicity in any species at environmentally relevant strong acid concentrations.

4. HUMAN HEALTH

4.2 Effects on Human Health

Preliminary remarks:

- ✓ Reliability of the studies was evaluated using the criteria for reliability categories adapted from Klimisch *et al.* (1997) and Rosner (1994). Reliability is differentiated and thus classified into 4 categories/codes as described below. In this scoring system, studies conducted and reported according to internationally accepted test guidelines and in compliance with GLP have the highest grade of reliability and should be used as reference standards.

  - *1 : Reliable without restriction* :
    - 1a GLP guideline study (OECD, EC, EPA, FDA, etc…)
    - 1b Comparable to guideline study
    - 1c Test procedure in accordance with national standard methods (AFNOR, DIN, etc)
    - 1d Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

  - *2: Reliable with restrictions*
    - 2a Guideline study without detailed documentation
    - 2b Guideline study with acceptable restrictions
    - 2c Comparable to guideline study with acceptable restrictions
    - 2d Test procedure in accordance with national standard methods with acceptable restrictions
    - 2e Study well documented, meets generally accepted scientific principles, acceptable for assessment
    - 2f Accepted calculation method
    - 2g Data from handbook or collection of data

  - *3: Not reliable*
    - 3a Documentation insufficient for assessment
    - 3b Significant methodological deficiencies
    - 3c Unsuitable test system

  - *4: Not assignable*
    - 4a Abstract
    - 4b Secondary literature
    - 4c Original reference not yet available
    - 4d Original reference not translated (e.g. Russian)
    - 4e Documentation insufficient for assessment

- ✓ Studies selected for discussion are identified in the following tables by a black bullet (•).

4.2.1 Mode of action of the chemical, toxicokinetics and metabolism

Sulfuric acid is corrosive and irritating and causes direct local effects on the skin, eyes and gastrointestinal tracts after direct exposure to sufficient concentrations. Small droplets of sulfuric acid (aerosol/mist) can also be inhaled and cause direct local effects on respiratory tract. The effects of inhaled sulfuric acid aerosols will depend on many factors: - exposure concentrations; - exposure time; - particle size of the aerosol, which determines the location in the respiratory tract where sulfuric acids aerosols will deposit; - humidity, both in the environment and in the respiratory tract, which determines the particle size; - endogenous ammonia that can neutralize sulfuric acid; - pattern of respiration and the inhalation route (oral or nasal); - buffering capacity of the airways; - species studied (e.g. respiratory tract dimension and architecture) (see ref. 10, 102, 144).

The effects of sulfuric acid are the result of the H+ ion (local deposition of H+, pH change) rather than an effect of the sulfate ion. Sulfuric acid per se is not expected to be absorbed or distributed throughout the body. The acid will rapidly dissociate and the anion will enter the body electrolyte pool, and will not play a specific toxicological role (102, 144). This is supported by experiments which have studied the active component in inorganic acids on various endpoints, using different

acids or salts (HCl, NH4HSO4, $(NH4)_2SO4$, Na2SO4). In these studies, the authors have concluded that the observed effects seemed to be due to the H+ ion while the anion appeared to have no effect (157, 161, 162, 166, 202). In an experiment studying the clearance via the blood of radiolabeled sulfuric acid aerosol in different species, the authors have observed that sulfur from sulfuric acid was rapidly cleared (from 2 to 9 minutes) from the lungs of animals into the blood following inhalation exposure (45). Sulfate is a normal constituent of the blood and is a normal metabolite of sulfur-containing amino acids, and excess sulfate is excreted in the urine. The body pool of this anion is large, and it is therefore unlikely that occupational aerosol exposures significantly modify the normal body load (102, 144).

4.2.2 Acute toxicity

The acute toxicity studies conducted with sulfuric acid that could be checked are summarized in the following tables. None of these studies have been carried out recently, under national or international guidelines, and according to GLP. Collectively, however, these studies show effects in the similar range of doses for given animal species.

4.2.2.1 Acute oral toxicity

Acute Oral Toxicity studies with sulfuric acid						
	Species, strain	**Ref. (year)**	**Protocol**	**Administration**	**Endpoint**	**Value (mg/kg)**
●	RAT (NS)	172 (1969)	Other	Oral (Intubation) 0.25 g/ml of diluted sulfuric acid	LD_{50}	2140 mg/kg

Only one acute oral toxicity study is available. This study indicates an LD50 = 2140 mg/kg in the rat. However, due to irritant and/or corrosive effects of sulfuric acid, the oral route of exposure is not appropriate for testing possible toxic endpoints. Gavage dosing of animals will not represent oral exposures in humans, which itself will be limited. Toxic signs of oral exposure in human are of irritation/corrosion of the gastrointestinal tract.

4.2.2.2 Acute inhalation toxicity

Acute Inhalation Toxicity studies with animals exposed to sulfuric acid aerosol/mist or oleum								
	Species (strain)	**Ref. (year)**	**Protocol**	**Source of mists**	**Exposure Time**	**Particle size (µm)**	**Endpoint**	**Value**
●	GUINEA PIG, (HARTLEY)	200 (1979)	Inhalation, whole body	SO3 + H2O	8 h 8 h	0.8 0.4	LC_{50} LC_{50}	0.030 mg/l/8h >0.109 mg/l/8h
●	GUINEA PIG (NS)	9 (1952)	Inhalation, whole body	NS	8 h	1	LC_0 (old animal) LC_{50} (old animal) LC_0 (young animal) LC_{50} (young animal)	0.020 MG/L/8H 0.050 mg/l/8h 0.008 MG/L/8H 0.018 MG/L/8H
	Guinea pig (NS)	185 (1950)	Inhalation, whole body	diluted SA (10-60% w/v)	2.75 h	1-2	LC_{100}	0.087 mg/l/2.75
●	(FISCHER-344)	150 (1976)	Inhalation, whole body	SO3 + humid air	4 h 8 h	1	LC_{50} LC_{50}	0.375 mg/l/4h 0.425 mg/l/8h

•	Rat (NS)	185 (1950)	Inhalation, whole body	diluted SA (10-60% w/v)	7 h 3.5 h	1-2	LC_0 LC_{100} LC_0 LC_{100}	0.461 mg/l/7h 0.699 mg/l/7h 0.718 mg/l/3.5h 1.470 mg/l/3.5h
	RAT (NS)	93 (1982)	Inhalation	NS	2 h	NS	LC_{50}	0.510 mg/l/2h
•	MOUSE (CD-1)	150 (1976)	Inhalation, whole body	SO3 + humid air	4 h 8 h	1	LC_{50} LC_{50}	0.850 mg/l/4h 0.600 mg/l/8h
•	Mouse (NS)	185 (1950)	Inhalation, whole body	diluted SA (10-60% w/v)	7 h	1-2	LC_0 LC_{40}	0.461 mg/l/7h 0.699 mg/l/7h
	Mouse (NS)	93 (1982)	Inhalation	NS	2h	NS	LC_{50}	0.320 mg/l/2h
•	Rabbit (NS)	185 (1950)	Inhalation, whole body	diluted SA (10-60% w/v)	7 h 3.5 h	1-2	LC_0 LC_{50} LC_0 LC_{50}	0.699 mg/l/7h 1.610 mg/l/7h 0.718 mg/l/3.5h 1.470 mg/l/3.5h

NS: Not specified, SA: sulfuric acid

In rats, mice and rabbits, as well as in guinea pigs, concentration of acid aerosol, time of exposure and particle size are important factors in determining lethality by inhalation. Among the different species tested, the guinea pigs appear to be the most sensitive to the acute inhalation effects of sulfuric acid mist/aerosol. For the guinea pig, the apparent LC50 for an 8 hour-exposure period to sulfuric acid mist/aerosol with a particle size of about 1µm, ranges from 0.018 to 0.050 mg/l depending on the age of the animals. Younger guinea pigs seem to be more sensitive to sulfuric acid aerosol than older animals.

According to the duration of exposure, the LC 50 appear to be about 0,375 - 0,425 mg/l in rats, 0.600 - 0.850 mg/l in mice, and 1.470 - 1.610 mg/l in rabbits, when taking into account the more reliable/relevant studies.

The sensitivity of the guinea pig may be caused by its tendency for bronchoconstriction and laryngeal spasm compared to other small laboratory animals.

The main macroscopic and/or microscopic alterations observed in respiratory tract after acute exposure to sulfuric acid aerosol were hemorrhage, edema, atelectasis and thickening of the alveolar wall in the lung of guinea pigs, hemorrhage and edema of the lungs and/or ulceration of the turbinate, trachea and larynx in rats and mice. These lesions are related to the corrosive/irritant effect of sulfuric acid.

No data are available on the acute dermal toxicity or on acute toxicity by other routes for sulfuric acid.

4.2.3 Irritation and Corrosiveness

4.2.3.1 Skin irritation

According to Annex I of the Directive 67/548/EEC, sulfuric acid is classified as C; R 35: Corrosive; Causes severe burns. Specific concentration limits are: C; R35 for concentration ≥ 15 % and Xi; R36/38 when concentrations are ≥ 5%, and < 15 %.

The skin irritation studies, that could be checked, were performed using diluted sulfuric acid and are summarized in the following table.

Skin irritation testing with sulfuric acid					
	Species, Test Type	**Ref. (year)**	**Protocol**	**Doses**	**Result**
•	RABBIT, GUINEA-PIG, HUMAN, SKIN IRRITATION TEST ON ABRADED AND INTACT SKIN	135 (1975)	FDA, FSHA, Federal register V37, 1972	0.5 ml of sulfuric acid, 10 %	Not irritating
•	RABBIT, HUMAN, STANDARD SKIN IRRITATION TEST AND HILL TOP CHAMBERS TEST	134 (1990)	CODE OF FEDERAL REGULATION, DOT 1986 (RABBIT) AND 1988 (HUMAN) + HILL TOP CHAMBER	0.4 or 0.5 ml of sulfuric acid 10 % in standard test 0.2 ml of sulfuric acid 10 % in Chamber	Not irritating

Sulfuric acid 10 % appears not to be irritating to the skin in rabbit, guinea pig and human.

4.2.3.2 Eye irritation

The eye irritation studies conducted with diluted sulfuric acid are summarized in the following table. Only available studies are presented.

Eye irritation testing with sulfuric acid					
	Specie, Test type	**Ref. (year)**	**Protocol**	**Doses**	**Result**
•	RABBIT	95 (1992)	OECD Guideline 405	0.1 ml of sulfuric acid 10 %	Not irritating
•	RABBIT	94 (1989)	Directive 79/831/EEC, Annex V, part B	0.1 ml of sulfuric acid 10 %	Not irritating
•	RABBIT	68 (1980)	US.FHSA (CFR, 1979) and NAS 1138 Committee (1977)	0.01 ml, 0.05 ml, 0.1 ml of sulfuric acid 10 %	0.01ml: slightly irritating 0.05ml: severely irritating 0.1 ml: severely irritating
•	RABBIT, WASHED AND UNWASHED EYE	128 (1982)	US.FHSA Fed. Reg. Vol. 38 (187) Part II and 16 CFR 1500.42 (1973) and Draize method (1944)	0.1ml of sulfuric acid 10 % or 5 %	10% : SEVERE IRRITANT 5%: MODERATE IRRITANT

Conflicting results are observed in eye irritation studies according to the protocol used (OECD/EU or US). However, buffering and dilution effects of tears could explain the different conclusions since sulfuric acid was instillated into the conjunctival sac of the eye in studies n° 95 and 94 while acid was administered directly to the central corneal surface in experiments 68 and 128. In this last study, the authors have observed that the washing procedure (eye washed 2 min. with tap water 30 sec. after exposure) reduced the time to onset of opacity induced by 5% sulfuric acid and slightly decreased the severity of the iritis induced by 10 % sulfuric acid.

4.2.4 Skin sensitization

No study was identified for skin sensitization potential with sulfuric acid.

Sulfuric acid has been in industrial use for many decades, and skin burns due to concentrated sulfuric acid are well documented (ILO Encyclopedia of Occupational Health and Safety, 1985). However, skin sensitisation secondary to skin irritation or burns has never been described, despite the fact that severe chemical irritation and burns are known to create favorable conditions for the induction of contact allergy (this is a strategy employed in routine skin sensitisation testing such with the Magnusson-Kligmann test).

Repeated contact with more diluted sulfuric acid is known to cause skin dessication, ulceration and chronic purulent inflammation around the nails (ILO Encyclopedia of Occupatioal Health and Safety, 1985). These symptoms are quite different from those seen in acute or chronic allergic dermatitis.

Skin contact with weak solutions of sulfuric acid (about 10%) has been quite common in the viscose rayon industry for nearly a century. Yet sulfuric acid allergy has never been noted.

Sulfate ions are unlikely to cause allergy, since the body contains large amounts of sulfate ions (~0.33 mmol/L in serum and about 50 times higher concentration intracellularly). Various metal sulfates (e.g. nickel sulfate, cobalt sulfate) are used in routine allergy testing, but positive reactions are related to the metal ion, not to the sulfate, as can be deduced from the definitely non-allergenic zinc sulfate (ECETOC Technical Report n° 77, 1999).

Based on the above, it may be concluded that sulfuric acid is not an allergen in humans, and that animal testing for sensitisation potential would not provide any information relevant for risk assessment.

4.2.5 Repeated dose toxicity

Repeated dose toxicity studies with sulfuric acid are summarized in the following tables. All of them have been realized by inhalation of sulfuric acid aerosol/mist, in several animal species. However, among them, only one study has been conducted using methodology in accordance with relevant inhalation guidelines for a 28-day study (OECD guideline n° 412 and Directive 67/548 EEC, Annex V, test method B8) and according to GLP.

NOTE: this study is not a full OECD protocol – only the respiratory tract was subject to pathology.

Repeated dose toxicity studies by inhalation conducted with sulfuric acid aerosol

	Species (strain, sex)	Ref. (year)	Protocol	Duration, frequency	Administration	Doses	Particle size (µm)	T°(C/F) RH (%)	End-point	Value (unit)/ results
•	RAT (ALPK:AP$_F$SD, FEMALE)	74 (IN PREP.)	OECD N° 412 / DIR. 67/548/EEC ANN. V, B8 GLP	28 DAYS 6H/D, 5D/WK	Inhalation, nose only	0.00, 0.30, 1,38, 5.58 mg/m3	 0.62 0.83 0.94	~19.5°C ~50 %	Death: Body and lung weight: Histopathology: Cell proliferation:	No death due to SA No alteration Alteration in larynx only Alteration in larynx only
•	Rat (Sprague-Dawley, male)	106 (1997)	other	30 or 90 days 23.5 h/d, 7d/wk or intermittent (12 h/d)	Inhalation, whole body	0, 20, 100, 150 µg/m3 (SA) ± 0.12, 0.20 ppm (O3)	0.4 - 0.8	22°C 80%	Lung histopathology: Lung biochemical analyses: Morphometric analyses of alveolar tissues: Body and lung weight: +O3:	No alterations No alteration No change due to SA alone No alteration No interaction
	Rat (Sprague-Dawley, male)	111 (1979)	other	from 6 to 14 weeks, continuous	Inhalation, whole body	from 2.37 to 15 mg/m3	0.3 - 0.5	70/77°F 35-50%	Spontaneous locomotor activity: Blood gas parameters: Learning ability: Pulmonary functions: Food/water intake; body weight:	Alteration (at 2.49 mg/m3) Alteration (at 6.5 mg/m3 No alteration Alteration (at 4.05 mg/m3) No alteration
•	Rat (Fischer, male/female)	26 (1978)	other	6 months, 6h/d, 5d/wk	Inhalation, whole body	0, 10 mg/m3 (SA) ± 0.5 ppm (O3)	~ 1	82°F 60%	Hematology/blood chemistry: Lung histopathology: Body and lung weight: +O3:	No alteration Alteration (slight) No alteration No interaction
•	Rat (Fischer, male)	25 (1977)	Other	2 to 7, 14, 21 or 28 days, frequency: NS	Inhalation, whole body	0, 5, 10, 20, 30, 100 mg/m3 (SA) ± 1, 2 ppm (O3)	~ 1	70°F 55%	Death Hematology/blood chemistry: Lung histopathology: Body and lung weight: Lung lavage fluids: +O3:	No death No alteration No alteration No alteration No alteration No interaction

Repeated dose toxicity studies by inhalation conducted with sulfuric acid aerosol (continued)

	Species (strain, sex)	Ref. (year)	Protocol	Duration, frequency	Administration	Doses	Particle size (µm)	T°(C/F) RH (%)	End-point	Value (unit)/ results
	Guinea pig (NS, NS)	111 (1979)	other	from 6 to 14 weeks, continuous	Inhalation, whole body	from 6.56 to 15 mg/m3	0.2 - 0.5	70/77°F 35-50 %	Pulmonary functions:	No alterations
•	Guinea pigs (Hartley, male/female)	26 (1978)	other	6 months, 6h/d, 5d/wk	Inhalation, whole body	0, 10 mg/m3 (SA) ± 0.5 ppm (O3)	~ 1	82°F 60 %	Hematology/blood chemistry: Lung histopathology: Body and lung weight: +O3:	No alteration Alteration (slight) No alteration No interaction
•	Guinea pigs, (Hartley, female)	25 (1977)	other	2 to 7, 14, 21 or 28 days, frequency: NS	Inhalation, whole body	0, 5, 10, 20, 30, 100 mg/m3 (SA) ± 1, 2 ppm (O3)	0.53, 1, 1.66	70°C 55%	Death Hematology/blood chemistry: Lung histopathology: Body and lung weight: Lung lavage fluid: +O3:	Death at > 20mg/m3 No alteration Alteration at > 20mg/m3 No alteration No alteration No interaction
	Guinea pig (NS, NS)	184 (1958)	other	from 18 to 140 days, continuous	Inhalation whole body	0, 1 to 4 mg/m3 (medium or coarse) up to 26 mg/m3 (fine aerosol)	3.6-4.3 or 0.9 or 0.6	NS NS	Respiratory tract histopathology:	Alterations (slight); medium size (0.9µm) aerosol was the most active
	Guinea pig (Harley, female)	168 (1979)	other	7 days, continuous	Inhalation, whole body	38 to 220 mg/m3	0.32 - 0.4	NS NS	Mortality (LD50):	100 mg/m3
•	Guinea pig, (Hartley, male/female)	2 (1973)	other	12 months 23 h/d	Inhalation, whole body	0.00, 0.08, 0.10 mg/m3	0.84, 2.78	22°C 50 %	Body weight: Survival: Hematology/blood chemistry: Pulmonary function: Histopathology:	Alteration (small in female) No death No alteration No alteration No alteration
•	Guinea pig, (Hartley, male/female)	3 (1975)	other	12 months 22-23 h/d	Inhalation, whole body	0, 0.9 mg/m3 SA or 0.08 mg/m3 SA ± 0.46 mg/m3 fly ash	0.49, 0.54 or 2.23	22°C 50%	Body weight: Survival: Hematology/blood chemistry: Pulmonary functions: histopathology: + pollutants	No alteration No death due to exposure No alteration No alteration No alteration No interaction

Repeated dose toxicity studies by inhalation conducted with sulfuric acid aerosol (continued)

	Species (strain, sex)	Ref. (year)	Protocol	Duration, frequency	Administration	Doses	Particle size (µm)	T°(C/F) RH (%)	End-point	Value (unit)/ results
•	RABBIT (NEW ZEALAND WHITE, MALE)	165 (1992)	OTHER	4, 8, 12 MONTHS, 2H/D, 5D/WK	Inhalation, nose only	0, 125 µg/m3 (SA), ± 0.1 ppm (O3)	0.3	25°C 60 %	Tracheobronchial clearance: Lung fluids: Lung histopathology: Body and lung weight: + O3:	Altered (speed then slow) No alteration Transient alteration No change Interactions (+ and -)
•	RABBIT (NEW ZEALAND WHITE, MALE)	64 (1989)	OTHER	4, 8, 12 MONTHS, 1H/D, 5D/WK	Inhalation, nose only	0, 250 µg/m3	0.3	25°C 80 %	Tracheobronchial clearance: Pulmonary functions: Lung histopathology:	Altered (decreased) Altered Altered
•	RABBIT (NEW ZEALAND WHITE, MALE)	63 (1988)	OTHER	4, 8, 12 MONTHS, 1H/D, 5D/WK	Inhalation, nose only	0, 250 µg/m3	0.3	25°C 80 %	Tracheobronchial clearance: Lung histopathology:	Altered (decreased) Altered
•	RABBIT (NEW ZEALAND WHITE, MALE)	155 (1987)	OTHER	14 days 2h/day	Inhalation, nose only	0, 500 µg/m3 (SA) ± 0.3, 1 ppm (NO2)	0.3	25°C 60 %	Respiratory region clearance: +NO2:	Altered (decreased) Interactions (at 1 ppm)
•	RABBIT (NEW ZEALAND WHITE, MALE)	160 (1987)	OTHER	14 days 2h/day	Inhalation	0, 500 µg/m3 (SA) ± 0.3, 1 ppm (NO2)	0.3	25°C 60 %	Tracheobronchial clearance: +NO2:	Altered (decreased) Interactions (at 0.3 and 1 ppm)
•	RABBIT (NEW ZEALAND WHITE, MALE)	154 (1986)	OTHER	8 months 1h/d, 5d/wk	Inhalation, nose only	0, 250 µg/m3	0.3	25°C 80 %	Alveolar clearance:	Altered (increased)
•	RABBIT (mixed breed, male)	156 (1983)	OTHER	4 weeks, 1h/d, 5d/wk	Inhalation, nose only and oral tube (at 250 µg/m3, only)	0, 250, 500 µg/m3	0.3	27°C 80 %	Tracheobronchial clearance: Lung histopathology:	Altered (increased) Altered
•	RABBIT (NEW ZEALAND WHITE, MALE)	167 (1990)	OTHER	14 days 1, 2 or 4h/d (for 50 µg/m3) 0.5, 1 or 2 h/d (for 100µg/m3)	Inhalation, nose only	0, 50, 100 µg/m3	0.3	20°C 80 %	Respiratory region clearance:	Altered (increased) only at 50 µm/m3 for 4h/d and 100 µg/m3 for 2h/d

Repeated dose toxicity studies by inhalation conducted with sulfuric acid aerosol (continued)

	Species (strain, sex)	Ref. (year)	Protocol	Duration, frequency	Administration	Doses	Particle size (µm)	T°(C/F) RH (%)	End-point	Value (unit)/ results
•	Monkey (Macaca irus, male/female)	2 (1973)	other	18 months, 23 h/d	Inhalation, whole body	0, 0.38, 2.43, 0.48, 4.79 mg/m3	2.15, 3.60, 0.54, 0.73	22°C 50 %	Body weight: Survival: Hematology/blood chemistry: Pulmonary function: Histopathology:	No alteration No death due to SA No alteration Alteration (with high dose) Alteration in lung (with high dose)
	Monkey (Macaca irus, male/female)	3 (1975)	other	18 months, 22-23 h/d	Inhalation, whole body	0, 0.1 to 5 ppm (SO2) ± 0.5 mg/m3 (fly ash) and/or 0.1 to 1 mg/m3 (SA)	0.5 to 3.35	22° 50%	Body weight: Survival: Hematology/blood chemistry: Pulmonary functions: Histopathology: + pollutants	No alteration No death due to exposure No alteration Alteration (when 1 mg/m3 SA in mixture) Alteration in lung (when 1 mg/m3 SA in mixture) No interaction
	Mouse (Swiss webster, male)	168 (1979)	other	10 to 14 days continuously	Inhalation, whole body	0, 125, 141, 154 mg/m3	0.32, 0.45, 0.62	NS NS	Death: Histopathology: Hematology: Blood and urine chemistry: Interferon (tracheal explant and alveolar macrophages):	Yes, in each group Alteration in larynx/trachea Alteration Alteration Alteration
•	Hamster, (Syrian golden, male)	105 (1978)	other	30 days, 6h/d, 5d/wk	Inhalation whole body	0, 100 mg/m3	2.6	70% 50%	Mortality: Body weight: Clinical signs: Histopathology:	No death Transient alteration Transient alteration Alteration only in larynx and trachea
•	Dog, (Beagle, female)	110 (1978)	other	620 days, 21h/d	Inhalation whole body	0, 0.9 mg/m3 (SA) ± 13.4mg/m3 (SO2)	0.5	73-76°F 43-45 %	Bodyweight: Organ weight: Hematology: Pulmonary functions: Histopathology:	No alteration Alteration for lung, heart No alteration Alteration No alteration

NS: not specified; SA: sulfuric acid; T°: temperature; RH: relative humidity

In this study, nose-only exposure of rats for 6h/d, 5d/wk for a period of 28 days to sulfuric acid aerosols resulted in pathological changes (squamous metaplasia) and in increase in cell proliferation in the larynx only. Changes of this type are commonly seen in rats exposed to irritants. Mimimal squamous metaplasia was observed in the laryngeal epithelium following exposure to the lowest concentration used (0.3 mg/m3). This effect was fully reversible. Exposure to 1.38 mg/m3 caused more severe metaplasia accompanied by cell proliferation.

Whereas the other studies presented some deficiencies and were performed using different experimental conditions, collectively, they show consistent effects in the different animals species studied.

Among the different end points measured in rats and guinea pigs, few or no alterations were observed after repeated exposure to sulfuric acid aerosol at concentration up to 10 and 20 mg/m3 in rat and guinea pig, respectively. The main alterations observed were microscopic changes in the respiratory tract (minimal proliferation of alveolar macrophages and loss of cilia in mild trachea). Sulfuric acid aerosols had no effect on hematology, blood chemistry and body weight and/or lung weight, as far as considered biological endpoints were concerned. Taken together, these results suggest that sulfuric acid aerosols seem to have a local effect and no systemic effects in these species.

Studies performed in rabbits have investigated mainly effects of sulfuric acid aerosol on respiratory tract clearance rates of labeled particles and histologic changes. Sulfuric acid aerosol at concentration ranging from 50 to 500 µg/m3 induced alterations of both tracheobronchial and respiratory region clearance as well as microscopic changes (mainly increase in epithelial secretory cell number in pulmonary airways, which could resolve by 6 months post exposure; but no evidence of inflammation) after exposure periods from 14 days to 12 months. Note that both tracheobronchial and respiratory region clearances could be accelerated or retarded according to the study considered.

In monkeys, only the highest concentrations of sulfuric acid mist (2.43 and 4.79 mg/m3) presented deleterious effects on pulmonary structures and functions while no effect on body weight, survival or hematology and blood chemistry were observed. In hamsters exposed to high concentration of sulfuric acid mist (100 mg/m3) with large particle size (2.6 µm), microscopic alterations were seen in larynx and trachea. Exposure of dogs to 0.9 mg/m3 sulfuric acid mist have induced alterations in pulmonary functions and in organ weights (lung and heart).

Overall, these results indicate that high variability in responses to repeated inhalation with sulfuric acid aerosol is found according to animal species and endpoints studied.

Taken together, these studies have shown that toxicity was confined to changes in the structure and function of the respiratory tract, suggesting that it has a local effect and no systemic effects. The observed changes are related to the irritant properties of sulfuric acid and are most likely due to the H+ ion.

No data are available on repeated dose toxicity studies by oral, dermal or by other routes for sulfuric acid.

4.2.6 Genetic Toxicity

4.2.6.1 Genetic toxicity in vitro

Sulfuric acid has been shown to be without effect in the Ames test using various strains of *S. typhimurium* (pH4 to 9) and *E. coli* (0.002 to 0.005%), both with and without S9. It has been shown to cause chromosomal aberrations in CHO cells (pH 3.5 to 7.4,both with and without S9), and in a non-standard assay in developing sea urchin embryos (pH 5 – without S9) (Scott *et al.,* 1991).

4.2.6.2 Genetic toxicity in vivo

No studies on the in-vivo mutagenicity of sulfuric acid are available.

Conclusions:
In-vitro studies have shown an effect of sulfuric acid in chromosomal assays, but not point mutation assays.

The chromosomal effects are well known to be a consequence of reduced pH, being seen using any strong acid.

Whilst the mutagenicity of sulfuric acid has not been studied using in-vivo systems, such testing would seem inappropriate because sulfuric acid will dissociate in contact with biological systems and depending on the concentration it will buffer and lead to a lowering of pH. As such, only sulfate ions would be presented to the remote target cells of the standard assay systems, including germ cells, and would be predicted to be without effect. No standard assay systems are available to study such effects in relevant target organs (e.g. larynx). Moreover, it is likely that any long-term effects of sulfuric acid on such organs would be dominated by the anticipated irritant/necrotic effects so that such mutagenicity testing would seem to be unnecessary.

4.2.7 Carcinogenicity

Carcinogenicity studies performed with sulfuric acid solution or mist are summarized in the table below. However, all of these studies present several important deficiencies (e.g. small numbers of animals per group, only pathological report available for studies n° 54 and 55). The code **3** (not reliable) for reliability/validity has been assigned to all these studies.

Carcinogenicity studies conducted with sulfuric acid

	Test Type, Species, Strain	Ref. (year)	Protocol	Duration, Frequency	Animal /group	Dose	Result
●	CARCINOGENICITY, RAT, WISTAR	187 (1997)	Chronic gastric intubation	Life-time, 1X/WK FOR LIFE	30 M + 30 F	0.5 ML OF 0.6 % SA SOLUTION (MTD)	Local and weak carcinogen.
●	CARCINIGENICITY OR CO-CARCINOGENICITY, RAT, WISTAR	187 (1997)	Chronic intratracheal instillation	LIFE-TIME, 2x/month for 12 months	30 M + 30 F	0.3ml of 0.6 % SA solution (MTD) ± BaP	Local and weak carcinogen. Synergy with BaP
●	CARCINOGENICITY OR CO-CARCINOGENICITY, MOUSE, CBAXC57BL	187 (1997)	Chronic gastric intubation	Life-time 1x/wk for life	30 M + 22 to 27 F	0.2ml of 0.2 % SA solution (MTD) ± Urethane	Local and weak carcinogen. No synergy with Urethane
●	Initiation/Promotion or co-carcinogenicity Hamster ,	105 (1978)	Inhalation (mist)	Lifetime, 6h/d, 5d/wk	60 M	0, 100 mg/m3 (particle size: 2.6 µm) ± BaP	No evidence of carcinogenic potential. Equivocal for

	Syrian golden						promoting or co-carcinogenic effect with BaP
●	Carcinogenicity Rat, Fischer 344	55 (1978)	Inhalation (mist)	2 years	No data	0, 10 mg/cm3 (SA) ± 0.5 ppm (O3)	No carcinogenic effect
●	Carcinogenicity Guinea pig	54 (1978)	Inhalation (mist)	2 years	No data	0, 10 mg/cm3 (SA) ± 0.5 ppm (O3)	No carcinogenic effect

SA: sulfuric acid; MTD: Maximal Tolerated Dose; BaP: Benzo(a)pyrene; O3: Ozone; M: male; F: female

A local and weak carcinogenic effect was observed after treatment with sulfuric acid solution by intratracheal instillation or gastric intubation in both rats and mice. Tumors appeared the second year in those organs where sulfuric acid acted directly. Tumors observed in rats and mice after exposure to sulfuric acid by gastric intubation were mainly benign forestomach tumors (papillomas or micropapillomas): 16 tumors in the treated group and 9 in untreated control for rats, and 4 tumors in the treated group and 2 in the control group for mice. Hyperplasia of the epithelium of the forestomach, hyperkeratosis and acanthosis were also seen more frequently in animals receiving sulfuric acid alone. One malignant lung tumor (a poorly differentiated adenocarcinoma was also noticed in a rat treated with sulfuric acid by gavage. The type of lesions/tumors observed in both rats and mice treated by gavage with sulfuric acid are generally related to repeated irritation/cytotoxicity. Following intratracheal instillations of sulfuric acid solution, various tumors appeared, mainly of the respiratory tract (1chrondrosarcoma of trachea, 1 bronchial adenocarcinoma and 1 histiocytoma of lung), forestomach (6 malignant oesophagus/forestomach tumors) and lymphomas with a higher incidence than the untreated control. However, this study is compromised by several deficiencies (e.g. too few animals/group, inappropriate control groups, design of the study, analyses, and reporting of the results).

No carcinogenic effects were observed in studies performed with sulfuric acid mist although these studies also have been compromised by deficiencies.

It is noticeable that, in chronic/long term studies performed with sulfuric acid mist, no neoplastic lesions were evidenced in different animal species (see chapter *4.2.5: Repeated dose toxicity*).

4.2.8. Toxicity to reproduction and developmental toxicity/teratogenicity

4.2.8.1 Effects on Fertility

No studies were identified regarding toxicity to reproduction in animals after oral, dermal or inhalation exposure to sulfuric acid.

However, due to irritant/corrosive effects of H_2SO_4, oral and dermal routes are not appropriate for testing toxicity to reproduction. In addition, H_2SO_4 is a direct-acting toxicant. The acid as such, is not expected to be absorbed or distributed throughout the body. Therefore, it is not likely that it will reach male and female reproductive organs following exposures by any route. The anion sulfate probably does not play a specific toxicological role because it is a normal metabolite of sulfur-containing amino acids and it is excreted in the urine when in excess (144).

In long term/chronic or carcinogenicity studies no gross histological alterations were found in reproductive organs in 2 different species (rat and guinea pig) after exposure to 1-10 mg/m3 sulfuric acid aerosol, and therefore, microscopic examination was not judged necessary (54, 55, 184).

4.2.8.2 Developmental toxicity/teratogenicity

In a developmental toxicity study conducted under a method similar to OECD test Guideline 414, no significant effects on mean numbers of implants/dam, live fetuses/litter or resorptions/litter were observed in mice and rabbits exposed by inhalation to sulfuric acid aerosol at 5 and 20 mg/m3 during gestation (129).

Developmental toxicity/teratogenicity studies conducted with sulfuric acid mist								
	Species, Strain	**Ref. (year)**	**Protocole**	**Administration**	**Exposure time, frequency**	**Doses**	**Endpoint**	**Value**
●	Mouse, CF-1	129 (1979)	Similar to OECD Test guideline 414	Inhalation, whole body	Day 6 to 15 of gestation, 7h/d	0, 5, 20 mg/m3	NOAEL maternal NOEL teratogenicity	20 mg/m3 20 mg/m3
●	Rabbit, New Zealand white	129 (1979)	Similar to OECD Test guideline 414	Inhalation, whole body	Day 6 to 18 of gestation, 7h/d	0, 5, 20 mg/m3	NOAEL maternal NOEL teratogenicity.	20 mg/m3 20 mg/m3

NOAEL for maternal toxicity appear to be 20 mg/m3 for both species. No evidence of foetotoxicity or teratogenicity was seen in either species.

As demonstrated by numerous studies, sulfuric acid is a direct-acting toxicant. Because of the irritant/corrosive effect of sulfuric acid and the absence of effects observed on reproductive organs in long term/chronic studies as well as in a study related to reproduction, it may be concluded that a specific study to reproduction is not necessary.

4.2.9 Other relevant information

Among the experiments studying sulfuric acid effects that could not be integrated into the above chapters due to their special design, the most reliable or informative of them are summarized in the following table.

Other studies conducted with sulfuric acid									
Species, Strain	**Ref. (year)**	**Test Type**	**Administra-tion**	**Exposure time, frequency**	**Doses**	**Particle size (µm)**	**T° RH**	**Endpoint**	**Result**
Guinea pig NS	6 (1958)	Acute inhalation Influence of aerosol particle size on alteration of pulmonary functions	Inhalation, head only	1 hour	1.9-43.6 mg/m3	0.8, 2.5, 7	NS 38 %	Pulmonary functions:	Alterations : various degree according to particle size, the 7 µm is the less effective
Guinea pig Hartley	171 (1981)	Acute inhalation, pulmonary functions	Inhalation, head only	1 hour	0, 1.2, 14.6, 24.3, 48.3 mg/m3	1	NS, 40 or 80%	Pulmonary functions:	All-or- non response, 2 polpulations: responsive and non-responsive animals
Guinea pig Hartley	148 (1998)	Acute inhalation, pulmonary functions	Inhalation, whole body	4 hours	0, 14.1, 20.1, 43.3 mg/m3	0.95	21-22 °C, 70-80 %	Pulmonary functions: Lung histopathology: Bronchoalveolar lavage fluis:	Alteration dose- and time-dependent Alteration (high dose) Alteration (high dose)
Guinea pig NS	198 (1986)	Acute inhalation, Tracheal clearance Airway fluid	Inhalation, whole body	6 hours	0, 1, 10, 27 mg/m3	~0.9	NS 80%	Tracheal clearance: Bronchoalveolar fluids: Lung and trachea histopathology:	Transient alteration (slower at 1 mg/m3) Transient alteration in responsive animals Marked alterations in responsive animals
Guinea pig, Hartley	37 (1978)	Respiratory changes	Inhalation, whole body	2days, 6h/d	0, 25 mg/m3	1	55-60 %	Respiratory tract histopathology:	Alteration in all animals
Guinea pig, Hartley	143 (1993)	Acute/repeated inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	3 hours or 3h/d, 5 days	0, 970 µg/m3	0.3	NS, NS	Lavage fluids: Macrophage intracellular pH :	No alteration Alteration
Guinea pig, Hartley	31 (1992)	Acute/repeated inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	3 hours or 3h/d, 4 days	0, 300 µg/m3	0.04 or 0.3	NS, NS	Lavage fluids: Macrophage intracellular pH: Products: Phagocytic activity Effect of particle size:	Transient alteration Alteration Alteration Alteration Different effect for fine or ultrafine

Other studies conducted with sulfuric acid (continued)									
Species, Strain	**Ref. (year)**	**Test Type**	**Administration**	**Exposure time, frequency**	**Doses**	**Particle size (µm)**	**T° RH**	**Endpoint**	**Result**
Guinea pig Hartley	57 (1975)	Acute inhalation, Respiratory deposition of ^{33}P-labeled bacteria aerosol	Inhalation, whole body	1 hour	0 30, 300, 3020 µg/m3	 0.25 0.6 1.8	24-26 °C, 50-55 %	Respiratory functions: Aerosol deposition in respiratory tract:	No alteration Increased in trachea and nasopharynx at 30 and 3020 µm/m3, respectively
Guinea pig, Hartley	101 (1993)	Chronic inhalation Airway responsiveness to histamine	Inhalation, whole body	3, 7, 14, 30 days, 24h/d	0, 1, 3.2 mg/m3	0.55	25 °C, 55 %	Lung wet weight Airway responsiveness:	No alteration Transient alteration at 3.2 mg/m3
Guinea pig, Hartley	61 (1992)	Chronic inhalation Lung mast cell function in culture	Inhalation, whole body	2, 4 wk 24h/d	0, 0.3, 1, 3.2 mg/m3 (SA) ± NO2	0.65 0.55 0.73	NS NS	Number of isolated cell: Mast cell histamine release: + NO2	No alteration Transient alteration at ≥ 1 mg/m3 No interaction
Rabbit, Mixed breed	30 (1983)	Acute inhalation, Tracheobronchial clearance Comparison between effects of sulfuric acid mist and other sulfites: (Fe(III)-S(IV) or Na2SO3	Oral delivery	1 hour	0, 260-2155 µg/m3 (SA) or 238–1227 µg/m3 Fe(III)-S(IV) or 270–1950 µg/m3 Na2SO3	0.3	24°C 75%	Tracheobronchial clearance	Alteration, dose-related, for SA No alteration with Fe(III)-S(IV) Alteration with Na2SO3 at ≥ 1200 µg/m3
Rabbit, New Zealand White	159 (1984)	Acute inhalation, Tracheobronchial clearance	Oral delivery	1 hour	100-1084 µg/m3	0.3	24°C 75%	Tracheobronchial clearance	Alteration, dose-related: transient acceleration at low doses / retardation at higher doses
Rabbit, New Zealand White	166 (1989)	Acute/Repeated inhalation, Tracheobronchial and alveolar clearance Comparison: effects of SA, NH4HSO4, $(NH4)_2SO4$	Oral delivery or nasal mask	2-4 hours , or 2-4h/d, 14 day 2 HOURS 2 HOURS	0.1-2 mg/m3 (SA) or 0.5, 1, 2 mg/m3 NH4HSO4 or 2 mg/m3 $(NH4)_2SO4$	 0.3	24-25°C 75 or 80%	Tracheobronchial and alveolar Clearance Comparison effect of the different acids	Alteration concentration and time dependent SA is the more irritant

Other studies conducted with sulfuric acid (continued)									
Species, Strain	**Ref. (year)**	**Test Type**	**Administra-tion**	**Exposure time, frequency**	**Doses**	**Particle size (µm)**	**T° RH**	**Endpoint**	**Result**
Rabbit, New Zealand White	163 (1992)	Acute inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	3 hours	0, 50, 75, 125 µ/m3 (SA) ± O3	0.3	25 °C, 55%	Lavage fluids: Macrophage products: Phagocytic activity: +O3	No alteration Alteration (high dose) Alteration (high dose) Interaction
Rabbit, New Zealand White	201 (1992)	Acute inhalation , in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	2 hours	0, 50, 75, 125, 500 µg/m3	0.3	25 °C, 60%	Lavage fluids: Macrophage products:	No alteration Alteration (except 50 µg/m3)
Rabbit, New Zealand White Human	203 (1997)	Acute inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, Rabbit: nose only, at rest. Human: whole body, exercising	3 hours	0, 1mg/m3	0.8	25 °C, 60% (rabbit) 21°C 38% (human)	Lavage fluids: Macrophage products and properties: Phagocytic activity:	Few alteration in rabbit Few alteration, mainly in rabbit Alteration in rabbit No alteration in human
Rabbit, New Zealand White	32 (1995)	Acute inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	3 hours	0, 50, 125 µg/m3 (SA) ± O3	0.3	25 °C, 55 %	Lavage fluids: Macrophage intracellular pH : and H+ extrusion: +O3	No alteration Alteration at 125 µg/m3 Alteration Some interaction
Rabbit, New Zealand White	153 (1987)	Repeated inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	2, 6, 13 days 2h/d	0, 500µg/m3	0.3	25 °C, 60%	Lavage fluids: Macrophage properties : Phagocytic activity:	Transient alteration Alteration (for mobility) Alteration
Rabbit, New Zealand White	202 (1994)	Repeated inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	4 days 2h/d	0, 500, 750, 1000 µg/m3 (SA) or 1 mg/m3 (NH4HSO4)	0.3	25 °C, 60%	Lavage fluids: Macrophage products: Phagocytic activity: NH4HSO4 :	Alteration at 1 mg/m3 for some endpoints Alteration Alteration at 1 mg/m3 No alteration
Rabbit, New Zealand White	161 (1990)	Repeated inhalation, in vivo, Bronchoalveolar lavage Lung macrophage culture	Inhalation, nose only	5 days, 1h/d	0, 0.25, 0.5, 1, 2 mg/m3 (SA) or 0.5-4mg/m3 (NH4HSO4)	0.3	25 °C, 60%	Lavage fluids: Macrophage phagocytic activity:	No alteration Alteration (at smaller doses than NH4HSO4)

Other studies conducted with sulfuric acid (continued)									
Species, Strain	**Ref. (year)**	**Test Type**	**Administra-tion**	**Exposure time, frequency**	**Doses**	**Particle size (µm)**	**T° RH**	**Endpoint**	**Result**
Rabbit, New Zealand White	162 (1990)	In vivo repeated inhalation, in vivo, bronchoalveolar lavage In vitro exposure of tracheal explants : pH, osmolarity and associated anion effects	Inhalation, nose only Culture with various medium	5 days, 1 h/d 5 hours	0, 250, 500, 1000 µg/m3 Effect of HCl and Na2SO4, (in vitro)	0.3	24 °C, 60 %	PGE2,PGF2, TxB2: LTB4 : pH effect (in vitro) on eicosanoid products: associated anion:, osmolarity effect	Decreased: in vivo, No alteration: in vivo Similar than in vivo exp. No alteration No alteration
Rabbit, New Zealand White	65 (1986)	Repeated inhalation, Bronchial responsiveness to Ach	Inhalation, nose only	4, 8, 12 months 1h/d, 5d/wk	0, 250 µg/m3	0.3	25 °C, 80 %	Pulmonary functions: Bronchial responsiveness to Ach:	No alteration Hyperresponsive airways
Mice Swiss-Webster derived	56 (1975)	Acute/repeated inhalation, Respiratory tract clearance of ^{33}P-labeled bacteria	Inhalation	4 hours or 90 min/d, 4 days	1.5 mg/m3 15 mg/m3	0.6 3.2	23 °C, 70 %	Respiratory tract histopathology: Respiratory tract clearance of bacteria:	No alteration Alteration with concentrated acid only
Mice Swiss-Webster	138 (1980)	Intermittent inhalation, Enhancement of allergic lung sensitization	Inhalation	Repeated period of 3 to 7 days	0, 1 mg/m3 (SA) ± O3	0.041 (CMD)	25 °C, 50 %	Immune responsiveness to inhaled antigen: Allergic sensitization : + O3	No alteration No alteration Interaction
Donkey	157 (1978)	Acute inhalation, Pulmonary functions and tracheobronchial clearance Comparison:effects of SA and $(NH4)_2SO4$	Inhalation, nasal catheter	1 hour	71-1506 µg/m3 (SA) 290-3140 µg/m3 $(NH4)_2SO4$	0.3-0.6	28°C 45%	Pulmonary functions: Tracheobronchial clearance: $(NH4)_2SO4$:	No alteration Transient or more persitent alteration according to animal No effect on clearance
Donkey	158 (1979)	Repeated inhalation, Tracheobronchial clearance	Inhalation, nasal catheter	6MONTHS, 1h/d, 5d/wk	~104 µg/m3	0.5	28°C 45%	Tracheobronchial clearance	Alteration :variable degree among animals

Other studies conducted with sulfuric acid (continued)									
Species, Strain	**Ref (year)**	**Test Type**	**Administra-tion**	**Exposure time, frequency**	**Doses**	**Particle size (µm)**	**T° RH**	**Endpoint**	**Result**
Rat, F344	198 (1986)	Acute inhalation, Tracheal clearance Airway fluid	Inhalation, whole body	6 hours	0, 1, 10, 100 mg/m3	~0.9	NS 80%	Tracheal clearance: Bronchoalveolar fluids: Lung and trachea histopathology:	Transient alteration (faster at 10 mg/m3) No alteration Alteration in trachea
Rat , Sprague Dawley	98 (1997)	Repeated inhalation Influence of acid aerosol droplet size	Inhalation, Nose only	2days, 4h/d	0, 0.5 mg/m3 (SA) ± O3	0.06 (ultrafine) and 0.3 (fine) for labeling : 0.7	NS NS	Morphology Pulmonary functions: Pulmonary lesions: Lung labeling index in periacinar region: +O3	No alteration Change: ultrafine only Change: ultrafine only Change: ultrafine only Interaction with ultrafine
Dog, Beagle; Rat, F344; Guinea pig, Hartley	45 (1983)	Acute inhalation, Clearance via blood	Inhalation, nose only or nasal instillation	1minute (dog), 30 seconds (other)	1-20 mg/m3	0.45-1.10	NS 20 or 80%	Blood clearance half-time of an ^{35}S-labeled sulfuric acid solution	Half time of clearance from lung to blood ranges from2 to 9 min. No effect of RH
Human, Rats, Rabbits, Guinea pigs	164 (1992)	Lung macrophage culture, Sulfuric acid challenge in vitro (up to pH:4.5)						Macrophage viability: Phagocytic acivity: Sensitivity:	No alteration Decreased with decreasing pH in all species Guinea pig> rat> rabbit> human

NS: not specified; RH: relative humidity

Several experiments have examined changes in pulmonary structures and functions, in respiratory tract clearance, in bronchoalveolar lavage fluids, and in i*n vitro* pulmonary macrophage properties in different laboratory animal species, after acute or short-term repeated exposures to sulfuric acid mist. Taken together, these results indicate that there is a considerable interspecies variation in sensitivity to sulfuric acid aerosols among laboratory animals. Effects of sulfuric acid are also highly dependent on the characteristics of the aerosol, on the endpoint measured and on the experimental conditions.

In experiments studying the active component in inorganic acids on various endpoints, the observed responses seem to be due to the H+ ion while the anion appears to have no effect. The sulfur from sulfuric acid is rapidly cleared from the lungs of animals into the blood following inhalation exposure (see also Chapter *4.2.1 Mode of action of the chemical, toxicokinetics and metabolism*).

Human appears to be the less sensitive to the effects of the acid in studies investigating *in vitro* functional properties of pulmonary macrophages recovered from different species exposed *in vivo* or *in vitro* to sulfuric acid. For some authors, one of the reason of higher tolerance of human cells to the effects of sulfuric acid aerosol could be that human cells are normally exposed *in situ* to pollutants and microbes from ambient environment, while laboratory animals are raised and housed in facilities that are relatively free of ambient pollutant and microorganisms.

4.2.10 Human data

Acute inhalation exposure to sulfuric acid aerosols causes a range of effects in the respiratory system including decrease in particle clearance rates at lower concentrations (< 1.0 mg/m^3) to changes in lung function (>1.0 mg/m^3). Asthmatics and those with hyper-reactive airways appear more sensitive to the broncho-constrictive effects of the aerosol. Repeated exposure to higher concentrations of aerosol (>3.0 mg/m^3) has been reported to cause damage to the incisors.

Sixteen retrospective mortality or cancer incidence studies have been reported on populations with potential exposure to sulfuric acid aerosols or mists from a wide range of industries, including the manufacture of sulfuric acid, isopropanol, fertilisers and soaps and detergents, lead battery manufacture, metal pickling and the steel industry. In general, these studies have shown increases in lung cancer incidence or cancer of the respiratory tract and, in some cases, laryngeal cancer. Other studies in similar populations have shown no such increases. A feature of all of the studies was the potential for co-exposure to a range of different chemicals, some of which are known to be carcinogenic. Some of the studies were also inadequately controlled for known confounding factors such as smoking.

The occupational factors associated with the in occurrence of laryngeal cancer have been studied in three case-control studies, in which increased odds ratios for laryngeal cancer have been shown for those with occupational exposure to sulfuric acid mist. A fourth case-control study of laryngeal cancer cases on the Texas Gulf Coast failed to demonstrate this relationship.

A case-control study of stomach cancer showed an increased odds ratio in those with occupational exposure to sulfuric acid mists. This study could only be considered as an hypothesis-generating study.

These studies suggest that there is a moderate association between occupational exposure to acid mists containing sulfuric acid and laryngeal cancer that cannot be wholly explained by chance or by confounding by smoking or alcohol. However, given the uncertainty regarding a possible carcinogenic mechanism for sulfuric acid and the likelihood of multiple exposures to other agents in

the work environment, of which sulfuric acid mist is a part, these data are insufficient to demonstrate a causal relationship for this association. There is also little evidence to support a causal relationship between occupational exposure to sulfuric acid mist and lung cancer and there is inadequate information for drawing any meaningful conclusion about an association between occupational exposure to sulfuric acid mist and nasal and other respiratory tract cancers.

The WHO International Agency for Research on Cancer (IARC) reviewed the epidemiology studies and reported in a Monograph in 1992 that "there is sufficient evidence that occupational exposure to strong inorganic mists containing sulfuric acid is carcinogenic to humans". This conclusion has led IARC to classify "occupational exposure to strong inorganic acid mists containing sulfuric acid" as a Group 1 carcinogenic activity (88). It is stressed this classification applies to exposure to the mist (or aerosol) and not to sulfuric acid per se

However, it seems likely that sulfuric acid aerosols in sufficiently high concentrations are deposited in preferred locations in the nasopharyngeal and/or laryngeal regions, where they cause repetitive injury, inflammation and repair. The resulting increased cell proliferation, in conjunction with other carcinogenic agents, may well be responsible for the observed, rather weak association between exposure and effect. Such preferential deposition and extremely localised induced effects (squamous metaplasia and persistent proliferation) have recently been demonstrated in rodents in a 28 day inhalation study in rats (74).

CONCLUSIONS AND RECOMMENDATIONS

The chemical is a candidate for further work :

Environment: the collection of information about exposure during agricultural use should be considered

Health: the collection of information about occupational exposure to sulfuric acid mist should be considered.

REFERENCES

References not reported in the IUCLID Dossier:

- Klimish *et al.,* (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology, 25, 1-5.
- Rosner G (1994), Fraunhofer-Institut fur Toxikologie und aerosolforschung, VAL0811. doc
- ILO encyclopedia of Occupatioal health and Safety, Vol. 2, 3d ed, (1985) ISBN 92-2-103291-4
- ECETOC Technical Report n° 77: Skin and Respiratory Sensitisers: Reference Chemical Data Bank. Aug 99, ECETOC, Brussels.
- Scott *et al*., (1991). Genotoxicity under extreme culture conditions. A report from ICPEMC Task Group 9. Mutation Res. 257, 147-205.
- Food and Environment Protection Act, 1985, Part III, Control of Pesticides Regulations 1986, Evaluation on : Sulphuric acid, April 1998, Ministry of Agriculture, Fisheries and Food, Pesticides Safety Directorate, UK.

References reported in the IUCLID Dossier :

(1) Ahlborg G, Hogstedt C, Sundell M and Aman C. Laryngeal cancer and pickling house vapours. Scand. J Work. Environ. Health, 7, 239, 1981

(2) Alarie et al. (1973). Long-term continuous exposure to sulfuric acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27, 16-24.

(3) Alarie et al., (1975). Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures. Arch. Environ. Health; 30, 254-262.

(4) Alderson M and Rattan N. Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. Br. J. Ind. Med., 37, 85, 1980.

(5) Amdur et al., Arch. Ind. Hyg. Occup. Med. 6, 305-329 (1951) zitiert in Wolff et al., J. Toxicol. Environ. Health 5, 1037-1047 (1979)

(6) Amdur M.O. (1958). The respiratory response of guinea pigs to sulfuric acid mist. Arch. Ind. Health, 18, 407-414.

(7) Amdur M.O., (1989). Health effects of air pollutants: sulfuric acid, the old and the new. Environ. Health Perspect., 81, 109-113.

(8) Amdur M.O., (1989). Sulfuric acid: the animals tried to tell us. Appl. Ind. Hyg. 4(8), 189-197.

(9) Amdur MO, Schulz RZ, Drinker P. (1952) Toxicity of sulfuric acid mist to guinea pigs. Arch. Ind. Hyg. Occup. Med. 5, 318-329.

(10) Amdur MO. (1971). Aerosols formed by oxidation of sulfur dioxide. Arch. Environ. Health, 23, 459-468.

(11) Ato-Fina data

(12) Avol et al., Toxicol. Ind. Health 4, 173-184 (1988).

(13) BASF AG data

(14) BASF AG, Werksaerztlicher Dienst, unveroeffentlichte Mitteilung, 1992.

(15) Bayer A G results

(16) Bayer AG data

(17) Beaumont JJ, Leveton J, Knox K, Bloom T et al. Lung cancer mortality in workers exposed to sulphuric acid mist and other acid mists. J. N. C. I., 79, 911, 1987.

(18) Belding D.L. (1927) Trans. Amer. Fish. Soc. 57, 100-119

(19) Bell H.L. (1970) Effects of pH on the life cycle of the midge Tanytarsus dissimilis Can. Ent. 102, 636-639.

(20) Birnbaum et al., (1983). The pathogenesis of synergistic lung damage in mice by an environmental irritant (H2SO4) and particulate antigen. Toxicology 28, 261-269.

(21) Block T, Mantanoski G, Seltser R and Mitchell T. Cancer morbidity and mortality in phosphate workers. Cancer Res., 48, 7298, 1988.

(22) Boulet, Chest 94, 476-481 (1988).

(23) Bretherick (1979) Handbook of Reactive Chemical Hazards,Butterworths, London

(24) Brown L, Mason T, Pickle L, Stewart P et al. Occupational risk factors for laryngeal cancer on the Texas Gulf coast. Cancer Res., 48, 1969, 1988.

(25) Cavender et al., (1977). Effects in rats and guinea pigs of short-term exposures to sulfuric acid mist, ozone, and their conmbination. J. Toxicol. Environ. Health. 3, 521-533.

(26) Cavender et al., (1978). Effects in rats and guinea pigs of six-month exposures to sulfuric acid mist, ozone, and their combination. J. Toxicol. Environ. Health 4, 845-852.

(27) Chaney et al., Arch. Environ. Health 35, 211-215 (1980).

(28) Checkoway H, Matthew R, Hickey J, Shy C et al. Mortalijty among workers in the Florida phosphate industry (I). Industry wide cause-specific patterns. J. Occup. Med., 27, 885, 1985.

(29) Checkoway H, Matthew R, Hickey J, Shy C et al. Mortalijty among workers in the Florida phosphate industry (II). Cause-specific mortality relationships with work areas and exposures. J. Occup. Med., 27, 893, 1985.

(30) Chen and Schlesinger, (1983). Response of the bronchial mucociliary clearance system in rabbits to inhaled sulfite and sulfuric acid aerosols. Toxicol. Appl. Pharmacol., 71, 123-131.

(31) Chen et al., (1992). Effects of fine and ultrafine sulfuric acid aerosols in guinea pigs: alterations in alveolar macrophage function and intracellular pH. Toxicol. Appl. Pharmacol., 113, 109-117.

(32) Chen et al., (1995). Alteration of pulmonary macrophage intracellular pH following inhalation exposure to sulfuric acid/ozone mixtures. Exp. Lung Res. 21, 113-128.

(33) Cipollaro M. et al., (1986). Sublethal pH decrease may cause genetic damage to eukaryotic cell: a study on sea urchins and Salmonella typhimurium. Terat. Carc. and Mutagen, 6, 275 - 287.

(34) Cocco P, Ward M, Dosemeci M. Occupational risk factors for cancer of the gastric cardia. J. Occup. Environ. Med. 40, 855 - 861, 1998.

(35) Cockrell et al. (1976), Am. Rev. Respir. Dis. 113, 91

(36) Cockrell et al., (1977). Correlation of light and electron microscopic pulmonary lesions in guinea pigs exposed to sulfuric acid mist. Lab. Invest. 36, 334 (abstract).

(37) Cockrell et al., (1978) . Respiratory tract lesion in guinea pigs exposed to sulfuric acid mist. J. Toxicol. Environ.Health, 4, 835-844.

(38) Cockrell et al., Am. Rev. Respir. Dis. 113, 91 (1976).

(39) Coggon D, Pannett B, Wield G. Upper aerodigestive cancer in battery manufacturers and steel workers exposed to mineral acid mists. Occupational and Environmental Medicine, 1996, 53, 445 - 449.

(40) Cookfair D, Wende K, Michalek A and Vena J. A case-control stiudy of laryngeal cancer among workers exposed to sulfuric acid (abstract). Am. J. Epidemiol., 122, S21, 1985.

(41) Cooper WC and Gaffey WR. Mortality of lead workers. J. Occup. Med., 17, 100, 1975.

(42) Cooper WC, Wong O and Kheifets L., Mortality among workers at lead battery plants and lead producing plants, 1947 - 1980. Scand. J. Work. Environ. Health, 11, 331, 1985.

(43) Craig G.R. and W.F. Baski (1977). The effects of depressed pH on flagfish reproduction, growth and survival. Water Research, 11, 621-626.

(44) CRC Handbook of chemistry and Physics, 71th Ed., 1990-1991, CRC Press Inc.

(45) Dahl et al., (1983). Clearance of sulfuric acid-introduced 35S from the respiratory tracts of rats, guinea pigs and dogs following inhalation or instillation. Fundam. Appl.Toxicol. 3, 293-297.

(46) Davis P. and G.W. Ozburn (1969). The pH tolerance of Daphnia pulex (Leydig, emend., Richard). Can. J. Zool., 47, 1173-1175.

(47) Demerec M. et al., (1951). A Survey of chemicals for mutagenic action on E. coli. The Amer. Naturalist, 85, 119 - 136.

(48) Denzer (1961), Merkblatt uber die Schaedigung der Fischerei durch Abwaesser, Landesanstalt fuer Fischerei NW.

(49) Elgaard E.G. and J.Y. Gilmore III (1984) J. Fish. Biol. 25 (2), 133-138

(50) Ellis (1937), Bulletin of the Bureau of Fisheries 48, 365-437

(51) Ellis M.M. (1937), Bulletin of the Bureau of Fisheries 48, 365-437

(52) Englander V, Sjoberb A, Hagmar L, Attewell R et al. Mortality and cancer morbidity in workers exposed to sulphur dioxide in a sulphuric acid plant. Int. Arch. Occup. Env. Health, 61, 157, 1988.

(53) Enterline P. Importance of sequential exposure in the production of epichlorhydrin and isopropanol. Ann. NY Acad. Sci., 381, 344, 1982.

(54) Experimental pathology Laboratories, Inc. (1978) : 2-year inhalation - Guinea pigs, EPL 119-009, Pathology Report. Project DB-009, revised in 1979.

(55) Experimental pathology Laboratories, Inc. (1978) : 2-year inhalation - Rats, EPL 119-009, Pathology Report. Project DB-009.

(56) Fairchild et al., (1975). Sulfuric acid and streptococci clearance from respiratory tracts of mice. Arc. Environ. Health, 30, 538-545.

(57) Fairchild et al., (1975). Sulfuric acid effect on the deposition of radioactive aerosol in the respiratory tract of guinea pigs. Am. Ind. Hyg. Assoc. J., pp.: 584-594.

(58) Findlay D.L. and S.E.M. Kasian (1986). Phytoplankton community responses to acidification of Lake 223, experimental lakes area, Northwestern Ontario Water, Air and Soil Pollution, 30, 719-726.

(59) Forastiere F, Valesini S, Salimei E, Magliola E et al. Respiratory cancer among soap production workers. Scand. J. Work. Environ. Health, 13, 258, 1987.

(60) France R.L. (1987). Reproductive impairment of the crayfsh Orconectes virilis in response to acidification of lake 223. Can. J. Fish. Aquat. Sci., 44, 97-106

(61) Fujimaki et al., (1992). Enhanced histamine release from lung mast cells of guinea pigs exposed to sulfuric acid aerosols. Environ. Res., 58 (1), 117-123.

(62) Fujisawa et al., Arerugi 35, 137-144 (1986) zitiert in der Datenbank TOXLINE.

(63) Gearhart and Schlesinger (1988). Response of the tracheobronchial mucociliary clearance system to repeated irritant exposure: effect of sulfuric acid mist on function and structure. Exp. Lung Res. 14, 587-605.

(64) Gearhart and schlesinger (1989). Sulfuric acid-induced changes in the physiology and structure of the tracheobronchial airways. Environ. Health Pers. 79, 127-137

(65) Gearhart and Schlesinger. (1986). Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7, 681-689.

(66) Gomez et al., (1979). The effects on inhaled sulfuric acid aerosols on alveolar macrophage phagocytosis. Toxicol. Appl. Pharmacol. 48, A67 Abstract n¿134.

(67) Graham J.A., (1989). Review, discussion, and summary: toxicology. Environ. Health Perspect., 79, 191-194.

(68) Griffith et al. (1980) Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. Toxicology and Applied Pharmacology, 55, 501-513.

(69) Grose et al., (1978) The effect of ozone and sulfuric acid on ciliary activity of syrian hamsters. Pharmacologist 20, 211 (Abstract).

(70) Grose et al., (1982) Pulmonary host defense responses to inhalation of sulfuric acid and ozone. J. Toxicol. Environ. Health, 10, 351-362.

(71) Hagmar L, Bellander T, Anderson C, Linden K et al. Cancer morbidity in nitrate fertilizer workers. Int. Arch. Occup. Environ. Health, 63, 63, 1991.

(72) Hah et al., J. Cathol. Med. Coll. 41, 69-76 (1988) zitiert in der Datenbank TOXALL.

(73) Hermann (1959) Ind. Eng. Chem. 51 (4) 84A-87A

(74) Hext P. et al., (in preparation). Sulphuric acid: 28 day inhalation study in the rat. Zeneca Report No CTL/P/6278.

(75) Hoechst AG (1985) Unveroffentl. Unters. (Ber.-Nr. 85.0450)

(76) Hoechst AG (1985) Unveroffentl. Unters. (Ber.-Nr. 85.0487

(77) Hoechst AG (1985) Unveroffentl. Unters. (Ber.-Nr. 85.0525)

(78) Hoechst AG (1985) Unveroffentl. Unters. (Ber.-Nr. 86.1283)

(79) Hoechst AG (1985): Unveroffentl. Unters. (Ber.-Nr 85.0427)

(80) Hoechst AG (1985): Unveroffentl. Unters. (Ber.-Nr 85.0449)

(81) Hoechst AG data

(82) Hoffman and Campbell (1977) Embryotoxicity of irradiated and nonirradiated catalytic converter-treated automotive exhaust. J. Toxicol. Environ. Health 3, 705-712.

(83) Horton et al.Biological services division, Hoboken, USA, Report N DOT/MTB/ DHMO-76/2 (1976).

(84) HSDB, Hazardous Substances Data Bank, No. 1811 (28/04/1992)

(85) Hu, Diss. Abs. Int. 44, 2107-B (1984).

(86) Hurley G.V. and T.P. Foyle (1989). Differences in acid tolerance during the early life stages of three strains of Brook Trout, Salvelinus fontinalis. Water air soil pollut. 46, 387-398.

(87) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans - Occupational Exposures to mists and Vapours from strong Inorganic Acids; and Other industrial Chemicals .(1992), Vol 54, p41.

(88) IARC, IARC Monographs on the Evaluation of the Carcinogenic. Risk of Chemicals to Humans, 54, 41, 1992, Sulphuric acid and other strong inorganic acids, occupational exposures to mists and vapours from.

(89) Ichinose and Sagai (1992). Combined exposure to NO2, O3 and H2SO4-aerosol and lung tumor formation in rats. Toxicology. 74, 173-184.

(90) Iguchi et al. (1986), Arerugi 35, 402-408 ; citated in Toxline databank

(91) INRS (1988) Fiche Toxicolologique No. 30 (Acide sulfurique), Cahiers de notes documentaires 130, 167-171

(92) IRCHA et MinistÞre de l'Environnement et du Cadre de Vie, Les produits chimiques dans l'environnement (1981)

(93) Izmerov NF et al. (1982). Toxicometric Parameters of Industrial Toxic Chemicals. LIP Moscow, p107.

(94) Jacobs G. A. and Martens M. A. (1989) An objective method for the evaluation of eye irritation in vivo. Fd Chem. Toxic. 27(4), 255-258.

(95) Jacobs Guido A. (1992) OECD eye irritation tests on two strong acids. J. Am. Coll. Toxicol., 11 (6) 734

(96) Jelenko, Z>M. Surg. 40, 97-104 (1974) zitiert in U.S. Department.

(97) John et al. (1979) Teratology 19, 32A

(98) Kimmel et al., (1997). Influence of Acid aerosol droplet size on structural changes in the rat lung caused by acute exposure to sulfuric acid and ozone. Toxicol. Appl. Pharmacol. 144, 348-355.

(99) KIRK-OTHMER (1978-1984), Encyclopedia of Chemical Technology, 3rd Ed., 22, 190-232, J Wiley and Sons

(100) Kleinman et al., (1989) Health effects of acid aerosols formed by atmospheric mixtures. Environ. Health Perspect. 79, 137-145.

(101) Kobayashi and Shinozaki (1993). Effects of exposure to sulfuric acid-aerosol on airway responsiveness in guinea pigs: concentration and time dependency. J. Toxicol. Environ. Health, 39 (2), 261-272.

(102) Kristensen P (1993). Inorganic acid aerosols. Arbete och Halsa, 1, 7-54.

(103) Kulle et al., Am. Rev; Respir. Dis. 126, 996-1000 (1982).

(104) Kulle et al., National Technical Information Service, Bericht Nr. PB 2-255126 (1982).

(105) Laskin S. and Sellakumar A. (1978) Comparison of pulmonary carcinogenicity of know carcinogens with and without added H2SO4 mists, airborne respirable particles, and gases. Final

Report of Progress to the Environmental Protection Agency, Project n¿ 68-02-1750.

(106) Last and Pinkerton (1997). Chronic exposure of rats to ozone and sulfuric acid aerosol: biochemical and structural responses. Toxicology 116, 133-146.

(107) Last et al. (1978) A new model for health effects of air pollutants: evidence for synergistic effects of mixture of ozone and sulfuric acid aerosols on rat lungs. J Lab. Clin. Med. 91, 328-339

(108) Leikauf et al., Am. Ind. Hyg. Assoc. J. 45, 285-292 (1984?.

(109) Lewis (1991) Hazardous Chemicals Desk Reference, 2nd Ed., Van Nostrand, Reinhold

(110) Lewis et al., (1973). Toxicity of long-term exposure to oxides of sulfur. Arch. Environ. Health; 26, 16-21.

(111) Lewkowski et al. (1979). Effects of chronic exposure of rats to automobile exhaust, H2SO4, SO2, AL2(SO4)3 and CO. Assessing Toxic Eff. Environ. Pollut. Chapter 11, pp: 187-217.

(112) Linn et al., J. Air Pollut. Control Assoc. 36, 1323-1328 (1986).

(113) Lippmann and Schlesinger (1984). Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. J. Toxicol. Environ. Health, 13(2-3), 441-469.

(114) Logue JN, Koontz MD and Hatwick MAW. A historical prospective mortality study of workers in copper and zinc refineries. J. Occup. Med., 24, 398, 1982.

(115) Lynch J, Hanis N, Bird M, Murray K et al. An association of upper respiratory cancer and exposure to diethyl sulfate. J. Occup. Med., 21, 333, 1979.

(116) Malcolm D and Barnett H. A mortality study of lead workers. 1926 - 1976. Br. J. Ind. Med., 39, 404, 1982.

(117) Malcom et al., Brit. J. Indust. Med. 18, 63-69 (1961)

(118) Malley D.F. and P.S.S. Chang (1986). Increase in the abundance of Cladocera at pH 5.1 in experimentally-acidified lake 223, Experimental Lakes Area, Ontario. Water, Air, Soil Pollut., 30, 629-638.

(119) Mazumdar S, Lerer T and Redmond C. Long term mortality study of steel workers. IX. Mortality patterns among sheet and tin mill workers. J Occup. Med., 17, 751, 1975.

(120) McKee et al. (1963), Water Quality Criteria. The Resources Agency of California, State Water Quality Control Board, Publ. No. 3-A, 279, USA.

(121) McMahon et al. (1983), Freshwater crayfish Pap. Int. Symp. 5th 71-85

(122) Menendez R. (1976). Chronic effects of reduced pH on Brook Trout (Salvelinus fontinalis). J. Fish. Res. Boar. Can., 33, 118-123.

(123) Merck Index (1989) 11th Ed.

(124) Mills K.H., S.M. Chalanchuk, L.C. Mohr and I.J. Davies (1987). Responses of Fish populations in Lake 223 to 8 years of experimental acidification. Can. J. Fish. Aquat. Sci., 44, 114-125.

(125) Moeschlin, Klinik und Therapie der Vergiftungen, Thieme-verlag, S 172-174 (1956).

(126) Morita T. et al., (1989). Effects of pH in the in vitro chromosomal aberration test." Mut Res, 225, 55 - 60.

(127) Mount D.I. (1973). Chronic effect of low pH on fathead minnow survival, growth and reproduction. Water Res., 7, 987-993

(128) Murphy et al. (1982) Ocular irritancy responses to various pHs of acids and bases Toxicology

23, 281-291.

(129) Murray FJ. (1979). Embryotoxicity of inhaled sulfuric acid aerosol in mice and rabbits. J. Environ. Sci. Health C13(3), 251-266

(130) Musk et al., Br. J. Ind. Med. 45, 381-386 (1988)

(131) National Research Council Canada (1977), Sulphur and its inorganic derivates, 266-267 NRCC No. 15015

(132) Newhouse et al., Arch. Environ. Health 33? 24-32 (1978).

(133) Niederlehner B.R. and J. Cairns Jr. (1990). Effects of increasing acidity on aquatic protozoan communities. Water, Air and Soil Pollut., 52, 183-196.

(134) Nixon et al. (1990) Evaluation of modified methods for determining skin irritation. Regul. Toxicol. Pharmacol. 12(2), 127-126.

(135) Nixon et al., (1975) Interspecies comparisons of skin irritancy. Toxicol. Appl. Pharmacol. 31, 481-490.

(136) Occupational Health Guideline for Sulfuric Acid (1978), US Department of Health and Human Services.

(137) Oehme et al., (1996). A review of the toxicology of air pollutants: toxicology of chemical mixtures. Vet. Human. Toxicol., 38 (5), 371-377.

(138) Osebold et al., (1980). Studies on the enhancement of allergic lung sensitization by inhalation of ozone and sulfuric acid aerosol. J. Environ. Pathol. Toxicol., 3, 221-234.

(139) Parent S. and R.D. Chhetham (1980). Effects of acid precipitation on Daphnia magna. Bull. Environm. Contam. Toxicol., 25, 298-304.

(140) Pierson W.R. (1987) Environ. Sci. Technol. 21(7), 679-691, cited in HSDB.

(141) Portman et al. (1971) Ministry of Agriculture, Fisheries and Food, Shellfish Information Leaflet No. 22 (142) Pough F.H. and R.E. Wilson (1977) Acid precipitation and reproductive success of Ambystoma salamanders. Water, Air and Soil Pollut., 7, 307-316.

(143) Qu et al., (1993). Alteration of pulmonary macrophage intracellular pH regulation by sulfuric acid aerosol exposures. Toxicol. Appl. Pharmacol., 121,138-143.

(144) Research Triangle Inst. (1998) Toxicological profile for sulfur trioxide and sulfuric acid. U.S. Department of Commerce, National Technical information Service.

(145) Rhodia data

(146) Rhone-Poulenc (1993) Safety Data Sheet (23/03/93). Internal unpublished results.

(147) Roth (1982), Wassergefaehrdende Stoffe

(148) Roth et al., (1998). Ventilatory responses in awake guinea pigs exposed to acid aerosols. J. Toxicol. Environ. Health, 54, 261-283.

(149) RRhodia data

(150) Runkle BK. and Hahn FF., (1976). The toxicity of H2SO4 aerosols to CD-1 mice and Fischer-344 rats. Ann. Rep. Inh. Toxi. Res. Inst. pp.: 435-439.

(151) Sathiakumar N, Delzell E, Amoeteng-Adjepong Y, Larson R and Cole P. Epidemiological evidence on the relationship between mists containing sulphuric acid and respiratory tract cancer. Critical Reviews in Toxicology, 27(3) 233-251 (1997).

(152) Sax et al. (1988) Dangerous Properties of Industrial Materials, 7th Ed., Van Nostrand,

Reinhold

(153) Schlesinger (1987). Functional assessment of rabbit alveolar macrophages following intermittent inhalation exposures to sulfuric acid mist. Fundam. Appl. Toxicol. 8, 328-334

(154) Schlesinger and Gearhart (1986). Early alveolar clearance in rabbits intermittently exposed to sulfuric acid mist. J. Toxicol. Environ. Health 17, 213-220.

(155) Schlesinger and Gearhart (1987). Intermittent exposures to mixed atmospheres of nitrogen dioxide and sulfuric acid: effect on particle clearance from the respiratory region of rabbit lungs Toxicology 44, 309-319

(156) Schlesinger et al. (1983) Physiological and histological alterations in the bronchial mucociliary clearance system of rabbits following intermittent oral or nasal inhalation of sulfuric acid mist. J. Toxicol. Environ. Health 12, 441-465.

(157) Schlesinger et al., (1978). Effects of short-term exposures to sulfuric acid and ammonium sulfate aerosols upon bronchial airway function in the donkey. Am. Ind. Hyg. Assoc. J. 39, 275-286.

(158) Schlesinger et al., (1979). Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. J. Environ. Pathol. Toxicol., 2, 1351-1367.

(159) Schlesinger et al., (1984). Exposure-response relationship of bronchial mucociliary clearance in rabbits following acute inhalations of sulfuric acid mist. Toxicol. Lett., 22, 249-254.

(160) Schlesinger et al., (1987). Effect of repeated exposures to nitrogen dioxide and sulfuric acid mist alone or in combination on mucociliary clearance from the lungs of rabbits. Environ. Res. 44, 294-301.

(161) Schlesinger et al., (1990) Comparative potency of inhaled acid sulfates : speciation and the role of hydrogen ion. Environ. Res., 52, 210-224.

(162) Schlesinger et al., (1990). Modulation of pulmonary eicosanoid metabolism following exposure to sulfuric acid. Fundam. Appl. Toxicol., 15, 151-162.

(163) Schlesinger et al., (1992). Assessement of toxicologic interactions resulting from acute inhalation exposure to sulfuric acid and ozone mixtures. Toxicol. Appl. Pharmacol., 115, 183-190.

(164) Schlesinger et al., (1992). Interspecies differences in the phagocytic activity of pulmonary macrophages subjected to acid challenge. Fundam. Appl. Toxicol. 19, 584-589.

(165) Schlesinger et al., (1992). Long-term intermittent exposure to sulfuric acid aerosol, ozone, and their combination: altrations in tracheobronchial mucociliary clearance and epithelial secretory cell. Exp. Lung. Res., 18, 505-534.

(166) Schlesinger RB (1989) Factors affecting the response of lung clearance systems to acid aerosols: role of exposure concentration, exposure time, and relative acidity. Environ. Health Perpect., 79, 121-126 (167) Schlesinger RB (1990). Exposure-reponse pattern for sulfuric acid-induced effects on particle clearance from the respiratory region of rabbits lungs. Inhal. Toxicol., 2, 21-27.

(168) Schwartz et al. (1979). Pulmonary responses to sulfuric acid aerosols. Asses. Toxicol. Eff. Environ. Pollut., Chapter 10, pp: 173-186

(169) Serin I.F. Review and Evaluation of Recent Literature Relevant to Occupational Exposure to Sulphuric Acid. US National Institute of Environmental Health and Safety, PB87-213898, 1981

(170) Shinshima K., Ishikawa Y. (1992) Denryoku Chuo Kenkyusho Hokoku 1-25

(171) Silbaugh et al., (1981). Effects of sulfuric acid aerosols on pulmonary functions of guinea pigs. J. Toxicol. Environ. Health, 7, 339-352.

(172) Smyth et al., (1969) Range-finding toxicity data : list VII. Am. Ind. Hyg. Ass. J. 30, 470 - 476.

(173) Soskolne C, Jhangri G, Siemiatycki J, Lakhani R et al. Occupational exposure to sulphuric acid associated with laryngeal cancer, Southern Ontario, Canada. Scand. J. Work Environ Health, 18, 225, 1992.

(174) Soskolne C, Zeighami E, Hanis N, Kupper L et al. Laryngeal cancer and occupational exposure to sulfuric acid. Am. J. Epidemiol., 120, 358, 1984.

(175) Spector et al., Environ. Health Pers. 79, 167-172 (1989).

(176) Stayner L, Meinhardt T, Lemen R, Bayliss D et al. A retrospective cohort mortality study of a phosphate fertilizer production facility. Arch. Environ. Health, 40, 133, 1985.

(177) Steenland K and Beaumont J. Further follow-up and adjustment for smoking in a study of lung cancer and acid mists. Am. J. Ind. Med., 16, 347, 1989.

(178) Steenland K, Schnorr T, Beaumont J, Halperin W et al. Incidence of laryngeal cancer and exposure to acid mists. Br. J. Ind. Med., 45, 766, 1988.

(179) Swenberg and Beauchamp (1997) A review of the chronic toxicity, carcinogenicity and possible mechanisms of action of inorganic acid mists in animals. Crit. Rev. Toxicol. 27(3), 253-259.

(180) Tam W.H. and P.D. Payson (1986). Effects of chronic exposure to sublethal pH on growth, egg production and ovulation in Brook Trout, Salvelinus fontinalis. Can. J. Fish. Aquat. Sci., 43, 275-280.

(181) Teta M, Perlman G, Ott M. Mortality study of ethanol and isopropanol production workers at two facilities. Scand. J. Work Environ. Health, 18, 90, 1992.

(182) Theiss A, Oettel H and Uhl C. Occupational lung cancers. Long-term observations at BASF, Ludwigshafen am Rhein, 2nd Communication (German). Ab. Arbeitsmed Arbeitsschutz, 19, 97, 1969.

(183) Thiess, A. M., (1969); Sichere Arbeit 3/69, 11-18

(184) Thomas et al., (1958). Prolonged exposure of guinea pigs to sulfuric acid aerosol. Arch. Ind. Health 17, 70-80.

(185) Treon et al., (1950) Toxicity of sulfuric acid mist. Arch. Indust. Hyg. Occup. Med. 2, 716-734.

(186) Turner and Fairhurst (1992) Toxicology of substances in relation to major hazards - Sulphuric acid mist. Health and Safety Executive, published by HMSO Books, London, pp 1-21.

(187) Uleckiene and Griciute (1997) Carcinogenicity of sulfuric acid in rats and mice. Pathol. Oncol. Res. 3, 38-43 (1997).

(188) Utell et al., Aerosols SCi, Med. Technol. 14, 202-205 (1983).

(189) Utell et al., Am. Rev. Resp. Disp. 128, 444-450 (1983).

(190) Vernot et al. (1977). Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol., 42 (2), 417-423.

(191) Wakisaka et al., (1988). Combined effects of experimental exposures to sulfur dioxide and sulfuric acid aerosol on the respiratory response in mice. Acta Med. Univ. Kagoshima 30, 1-9.

(192) Walcek C.J., Chang T.S. (1987) Atmos. Environ. 21(5), 1107-1114, cited in HSDB.

(193) Wallen et al. (1957), Sewage and Industrial Wastes 29 (6) 695-711

(194) Warren and Last (1987). Synergistic interaction of ozone and respirable aerosols on rat lungs. Toxicol. Appl. Pharmacol. 88, 203-216.

(195) Weast R., Handbook of Chemistry and physics

(196) Weil C, Smyth H and Nale T. Quest for a suspected industrial carcinogen. Arch Ind. Hyg., 5, 535, 1952.

(197) Weiss (1980) Hazardous Chemicals Data Book, Noyes Data Corp., Park Ridge.

(198) Wolf et al., (1986). Effects of sulfuric acid mist inhalation on mucous clearance and on airway fluids of rats and guinea pigs. J. Toxicol. Environ. Health, 17(1), 129-142.

(199) Wolff R. K. (1986). Effects of airborne pollutants on mucociliary clearance. Environ. Health Perspect., 66, 223-237.

(200) Wolff RK et al., (1979) Toxicity of 0.4- and 0.8-µm sulfuric acid aerosols in the guinea pigs. J. Toxicol. Environ. Health 5, 1037-1047.

(201) Zelikoff and Schlesinger (1992). Modulation of pulmonary immune defense mechanisms by sulfuric acid: effects on macrophage-derived tumor necrosis factor and superoxide. Toxicology, 76, 271-281.

(202) Zelikoff et al., (1994). Immunotoxicity of sulfuric acid aerosol: effects on pulmonary macrophage effector and functional activities critical for maintaining host resistance against infectious diseases. Toxicology, 92, 269-286.

(203) Zelikoff et al., (1997). Effects of inhaled sulfuric acid aerosols on pulmonary immunocompetence: a comparative study in humans and animals. Inhal. Toxicol., 9, 731-752.

(204) Zmela B, Day N, Swiatnicka J and Banasik R. Larynx cancer risk factors. Neoplasma, 34, 223, 1987.

ANNEX 1

ACGIH TLV-STEL	3 MG/M3	DTLVS* TLV/BEI,1999
ACGIH TLV-TWA	1 MG/M3	DTLVS* TLV/BEI,1999
OSHA PEL (GEN INDU):8H TWA	1 MG/M3	CFRGBR 29,1910.1000,1994
OSHA PEL (CONSTRUC):8H TWA	1 MG/M3	CFRGBR 29,1926.55,1994
OSHA PEL (SHIPYARD):8H TWA	1 MG/M3	CFRGBR 29,1915.1000,1993
OSHA PEL (FED CONT):8H TWA	1 MG/M3	CFRGBR 41,50-204.50,1994
OEL-ARAB REPUBLIC OF EGYPT: TWA	1 MG/M3,	JAN1993
OEL-AUSTRALIA: TWA	1 MG/M3,	JAN1993
OEL-AUSTRIA: MAK	1 MG/M3,	JAN1999
OEL-BELGIUM: TWA	1 MG/M3,	
STEL	3 MG/M3,	JAN1993
OEL-DENMARK: TWA	1 MG/M3,	JAN1999
OEL-FINLAND: TWA	1 MG/M3,	
STEL	3 MG/M3, SKIN,	JAN1999
OEL-FRANCE: VME	1 MG/M3,	
VLE	3 MG/M3,	JAN1999
OEL-GERMANY: MAK	1 MG/M3,	JAN1999
OEL-HUNGARY: STEL	1 MG/M3,	JAN1993
OEL-JAPAN: OEL	1 MG/M3,	JAN1999
OEL-THE NETHERLANDS: MAC-TGG	1 MG/M3,	JAN1999
OEL-NORWAY: TWA	1 MG/M3,	JAN1999
OEL-POLAND: MAC(TWA)	1 MG/M3,	
MAC(STEL)	3 MG/M3,	JAN1999
OEL-RUSSIA: STEL	1 MG/M3, SKIN,	JAN1993
OEL-SWEDEN: NGV	1 MG/M3,	
TKV	3 MG/M3,	JAN1999
OEL-SWITZERLAND: MAK-W	1 MG/M3, KZG-W 2 MG/M3,	JAN1999
OEL-THAILAND: TWA	1 MG/M3,	JAN1993
OEL-TURKEY: TWA	1 MG/M3,	JAN1993
OEL-UNITED KINGDOM: TWA	1 MG/M3,	1996

OEL IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN, KOREA CHECK ACGIH TLV;
OEL IN NEW ZEALAND, SINGAPORE, VIETNAM **CHECK ACGIH TLV**