ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

SULFURIC ACID
SULFUR TRIOXIDE
OLEUM

(CAS Reg. No. 7664-93-9)
(CAS Reg. No. 7446-11-9)
(CAS Reg. No. 8014-95-7)

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommittee for AEGLS

2009

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicological and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels X AEGL-1, AEGL-2 and AEGL-3 X are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Sulfuric acid is one of the most produced chemicals in the world. It is a strong inorganic acid that is mainly used in the production of phosphate fertilizers. Due to its hygroscopic properties ambient sulfuric acid will be present as aerosols or mists.

A large number of controlled human volunteer studies with sulfuric acid is available. These studies were conducted in healthy and asthmatic subjects. The exposure concentrations in the studies ranged from 0.01 to 39.4 µg/m^3 with varying particle sizes, and different methods of exposure were used. The exposure durations ranged from 5 minutes to 6.5 hours.

Case reports of accidental human exposure were not useful for derivation of AEGL values due to the lack of adequate exposure estimates. There are no lethality data available in humans.

Endpoints that were investigated in experimental studies in animals included lethality, irritation, lung function, pathology of the respiratory tract, developmental toxicity, genotoxicity, and carcinogenicity.

In essence, the health effects of sulfuric acid are related to the direct irritation of the respiratory tract.

Time scaling for AEGL-3 was based on probit-analysis of the animal lethality data. No time scaling was applied to the other AEGLs because of the direct irritating properties of sulfuric acid.

The AEGL-1 values are based on respiratory irritation observed in many human volunteer studies at concentrations higher than 0.2 mg/m^3. Horvath *et al*. (1982) observed some irritation in some subjects at 0.23 mg/m^3 for 120 minutes, but Linn *et al.* (1994) detected no symptoms at all in 15 healthy and 30 asthmatic exercising subjects at concentrations of 0.28-0.39 mg/m^3 for 2x390 minutes with intermittent exposure on subsequent days. Considering the database of more than 600 subjects tested for symptoms, the level of 0.2 mg/m^3 is chosen as the point of departure for AEGL-1. No uncertainty factor is needed because the large database included exercising asthmatics, representing a susceptible subpopulation.

The AEGL-2 values are based on the absence of severe or disabling acute effects in the large number of experimental human volunteer studies as well as in the available occupational studies. The study with the highest concentrations of sulfuric acid without significant respiratory effects was the occupational study of El-Sadik *et al.* (1972) in which workers were exposed daily to levels of 26-35 mg/m^3. The level of 26 mg/m^3 for 8 hour was therefore taken as point of departure for AEGL-2. An uncertainty factor of 3 was used to account for human variation in susceptibility.

The AEGL-3 values are based on animal data, in absence of human lethality data. The study of Runckle and Hahn (1976) provides lethality data in mice with varying exposure durations and concentrations, which allows calculating a concentration-time-response relationship for this chemical. A probit analysis of these data allowed the prediction of the LC_{01} for each of the AEGL time points. No interspecies uncertainty factor was used because all data indicated that mice were more susceptible than rats, monkeys, and humans. Nevertheless, an intraspecies uncertainty factor of 3 was applied to account for human variation in susceptibility.

The calculated values are listed in the tables below.

Summary of AEGL Values for Sulfuric acid[1]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	Respiratory irritation in humans (Horvath *et al*. 1982, and many other studies)
AEGL–2 (Disabling)	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	Absence of severe or disabling effects (El-Sadik *et al*. 1972)
AEGL–3 (Lethal)	270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3	Lethality in mice (Runckle and Hahn 1976)

[1] For accidents with sulfur trioxide or oleum, the actual ambient exposure is to sulfuric acid mist. Therefore the sulfuric acid AEGLs should apply in such situations.

References

El-Sadik, Y.M., H.A. Osman, and R.M. El-Gazzar. 1972. Exposure to sulfuric acid in manufacture of storage batteries. JOM 14(3): 224-226

Horvath, S.M., L.J. Folinsbee, and J.F. Bedi. 1982. Effects of large (0.9 micrometers) sulfuric acid aerosols on human pulmonary function. Environ Res. 28: 123-130

Linn, W.S., D.A. Shamoo, K.R. Anderson, R.-C. Peng, E.L. Avol, and J.D. Hackney. 1994. Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. Am. J. Respir. Crit. Care Med. 150: 431-440

Runckle, B.K., and F.F. Hahn. 1976. The toxicity of H_2SO_4 aerosols to CD-1 mice and Fisher-344 rats. Ann. Rep. Inhal. Toxicol. Res. Inst. 435-439

1. INTRODUCTION

The acute health effects of sulfuric acid (H_2SO_4), sulfur trioxide (SO_3), and oleum are discussed in one TSD because sulfur trioxide and oleum will eventually be converted into sulfuric acid. Oleum (fuming sulfuric acid) is a mixture of sulfuric acid with up to 80% free sulfur trioxide.

When sulfur trioxide is released in the air, it will react with atmospheric water yielding sulfuric acid. This reaction is ultrafast when there is an excess of water, because complexes with clusters of more than 12 water molecules would be converted to sulfuric acid with nearly no energy barrier. However, the water content of our atmosphere precludes formation of such large clusters (Loerting and Liedl 2000). Kapias and Griffiths (1999), who studied the dispersion and thermodynamics of clouds generated from spills of SO_3 and oleum, confirmed that there is not usually enough atmospheric moisture in the air passing immediately above the pool for complete and rapid reaction to sulfuric acid mist. In early stage clouds, SO_3 vapor, H_2SO_4 vapor and H_2SO_4 aerosol will be present, and such clouds will behave as a dense gas. At some distance downwind, transition to passive dispersion behavior takes place and only sulfuric acid will be present in the cloud. This distance, although depending on several parameters like oleum content, relative humidity and wind speed, is typically within 50-100 m from the source (Kapias and Griffiths 1999).

Given the conversion of sulfur trioxide as described above, it can be expected that during incidents with SO_3 or oleum, people will most likely be exposed to sulfuric acid aerosols alone. If, at all, people would be exposed to SO_3, then the SO_3 will react with water when it comes into contact with moist surfaces of the respiratory tract or the skin, and sulfuric acid will be formed. Therefore, the adverse effects of sulfur trioxide and oleum are expected to be the same as those of sulfuric acid, and hence, the AEGLs derived for exposure to sulfuric acid, sulfur trioxide and oleum are based on the acute health effects of sulfuric acid. Consequently, only AEGL-values for sulfuric acid aerosols will be derived in this TSD.

Sulfuric acid is a strong acid that can be produced by two major processes: a chamber process and a contact process. Although the chamber process was predominant until the early 20^{th} century, nowadays the contact process is the primary method of production. The principle steps are 1) oxidation of sulfur to sulfur dioxide with dry air using (vanadium) catalysts, 2) cooling of the gases, 3) conversion or oxidation of the sulfur dioxide to sulfur trioxide, 4) cooling of the sulfur trioxide gas, and 5) absorption of the sulfur trioxide in water to produce sulfuric acid (ATSDR 1998).

The production of sulfuric acid in the USA increased over the years to 3.56×10^7 metric tons in 1995, thereby being the most produced chemical in the USA (ATSDR 1998). In 2002, the production increased to 1.70×10^8 metric tons (Suresh 2003). The production of phosphate fertilizer materials, especially wet-process phosphoric acid, is the major end-use market for sulfuric acid, accounting for nearly 60 percent of total world consumption. The balance is consumed in a wide variety of industrial and technical applications. The United States accounts for about 25 percent of the global sulfuric market, followed by Socialist Asia, which consumes about 17 percent. Africa, Western Europe and Russia are also large users, each accounting for about 10 percent of world consumption (Suresh 2003). Production data for sulfur trioxide are not available, but since it is a precursor in the primary manufacturing process of sulfuric acid, it will be present at the facilities where such production takes place. Oleum (fuming sulfuric acid is produced at contact process plants in special towers by adding sulfur trioxide to sulfuric acid.

1

Table 1. Chemical and Physical Properties for Sulfuric Acid		
Parameter	**Value**	**Reference**
Synonyms	Battery acid, Oil of vitriol	Merck 1989
Chemical formula	H_2SO_4	Merck 1989
Molecular weight	98.08	Merck 1989
CAS Reg. No.	7664-93-9	www.chemfinder.com
Physical state	oily liquid	Merck 1989
Color	Colorless	Merck 1989
Solubility in water	Soluble	www.chemfinder.com
Vapor pressure	1 mm Hg at 145.8 °C	Lide (ed) 1985
Vapor density (air = 1)	3.4	www.chemfinder.com
Liquid density (water = 1)	1.8	Lide (ed) 1985
Melting point	10.36 °C	Lide (ed) 1985
Boiling point	330 °C	Lide (ed) 1985
Odor	Odorless	Merck 1989
Flammability	Noflammable	ATSDR
Explosive	Yes	ATSDR
Conversion factors		

2

Table 2. Chemical and Physical Properties for Sulfur Trioxide		
Parameter	**Value**	**Reference**
Synonyms	Sulfuric anhydride, Sulfan	Merck 1989
Chemical formula	SO_3	Merck 1989
Molecular weight	80.0582	www.chemfinder.com
CAS Reg. No.	7446-11-9	www.chemfinder.com
Physical state	Gas, liquid or solid	ATSDR
Color	Silky fiber needle (α), Asbestos-like fiber (β)	ATSDR
Solubility in water	Decomposes	www.chemfinder.com
Vapor pressure	73 mm Hg at 25 °C for α form. 344 mm Hg at 25 °C for β form.	Lide (ed) 1985
Vapor density (air = 1)	no data	
Liquid density (water = 1)	1.9	www.chemfinder.com
Melting point	16.8 °C	www.chemfinder.com
Boiling point	44.8 °C	www.chemfinder.com
Odor	no data	
Flammability	Noflammable	ATSDR
Explosive	Combines with water with explosive violence	Merck 1989
Conversion factors		

3

Table 3. Chemical and Physical Properties for Oleum		
Parameter	**Value**	**Reference**
Synonyms	Sulfuric anhydride, Sulfan	Merck 1989
Chemical formula	SO_3	Merck 1989
Molecular weight	80.0582	www.chemfinder.com
CAS Reg. No.	7446-11-9	www.chemfinder.com
Physical state	Gas, liquid or solid	ATSDR
Color	Silky fiber needle (α), Asbestos-like fiber (β)	ATSDR
Solubility in water	Decomposes	www.chemfinder.com
Vapor pressure	73 mm Hg at 25 °C for α form. 344 mm Hg at 25 °C for β form.	Lide (ed) 1985
Vapor density (air = 1)	no data	
Liquid density (water = 1)	1.9	www.chemfinder.com
Melting point	16.8 °C	www.chemfinder.com
Boiling point	44.8 °C	www.chemfinder.com
Odor	no data	
Flammability	Noflammable	ATSDR
Explosive	Combines with water with explosive violence	Merck 1989
Conversion factors		

The odor threshold for sulfuric acid is 1 mg/m^3 (ATSDR 1998).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

In a prospective study into acute fatal poisonings in Trinidad, Daisly and Simmons (1999) reported one suicide where “battery acid” (sulfuric acid) was used. The victim had digestion of his gastrointestinal tract with dissolution of stomach and liver. The amount ingested and the pH of the solution was not reported.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Marked nonproductive cough, chest tightness, and dispnea was observed in a 45-years old woman immediately following a 45-minutes exposure to a cleaning compound containing sulfuric acid in an unventilated washroom. Three weeks later she had still persisting symptoms of daily cough and intermittent dispnea. Bronchodilators were still required two months later and bronchial responsiveness

to histamine was increased although spirometry was normal. Bronchoscopy revealed moderate inflammation of the mucosa of the large airways. Two years later the patient was asymptomatic and no respiratory changes were noted upon re-exposure to the same agent. Exposure concentrations were not estimated (Boulet 1988).

Accidental exposure of a 40-years male worker to liquid 35% oleum, and subsequently 8 minutes exposure to sulfuric acid mist and fumes from the action of (safety shower) water on oleum, caused severe burns on face and body, and respiratory difficulty requiring 10 days oxygen therapy. Eighteen months later the patient had disabling pulmonary fibrosis, residual bronchiectasis, and pulmonary emphysema. The exposure concentrations were not estimated (Goldman and Hill 1953).

Kikuchi (2001) described a sharp increase of the incidence of asthma, emphysema, bronchitis, and other respiratory ailments in an area in Japan with a huge complex of oil refineries and petrochemical and power plants. The author linked these increases to the high ambient sulfur trioxide concentrations, with an average of 130 $\mu g/m^3$. Ambient concentrations of sulfuric acid aerosols were not reported.

A 23-year old man who worked in a manhole where 95% sulfuric acid was being expelled from a pipe, inhaled sulfuric acid mist. He was unable to climb to safety due to respiratory distress and was exposed for 30 minutes before being rescued. Upon initial hospitalization he was diagnosed with adult respiratory distress syndrome. Later he developed a lung abscess that could be treated successfully, and pulmonary function tests were normal. The exposure concentration was not estimated (Knapp *et al.* 1991).

Nine people working next to a chemical plant suffered from an emission that was fog-like and layered out over the outdoor area. This emission lasted 2 hours. The authors state that the fog was sulfur trioxide but there was no mention of any measurement or exposure estimate. The patients experienced pleuretic chest pain, eye irritation, dizziness, light-headedness, cough, and acid taste in the mouth with nasal irritation. Four patients showed decreased FEV_1, which recovered in three of them. On follow-up patients still had burning sensations and pleuretic chest pain (Stueven *et al.* 1993).

2.2.2. Experimental Studies

A large number of controlled human volunteer studies with sulfuric acid is available. These studies were conducted in adult and senior healthy subjects, and in adolescent, adult, and senior asthmatics. The exposure concentrations in most of the studies ranged from 0.01 to 3.37 mg/m^3, and one study reported exposures of 20.8 and 39.4 mg/m^3. The studies were conducted with varying particle sizes, and exposures were given in environmental chambers or by using a mouthpiece, a facemask, a head dome, or a nasal mask. In a number of studies, the subjects gargled with a juice containing citric acid to deplete oral ammonia. Ammonia in exhaled air is capable of neutralizing sulfuric acid aerosols (see also 4.3.3).

The studies are presented in Table 4 on the next pages. More detailed descriptions of the key studies relevant for AEGL-development are given below the table.

1

2 **Table 4. Controlled human volunteer studies with sulfuric acid**

3

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
Healthy adult volunteers										
5 – 15	No	Males (number not given)	Particle size 1 (no further details)	Facemask	No	Odor, taste, irritation, lung function	0.35 – 5.0	• No irritation, odor or taste detected at 0.35 mg/m^3 • Detected from 1 mg/m^3 onwards • Objectionable at 5 mg/m^3 • All dose levels: RR ↑ (35%), IF and EF ↓ (20%), TV ↓	Total number of subjects, numbers per group, and concentrations are not clearly stated This study is considered not suitable for AEGL-development due to poor reporting.	Amdur *et al.* 1952b
60	Alternate 10 min	15 (M,F) (both concentrations, double-blind, 1 week apart)	MMAD 1.0 ± 2	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.98	No effects	In this study also asthmatic volunteers were tested (see below) RH 50% Subjects were exposed to both concentrations, double-blind, one week apart	Anderson *et al.* 1992
120	Alternate 15 min	6 (M)	MMAD 0.5 ± 3.0	Chamber	No	Lung function, symptoms (questionnaire)	0 0.1	No effects	In this study also asthmatic volunteers were tested (see below) RH 40% Subjects were exposed to both concentrations, single-blind, on separate days	Avol *et al.* 1979 [detailed description below the table]

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
60	3 periods of 10 min	22 (M,F)	VMD 10	Chamber	Yes, half of the subjects	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.65 1.10 2.19	Dose dependent (mainly lower) respiratory irritation at 0.65, 1.10, and 2.19 mg/m^3; observations indicated that irritation was noticeable upon entering the chamber at the higher acid concentrations. These symptoms were reversible within one hour after the end of exposure. No other effects NB no meaningful differences in response of subjects who did and did not gargle grapefruit juice, so results of these groups were combined	In this study also asthmatic volunteers were tested (see below) LWC 0.1 g/m^3 RH nearly 100% Subjects were exposed to all four concentrations, double-blind, at weekly intervals	Avol *et al*. 1988a
60	Alternate 10 min	21 (M,F)	MMAD 0.9 ± 2.5	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.36 1.12 1.58	Dose dependent coughing at 0.36, 1.12, and 1.58 mg/m^3 (despite its stat significance, the magnitude of change was only minimal ("barely perceptible") even at the highest dose); symptoms tended to persist for 24 h after exposure No other effects	In this study also asthmatic volunteers were tested (see below) RH 50% Subjects were exposed to all four concentrations, double-blind, at weekly intervals	Avol *et al*. 1988b
2 x 240 (1 day apart)	2x 15 min starting at t=30 and 90 min	37 (M)	MMD 0.5	Chamber	No	Biochemistry	0 0.1	No effects	RH 40% Generation of aerosols not described and unclear if actual exposure conc was measured A group of 17 subjects was exposed to clean air, and a group of 20 subjects was exposed to sulfuric acid aerosols	Chaney *et al*. 1980a

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
2 x 240 (1 day apart)	2x 15 min starting at t=30 and 90 min	35 (M)	MMD 0.5	Chamber	No	Lung function, biochemistry	0 0.1	No effects	RH 40% Generation of aerosols not described and unclear if actual exposure conc was measured A group of 17 subjects was exposed to clean air, and a group of 18 subjects was exposed to sulfuric acid aerosols	Chaney *et al*. 1980b
120	10 min of each half hour	12	MMAD 0.9 ± 1.9	Chamber	Yes	Airway mucins composition, symptoms (questionnaire)	Control 0 1.0	No effects on mucin composition. 3 to 4 subjects showed cough or throat irritation or detected odor upon H_2SO_4 exposure, whereas during NaCl exposures, one subject experienced cough, three complained of throat irritation and no odor was detected.	RH 40% There were 2 subgroups: one subgroup was exposed to clean air. The other subgroup was exposed to H_2SO_4 and NaCl aerosols (randomized double-blind, two weeks apart). The sizes of the subgroups were not specified.	Culp *et al*. 1995
120	Intermittent	8	MMAD 0.9 ± 2.1	Chamber	No	Lung function, BAL	Control 1.28	• No effects on lung function • % macrophages ↑, % lymphocytes ↓	Controls were exposed to NaCl aerosols. Generation of aerosols not described and unclear if actual exposure conc was measured. RH 40% All subjects received both exposure randomized with a two-week interval.	Frampton *et al*. 19?? (abstract only)
120	4x 10 min (each half-hour)	12 (M,F)	MMAD 0.9 ± 1.9	Chamber	Yes	Lung function, symptoms (questionnaire), BAL	Control 1.18	H_2SO_4 exposure: Odor/taste detection in 4/12 subjects; cough in 3/12 subjects; throat irritation in 4/12 subjects NaCl exposure: cough in 1/12 subjects; throat irritation in 3/12 subjects No other effects	Controls were exposed to NaCl aerosols. RH 40% All subjects received both exposures randomized, double-blind, 2 weeks apart.	Frampton *et al*. 1992

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
180	6 x 10 min (each half hour)	30 (M,F)	MMAD 0.64 ± 2.5	Chamber	Yes	Lung function, symptoms (questionnaire)	Control 0.11	No effects	In this study also asthmatic volunteers were tested (see below) Controls were exposed to NaCl aerosol RH 40% All subjects were exposed to both concentrations, double-blind, 4 weeks apart	Frampton *et al*. 1995 [detailed description below the table]
240	2 x 15 min (at t=90 and 210 min)	35 (M)	MMAD 0.5	Chamber	No	Lung function	0 0.11	No effects	RH 39% Experimental group (n=18) were exposed to H_2SO_4, a control group (n=17) to clean air.	Horstman *et al*. 1982
120	Alternate 20 min	11 (M)	MMD 0.90-0.93 ± 1.66-1.73	Chamber	No	Lung function, symptoms (interview)	0 0.23 0.42 0.94	No effects on lung function. Symptoms at 0, 0.23, 0.42, 0.94 mg/m^3 were as follows: throat irritation/dryness: 1/11, 3/11, 5/11, 8/11 cough: 0/11, 2/11, 5/11, 8/11 chest tightness: 0/11, 3/11, 3/11, 3/11 eye irritation: 0/11, 1/11, 1/11, 2/11 No other effects	RH 55% Subjects received all 4 concentrations randomized, at 1 week intervals	Horvath *et al*. 1982 [detailed description below the table]
120	Alternate 20 min	9 (M)	MMD 0.05	Chamber	No	Lung function, symptoms	0 1.6	No effects	RH 83%	Horvath *et al*. 1987
240	2 x 15 min starting at t=60 and t=180 min	28 (M,F)	MMD 0.14 ± 2.9	Chamber	No	Lung function, symptoms (method not specified)	0 0.1	No effects	Subjects were 14 smokers and 14 nonsmokers RH 60% All subjects were exposed to both concentrations, single blind, one day apart.	Kerr *et al* 1981
240	15 min starting at 180 min	12 (M,F)	MMD 0.13 ± 2.4	Chamber	No	Lung function, symptoms (method not specified), reactivity to metacholine	0 0.10	No effects apart from throat irritation in 1/12 subjects	RH 60% Subjects were exposed to both concentrations, one week apart.	Kulle *et al*. 1982 [detailed description below the table]

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
60	Last 20 min	7 (M)	MMAD 10.3	Head dome	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine, mucociliary clearance of ^{99m}Tc-ferric oxide aerosols	Control 0.471	• No effects on lung function, symptoms or reactivity to metacholine • Tracheal clearance ↑ • Pulmonary clearance ↑	Controls were exposed to NaCl aerosols LWC 481 mg/m^3 Fog 30 MOsm PH 2 RH 99% Subjects were exposed to both concentrations, double-blind, 1 week apart	Laube 1993
60	No	10 (M,F)	MMD 0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of ^{99m}Tc-ferric oxide aerosols	0 0.11 0.33 0.98	• No effects on lung function • T_{50} ↓ (-37%) at 0.11 mg/m^3, T_{50} ↑ (+47%) at 0.98 mg/m^3 (no significant change at 0.33 mg/m^3)	RH 46% All subjects were exposed to all concentrations, randomized	Leikauf *et al.* 1981
60	No	4 (M,F)	MMD 0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of ^{99m}Tc-ferric oxide aerosols	1.02	• No effects on lung function • T_{50} ↓	RH 46% All subjects were exposed to all concentrations, randomized	Leikauf *et al.* 1981
60	No	8 (M,F)	MMD 0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of ^{99m}Tc-ferric oxide aerosols	0 0.11 0.31 0.98	• No effects on lung function • T_{50} ↑ at 0.11 and 0.98 mg/m^3 (37 and 78%, resp.). Increase at 0.33 mg/m^3 (32%) was not statistically significant.	RH 49% All subjects were exposed to all concentrations, 1 week apart.	Leikauf *et al.* 1984

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
2 x 390, 1 day apart	6 x 50 min	15 (M,F)	MMAD 0.5 ± 2	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.39	No effects	In this study also asthmatic volunteers were tested (see below) Subjects were actually exposed to nominally 0.1 mg/m^3 plus an excess of H_2SO_4 that was generated to neutralize a calculated amount of background ammonia. The total aerosol mass concentration of sulfuric acid and its ammonium salt was at least twice the calculated concentration of sulfuric acid. Note that in addition subjects were given citrus juice. All subjects were exposed to both concentrations, randomized, double-blind, 1 week apart.	Linn *et al.* 1994 [detailed description below the table]
60	Alternate 10 min	22 (M,F)	VMD 0.83 VMD 11.4 VMD 20.3	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 1.50 (at VMD 0.83) 2.17 (at VMD 11.4) 2.50 (at VMD 20.3)	• No effects on lung function • No reactivity to metacholine • ↑ lower and upper resp irritation at 11.4 and 20.3 µm, not at 0.83 µm, including cough, burning sensations in the nose, throat ,or chest.	In this study also asthmatic volunteers were tested (see below) RH 74-79% for 1 µm aerosols and RH 100% for 10 an 20 µm fog. All subjects were exposed to all conditions, randomized, 1 week apart.	Linn *et al.* 1989 [detailed description below the table]
60	No	10	MMAD 0.5 ± 1.9	Nasal mask	No	Mucociliary clearance of 4 or 7.5 µm MMAD ^{99m}Tc-ferric oxide aerosols	0 0.13 0.27 1.28	• Dose dependent ↓ in clearance of 4 µm particles from 0.13 mg/m^3 on (not statistically significant). • Clearance of 7.5 µm particles was significantly ↑ at 1.28 mg/m^3 and significantly ↓ at 0.13 mg/m^3 (no data on 0.27 mg/m^3 presented).	RH 46% Limited study description No details on aerosol generation and concentration measurements	Lippmann *et al.* 1981

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
120	Five 4-min periods in the first 30 min	10 (M,F)	MMD 0.5 ± 2.59	Chamber	No	Lung function, mucociliary clearance of ^{99m}Tc-albumen saline aerosol	0 1.0	• No effects on lung function • The mean retention of ^{99m}Tc-albumen saline aerosol at 120 min. was 55.8% in controls and 47.3% at 1.0 mg/m^3	Only nominal concentration reported. Obligate mouth breathing. Controls were exposed to H_2O mist. RH 70% All subjects were exposed to both concentrations.	Newhouse *et al*. 1978
10	No	3 series of experiments 5 (M,F) 6 (M,F) 6 (M,F)	Size 0.1	Mouthpiece	No	Lung function, ventilation of N_2,arterial O_2 saturation, hemodynamics	Control 0.01 0.1 1.0	No effects	Only nominal concentration reported. In this study also asthmatic volunteers were tested (see below) Control exposure to NaCl aerosols. Subjects were exposed to all concentrations on the same day.	Sackner *et al* 1978
60	No	12 (M)	MMAD 0.99	Chamber	No	Lung function, symptoms, blood pressure, pulse rate, EC	0 39.4	Little coughing Lung resistance ↑ (+35-100%) No other effects	RH 62% Limited description	Sim and Pattle, 1957
30	No	Probably 12 (M)	MMAD 1.54	Chamber	No	Lung function, symptoms, blood pressure, pulse rate, EC	0 20.8	Intense coughing, lacrimation, and rhinorrhea. Lung resistance was 43 to 150% above normal No other effects	RH 91% Limited description	Sim and Pattle, 1957
60	No	10 (M)	MMAD 0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of gold and ferric oxide aerosols	0 0.10	• No effects on lung function • The T_{50} was doubled compared to controls	RH 47% Subjects were exposed to both concentrations	Spektor *et al*. 1989
120	No	10 (M)	0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of gold and ferric oxide aerosols	0 0.11	• No effects on lung function • The T_{50} was tripled compared to controls	RH 47% Subjects were exposed to both concentrations	Spektor *et al*. 1989

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
180	6 x 10 min every 30 min	30	0.64 ± 2.5	Chamber	Yes	Lung function	0 0.11	No effects	In this study also asthmatic volunteers were tested (see below) RH 40% Controls were exposed to NaCl aerosols All subjects were exposed to both concentrations, 1 week apart	Utell *et al*. 1994
Healthy senior volunteers										
40	Last 10 min	8 (M,F)	MMAD 0.6 ± 1.5	Mouthpiece	Yes/No	Lung function	0 0.082	No effects	In this study also senior asthmatic volunteers were tested (see below) RH 65% H_2SO_4 was delivered twice: with and without gargling lemonade. All subjects were exposed to both concentrations, randomized single-blind, one week apart	Koenig *et al*. 1993
Asthmatic adult volunteers										
60	Alternate 10 min	15 (M,F)	MMAD 1.0 ± 2	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.97	No effects	In this study also healthy volunteers were tested (see above) Asthmatics withheld short-acting bronchodilator drugs on the morning of a study. RH 50% Subjects were exposed to both concentrations, double-blind, 1 week apart	Anderson *et al*. 1992

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
16	No	18	VMD 0.4	Mouthpiece	Yes	SR_{aw}, symptoms (questionnaire)	Control 2.9	No effects	Subjects withheld medication from 24 h pre-exposure until study termination PH2 Control-exposure to NaCl aerosols. Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991
16	No	18	VMD 6.1 ± 1.5	Mouthpiece	Yes	SR_{aw}, symptoms (questionnaire)	Control 2.8	No effects	Subjects withheld medication from 24 h pre-exposure until study termination Control-exposure to NaCl aerosols. PH2, at isomolar and hyposmolar conditions	Aris *et al.*, 1991
16	No	9	VMD 5.8 ± 1.4	Mouthpiece	Yes	SR_{aw}, symptoms (questionnaire)	Control 3.02	No effects	Subjects withheld medication from 24 h pre-exposure until study termination Control-exposure to NaCl aerosols. RH 100% Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991
16	No	9	VMD 0.4	Mouthpiece	Yes	SR_{aw}, symptoms (questionnaire)	Control 3.37	Throat irritation at 3.37 mg/m^3 No other effects	Subjects withheld medication from 24 h pre-exposure until study termination RH < 10% Control-exposure to NaCl aerosols. Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
16	Yes (whole period)	6	VMD 0.4	Mouthpiece	Yes	SR_{aw}, symptoms (questionnaire)	Control 2.97	No effects	Subjects withheld medication from 24 h pre-exposure until study termination RH < 10% Control-exposure to NaCl aerosols. Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991
60	Alternate 15 min	10	See remark	Chamber	Yes	SR_{aw}, symptoms (questionnaire)	Control 0.96	No effects	Subjects withheld medication from 24 h pre-exposure until study termination Control-exposure to NaCl aerosols. Fog with a low-liquid-water content (0.5 g/m^3), pH 2 Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991
60	Alternate 15 min	10	See remark	Chamber	Yes	SR_{aw}, symptoms (questionnaire)	Control 1.4	No effects	Subjects withheld medication from 24 h pre-exposure until study termination Control-exposure to NaCl aerosols. Fog with a high liquid water content (1.8 g/m^3), pH 2 Subjects were exposed to both concentrations, single-blind, on separate days	Aris *et al.*, 1991
120	Alternate 15 min	6 (M)	MMAD 0.5 ± 3.0	Chamber	No	Lung function, symptoms (questionnaire)	0 0.1	Respiratory resistance ↑ in 2/6 subjects at the end of the exposure time (magnitude not stated) No other effects	In this study also healthy volunteers were tested (see above) RH 40% Subjects were exposed to both concentrations, single-blind, on separate days	Avol *et al.* 1979 [detailed description below the table]

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
60	3 periods of 10 min	22 (M,F)	VMD 10	Chamber	Yes, half of the subjects	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.52 1.09 2.03	Dose dependent (mainly lower) respiratory irritation at 0.52, 1.09, and 2.03 mg/m^3; observations indicated that irritation was noticeable upon entering the chamber at the higher acid concentrations. These symptoms were reversible within one hour after the end of exposure. No other effects NB no meaningful differences in response of subjects who did and did not gargle grapefruit juice, so results of these groups were combined No other effects	In this study also healthy volunteers were tested (see above) LWC 0.1 g/m^3 RH nearly 100% Subjects were exposed to all four concentrations, double-blind, at weekly intervals	Avol *et al*. 1988a
60	Alternate 10 min	21 (M,F)	MMAD 0.9 ± 2.5	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.40 1.00 1.46	• Dose dependent low resp. symptoms (a.o. coughing) and non-resp. symptoms (headache, fatigue, eye irritation) at 0.40, 1.00, and 1.46 mg/m^3 (only minimal to mild at 0.40 mg/m^3); some symptoms persisted for 24 h after exposure • Lower FVC and FEV_1 at 1.00 (10%) and 1.46 mg/m^3 (11%) • No other effects	In this study also healthy volunteers were tested (see above) RH 50% Subjects withheld medication from 12-48 h pre-exposure until study termination (depending on type of medication) Subjects were exposed to all four concentrations, double-blind, at weekly intervals	Avol *et al*. 1988b
120	4x 10 min starting at t=10, 35, 60, 90 min	19	Not reported	Chamber	No	Lung function	Control 0.075	No effects	Control exposure to NaCl 8 volunteers with asthma and 11 volunteers with COPD. Subjects were exposed to both concentrations, double-blind, separated by at least 1 week. Abstract only. This study is considered not suitable for AEGL development due to poor reporting	Bauer *et al*. 1988

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
180	6 x 10 min (each half hour)	30 (M,F)	MMAD 0.64 ± 2.5	Chamber	Yes	Lung function, symptoms (questionnaire)	Control 0.11	No effects	In this study also healthy volunteers were tested (see above) Controls were exposed to NaCl aerosol RH 40% Medication was withheld at least 6 hours before exposure All subjects were exposed to both concentrations, double-blind, 4 weeks apart	Frampton *et al*. 1995 [detailed description below the table]
60	3 x 5 min voluntary hyperventilation	14 (M,F)	MMAD 9 ± 0.5	Face mask	Yes	Lung function, reactivity to metacholine	0.50	No effects	Only nominal concentration reported Fog 300 mOsm RH 75% LWC = 0.5 g/m^3 Medication was withheld at least 18 hours before exposure	Leduc *et al*. 1995
2 x 390, 1 day apart	6 x 50 min	30 (M,F)	MMAD 0.5 ± 2	Chamber	Yes	Lung function, symptoms (questionnaire), reactivity to metacholine	0 0.28	No effects	In this study also healthy volunteers were tested (see above) Subjects were actually exposed to 0.1 mg/m^3 plus an excess of H_2SO_4 that was generated to neutralize a calculated amount of background ammonia. The total aerosol mass concentration of sulfuric acid and its ammonium salt was at least twice the calculated concentration of sulfuric acid. Note that in addition subjects were given citrus juice. All subjects were exposed to both concentrations, randomized, double-blind, 1 week apart.	Linn *et al*. 1994 [detailed description below the table]

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
60	Alternate 10 min	27 (M,F)	MMAD 0.6 ± 2.6	Chamber	No	Lung function, symptoms (questionnaire), reactivity to cold air	0 0.122 0.242 0.410	No effects	RH 52% Subjects were actually exposed to the targeted dose plus an excess of H_2SO_4 (at least 0.05 mg/m^3) which was generated to neutralize a calculated amount of background ammonia. Medication was withheld at least 8 hours before exposure. All subjects were exposed to all concentrations, randomized, 1 week apart.	Linn *et al.* 1986
60	Alternate 10 min	19 (M,F)	VMD 0.87 VMD 12.8 VMD 22.8	Chamber	Yes	Lung function, symptoms (questionnaire)	0 2.27 (at VMD 0.87) 1.97 (at VMD 12.8) 1.86 (at VMD 22.8)	• SR_{aw} ↑ at all VMDs (251-255% vs 157-206% in controls) • FEV_1 ↓ at all VMDs (21-24% vs 14-19% in controls) • Symptoms of irritation at all droplet sizes (slightly higher at 12.8 and 22.8 µm), including wheeze, chest tightness, substernal discomfort, cough, and throat irritation. • Lung function and excessive symptoms (more wheeze, dyspnea, and chest tightness than others) necessitated 4/19 subjects to stop exercise or terminate exposure (involving all VMDs) • More medication than normal was needed directly and in the 24 hours after exposure. • No other effects	In this study also healthy volunteers were tested (see above) RH 74-79% for 0.87 µm aerosols and RH 100% for 12.8 and 22.8 µm fog. Subjects withheld medication at least 12 hours before exposure. All subjects were exposed to all conditions, randomized, 1 week apart.	Linn *et al.* 1989 [detailed description below the table]

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
10	No	3 series of experiments 5 (M,F) 6 (M,F) 6 (M,F)	Size 0.1	Mouthpiece	No	Lung function, ventilation of N_2,arterial O_2 saturation, hemodynamics	Control 0.01 0.1 1.0	No effects	Only nominal concentration reported In this study also healthy volunteers were tested (see above) Control exposure to NaCl aerosols. Subjects withheld medication at least 8 hours before exposure. Subjects were exposed to all concentrations on the same day.	Sackner *et al* 1978
60	No	10 (M,F)	MMD 0.5 ± 1.9	Nasal mask	No	Lung function, mucociliary clearance of ^{99m}Tc-ferric oxide aerosols	0 0.11 0.32 0.97	• SG_{aw}, FEV_1, MMEF, and V_{max25} ↓ at 0.97 mg/m^3 (all <10%, except V_{max25} which was appr. 20%) • No effect on tracheal mucociliary clearance • T_{25} and T_{50} for bronchial mucociliary clearance ↑	RH 47% 9/10 subjects withheld medication at least 6 hours before treatment. Subjects were exposed to all concentrations.	Spektor *et al*. 1985
60	No	10 (M,F)	MMD 0.3	Head dome	No	FEV_1 after challenge with grass pollen allergen	0 0.11 1.14	Decrease in FEV_1 upon challenge was 14.1% in controls, 16.7% at 0.1 mg/m^3 (p=0.051), and 18.4% at 1.0 mg/m^3 (p=0.013)	RH 15% All subjects were exposed to all concentrations, randomized, double-blind, 2 weeks apart.	Tuncliffe *et al*. 2001
30	Last 10 min	15	MMAD 0.8 ± 1.7	Mouthpiece	No	Lung function	Control 0.35	No effects	Only nominal concentrations reported. Controls were exposed to NaCl aerosols. Medication was withheld 24 hours before exposure RH 20-25% All subjects were exposed to both concentrations, double-blind, 1 week apart	Utell *et al*. 1989

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
30	Last 10 min	15	MMAD 0.8 ± 1.7	Mouthpiece	Yes	Lung function	Control 0.35	Drop in FEV_1 ↑ following exercise	Only nominal concentrations reported. Controls were exposed to NaCl aerosols. Medication was withheld 24 hours before exposure RH 20-25% All subjects were exposed to both concentrations, double-blind, 1 week apart	Utell *et al.* 1989
16	No	17	MMAD 0.8 ± 2.2	Mouthpiece	No	Lung function	Control 0.1 0.45 1.0	• SG_{aw} ↓ at 1.0 mg/m^3 (21%) and at 0.45 mg/m^3 (19%) (not significant at 0.1 mg/m^3) • FEV_1 ↓ only at 1.0 mg/m^3 (5%) • V_{max60} and V_{max40} ↓ only at 1.0 mg/m^3	Only nominal concentrations reported. Control exposure to NaCl aerosol Medication was withheld 24 hours before exposure. Subjects were exposed to all concentrations, randomized, double-blind on separate days.	Utell *et al.* 1983
180	6 x 10 min every 30 min	30 (M,F)	0.64 ± 2.5	Chamber	Yes	Lung function	Control 0.11	No effects	In this study also healthy volunteers were tested (see above) Controls were exposed to NaCl aerosols RH 40% All subjects were exposed to both concentrations, 1 week apart	Utell *et al.* 1994
Asthmatic senior volunteers										

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
40	Last 10 min	9 (M,F)	MMAD 0.6 ± 1.5	Mouthpiece	Yes/No	Lung function	0 0.074	No effects	In this study also senior volunteers were tested (see above) RH 65% H_2SO_4 was delivered twice: with and without gargling lemonade. All subjects were exposed to both concentrations, randomized single-blind, one week apart	Koenig *et al.* 1993
Asthmatic young / adolescent volunteers										
40	Last 10 min	32 (M,F; 8-16 yr)	MMAD 0.5 ± 1.9	Chamber	Yes	Lung function, symptoms (questionnaire)	0 0.046 0.127	No effects	Unencumbered oronasal breathing RH 48% Subjects withheld medication from 8-48 h pre-exposure until study termination (depending on type of medication) Subjects were exposed to all three concentrations, double-blind, at weekly intervals	Avol *et al.* 1990
40	Last 10 min	21	MMAD 0.5 ± 1.9	Chamber	Yes	Lung function, symptoms (questionnaire)	0 0.134	No effects	Oral breathing RH 48% Subjects withheld medication from 8-48 h pre-exposure until study termination (depending on type of medication) Subjects were exposed to all three concentrations, double-blind, at weekly intervals	Avol *et al.* 1990
40	Last 10 min	14 (M,F; 12-19 yr)	MMAD 0.72 ± 1.5	Mouthpiece	No	Lung function, symptoms (questionnaire)	0.05 0.18	FEV_1 and FVC ↓ (average % not given) No other effects	RH 65% Subjects withheld medication at least 4 hours before exposure All subjects received both exposures, single-blind, one week apart	Hanley *et al.* 1992

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
45	2x 15 min (start and end of exp)	9 (M,F; 12-17 yr)	MMAD 0.72 ± 1.5	Mouthpiece	No	Lung function, symptoms (questionnaire)	0 0.05	FEV_1 and FVC ↓ (average % not given) No other effects	RH 65% Subjects withheld medication at least 4 hours before exposure All subjects received both exposures, single-blind, one week apart	Hanley *et al.* 1992
45	2x 15 min (start and end of exp)	9 (M,F; 12-17 yr)	MMAD 0.72 ± 1.5	Mouthpiece	Yes	Lung function, symptoms (questionnaire)	0 0.05	FEV_1 and FVC ↓ (average % not given) No other effects	RH 65% Subjects withheld medication at least 4 hours before exposure All subjects received both exposures, single-blind, one week apart	Hanley *et al.* 1992
50	Last 20 min	10 (M,F; 14-18 yr)	MMAD 0.6 ± 1.5	Mouthpiece, face mask	No	Lung function, symptoms (questionnaire), nasal power	0 0.10	• R_T ↑ (35-45%), V_{max50} and V_{max75} ↓ (-16-22%), FEV_1 ↓ (-7-8%) • No difference between exposure modes (mouthpiece, facemask) • No other effects	RH 75% Medication was withheld approximately 6 hours before exposure. All subjects were exposed to both concentrations on different days, randomized, single-blind.	Koenig *et al.* 1985
45	2x 15 min (start and end of exp)	14 (M,F; 13-18 yr)	MMAD 0.6 ± 1.5	Mouthpiece	Yes	Lung function	0 0.040 0.074	FEV_1 ↓ (3-6%) at both doses No other effects	RH 65% All subjects were exposed to all concentrations, randomized, one week apart	Koenig *et al.* 1992
90	Alternate 15 min	14 (M,F; 13-18 yr)	MMAD 0.6 ± 1.5	Mouthpiece	Yes	Lung function	0 0.033 0.081	No effects	RH 65% All subjects were exposed to all concentrations, randomized, one week apart	Koenig *et al.* 1992

Time (min)	Exercise	No. of subjects	MMAD ± GSD (µm)	Mouthpiece, facemask or chamber	Gargling with citric acid	Observations	Exposure concentrations (mg/m^3) – actual, unless otherwise indicated	Effects[1]	Remarks	Reference
40	Last 10 min	10 (M,F; 12-17 yr)	MMAD 0.6 ± 1.5	Mouthpiece	No	Lung function, symptoms (questionnaire)	Control 0.11	No effects at rest. Following exercise: FEV_1 ↓ (8%), R_T ↑ (40%), V_{max50} ↓ (21%) No other effects	Controls were exposed to NaCl aerosol RH 75% Medication was withheld approximately 6 hours before exposure. All subjects were exposed to both concentrations on different days, randomized, single-blind.	Koenig *et al.* 1983
40	Last 10 min	9 (M,F; 12-18 yr)	MMAD 0.6 ± 1.5	Mouthpiece	No	Lung function, symptoms (questionnaire)	0 0.061	FEV_1 ↓ (6%) No other effects	RH 65% All subjects were exposed to both exposures, one week apart	Koenig *et al.* 1989

[1] "no effects" or "no other effects" means "no (other) *treatment-related* effects"

↓ = decreased
↑ = increased
BAL = bronchoalveolar lavage
ECG = electrocardiogram
EF = expiratory flow
F = female
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
IF = inspiratory flow
LWC = low-liquid-water content
M = male
MMAD = mass median aerodynamic diameter
MMD = mass median diameter
MMEF = midmaximum expiratory flow
R_T = Respiratory resistance
RH = relative humidity
RR = respiration rate
SG_{aw} = specific airway conductance
SR_{aw} = specific airway resistance
T_y = the time to complete *y*% of tracheobronchial clearance
TV = tidal volume
V_{maxy} = maximum flow calculated at *y*% VC
VC = vital capacity
VMD = volume median diameter

The total number of volunteers in the studies sum up to more than a thousand. The studies were generally of good quality and the results were fairly consistent. In the following text, some of these studies are described in more detail, because they compared healthy and asthmatic people, were of adequate quality, the endpoints studied were relevant for AEGL development and are expected to provide information regarding the thresholds for these endpoints.

Groups of 6 healthy and 6 asthmatic male volunteers were exposed to clean air or to 0.1 mg/m^3 sulfuric acid aerosols in an environmental chamber (RH 40%, 31 °C) for 120 minutes (Avol *et al*. 1979). The target concentration was 0.1 mg/m^3 but a surplus of 0.05 mg/m^3 was generated to account for neutralization by breathing zone ammonia. Nevertheless, the measured concentrations of sulfuric acid were 0.1 mg/m^3. Subjects exercised the first 15 minutes of each half hour. Before and after exposure, the subjects underwent lung function tests and filled out symptom scoring questionnaires. Healthy volunteers showed no effects. Two out of six asthmatic volunteers showed some changes in respiratory resistance (magnitude not stated).

Frampton *et al.* (1995) investigated the effects of ozone on lung function and symptoms in healthy and asthmatic volunteers who were pre-exposed to sulfuric acid or sodium chloride aerosol. Results of ozone exposure are not summarized here. Thirty healthy nonsmoking subjects and 30 allergic asthmatics were included in the study. They underwent 3-hour exposures to sulfuric acid and sodium chloride (control) aerosols, in a randomized, double-blind fashion, given 4 weeks apart. The exposure took place in a 45 m^3 environmental chamber (RH 40%, 21 °C). Sulfuric acid aerosols were generated using a nebulizer. Mass concentrations were monitored by nephelometry and measured by collection on filters and subsequent analysis by ion chromatography. The MMAD ± GSD was 0.64 ± 2.5 µm and the achieved exposure concentration (means ± SD) was 107 ± 15 µg/m^3. Asthmatic subjects did not require therapy with inhaled or systemic corticosteroids and were asked to avoid use of bronchodilators for 6 hours prior to each exposure. Subjects gargled with a lemon mouthwash before each exposure to reduce oral ammonia. During the exposures the subjects had to exercise for 10 minutes, every half hour, at a workload of quadruple minute ventilation. Lung function tests were performed before and immediately after exposure. At the end of the exposure the subjects completed a standardized symptom questionnaire. Exposure to H_2SO_4 did not lead to responses that were different from control (NaCl) exposures.

Eleven healthy non-smoking male volunteers were exposed to filtered air or to sulfuric acid aerosols in an environmental chamber (RH 55%, 22 °C) during two hours (Horvath *et al*. 1982). The aerosols were generated with a nebulizer and had a measured mass median particle diameter in the range of 0.91-0.93 µm with respective GSDs of 1.66 and 1.73. The measured exposure concentrations of sulfuric acid were 0, 0.233, 0.418 and 0.939 mg/m^3 and were given to all volunteers on different occasions, randomized, at one week intervals. The 2-hour exposures consisted of three sequences of 20 minutes of exercise on a treadmill (ventilation 30 liters/min) followed by 20 minutes of rest. Lung function tests were performed before and after each exposure, and in addition FVC was measured during each period of rest. At the end of exposure the subjects were interviewed regarding the symptoms they may have experienced in the chamber. Most subjects were able to detect the presence of sulfuric acid by taste. There were no effects on lung function. The symptoms at 0, 0.233, 0.418, and 0.939 mg/m^3 were as follows. Sore throat, irritation or dryness was experienced in 1, 3, 5, and 8 of the eleven volunteers, respectively. Cough was reported by 0, 2, 5, and 8 of the volunteers, and eye irritation in 0, 1, 1, and 2 of the volunteers. In addition, dizziness, fatigue, and headache were reported at each exposure condition (including controls), but there was no dose-response relationship and the authors reported that these were associated with exercise.

Kulle *et al.* (1982) exposed 7 male and 5 female non-smoking healthy volunteers to sulfuric acid aerosols in a 22.2 m^3 environmental chamber (RH 60%, 22 °C) during 4 hours. The aerosols were generated by the reaction of SO_3 with water vapor rendering aerosols with a mass concentration of

0.10 mg/m^3 and a mass median diameter of 0.13 µm (GSD 2.4), as determined by real-time and hourly measurements. The subjects exercised at 100 W for 15 minutes, starting at 180 minutes. On other days, the subjects were also exposed to ozone or to sulfuric acid followed by ozone, but the result of these exposures are not discussed here. At the end of the exposure the subjects underwent whole body plethysmography and spirometry. At the end of the day the subjects were challenged with metacholine. Symptoms were also recorded at the end of the day, but the method of recording was not described. No effects on lung function were observed following exposure to sulfuric acid. Only 1 out of 12 subjects showed mild throat irritation (without coughing).

The effect of droplet size on respiratory responses to inhaled sulfuric acid in normal and asthmatic volunteers was investigated by Linn *et al.* (1989). Groups of male and female healthy (n=22) and asthmatic (n=19) volunteers were exposed to sulfuric acid aerosols with volume median droplet diameters (VMD) of 1, 10, and 20 µm, at nominal concentrations of 0 (water) and 2 mg/m^3, in a randomized order, 7 days apart. The fogs (10 and 20 µm) were generated from dilute sulfuric acid solutions by spray nozzles, and the 1 µm aerosols were generated using a nebulizer. The exposures took place in an environmental chamber and lasted 1 hour, including three periods of exercise (ventilation rate 40-45 L/min; 10 minutes) and rest (10 minutes). The subjects gargled grapefruit juice just prior to exposure to deplete oral ammonia. Asthmatics withheld their regular use of antihistamines 48 hours, oral bronchodilators 24 hours, and inhaled bronchodilators 12 hours before each exposure. Body plethysmography and spirometry was performed just after the first period of exercise and at the end of exposure. Symptoms were recorded on questionnaire forms before exposure, during exposure, and 1 and 7 days after exposure. Bronchial reactivity in normal subjects was measured by challenging with metacholine at 1 hour after exposure. The actual volume median droplet sizes and sulfuric acid concentrations were 0.83 µm (1.50 mg/m^3), 11.4 µm (2.17 mg/m^3), and 20.3 µm (2.50 mg/m^3 for healthy volunteers, and 0.87 µm (2.27 mg/m^3), 12.8 µm (1.97 mg/m^3), and 22.8 µm (1.86 mg/m^3) for asthmatic volunteers. Relative humidities were 74-79 for the 0.83-0.87 µm aerosols and 100% for both fog-conditions. Healthy subjects showed no effects on lung function or reaction to metacholine following any exposure to sulfuric acid. In asthmatics, lung function was altered as a result of exercise, and exposure to sulfuric acid enhanced these alterations somewhat. Specific airway resistance was increased at all VMDs to 251-255% of the pre-exposure values following sulfuric acid exposure, versus an increase of 157-206% in controls. Likewise, the FEV_1 was decreased at all VMDs of sulfuric acid with 21-24% versus 14-19% in controls. No signs of irritation were noted in healthy subjects exposed to the smallest droplets. However, the two fog-conditions produced lower and upper respiratory irritation, including cough (already from the start of exposure), and burning sensations in the nose, throat and chest. These symptoms were gone within one day. In asthmatics, all sulfuric acid exposure condition resulted in signs of respiratory irritation, although more at 10 and 20 µm aerosols. The symptoms of irritation included wheeze, chest tightness, substernal discomfort, cough (already from the start of exposure), and throat irritation, and were gone within one day although the subjects took some more medication than normal. Four of the asthmatic subjects failed to complete one or more of the exposures, involving all three droplet sizes, due to excessive symptoms during the second or third exercise period (i.e. 20-30 or 40-50 min). They reported more wheeze, dispnea, and chest tightness during control as well as during acid studies. Immediate testing showed lung function to be markedly reduced. A normal dose of inhaled bronchodilator relieved symptoms in all cases, and usually returned lung function to near its pre-exposure level, although in some cases decrements in lung function were still present 15 minutes later.

Linn *et al.* (1994) also studied the effects of repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. Here only the results from the sulfuric acid exposure are presented. Groups of male and female healthy (n=15) and asthmatic (n=30) volunteers were exposed to clean air and to sulfuric acid aerosols with an MMAD of 0.5 µm with a GSD of 2, at a nominal concentration of 0.1 mg/m^3 plus an excess to account for neutralization by respiratory ammonia, in a randomized order, double-blind, one week apart. Subjects were given lemonade or citrus juice repeatedly

before and during exposures to minimize oral ammonia. Asthmatics did not use medications during the exposures, and inhaled ß-adrenergic drugs at least 4 hours before exposures. They were allowed to continue the use of theophylline and inhaled corticosteroids as long as the doses were standardized before each exposure. The exposures took place in an environmental chamber (RH 50%, 21 °C) and lasted 6.5 hours, with a 30 minutes lunch break after the 3rd hour, and were repeated on the following day. The subjects exercised the first 50 minutes of each hour (target ventilation rate 8 times FVC), and then rested for the final 10 minutes, during which they underwent lung function tests and filled out symptom questionnaires. Within 10 minutes after leaving the chamber, the subjects were challenged with metacholine chloride to measure bronchial reactivity. The measured concentrations of sulfuric acid were 0.39 mg/m^3 for healthy subjects and 0.28 mg/m^3 for asthmatic subjects. Sulfuric acid exposure caused no effects on lung function, symptoms, or bronchial reactivity.

In Table 4, numerous human volunteer studies with sulfuric acid are presented, involving more than a thousand subjects in total. In these studies, several parameters have been investigated including lung function, symptoms, and mucociliary clearance. In the text below these parameters and their relevance for the development of AEGLs are discussed.

Lung function

A number of lung function parameters were affected as a result of exposure to sulfuric acid. Most asthmatics developed an increase in airway resistance (SR_{aw}) due to exercise at any condition, including clean air. These increases were sometimes enhanced as a result of exposure to aerosols (NaCl, H_2SO_4). However, SR_{aw} is a very sensitive parameter that can be affected without meaningful changes in other lung function parameters such as FEV_1. The intra-individual variation over time can be more than 80% under normal conditions and a 100% change in SR_{aw} is still considered as clinically insignificant. Moreover, the effects on SR_{aw} in asthmatics were mainly observed when they withheld their medication, and taking (short-acting) medication could easily reverse the effects. Therefore, SR_{aw} is not considered as a very suitable parameter for the development of AEGLs. Other lung function parameters, such as FEV_1 are considered more relevant. Given the normal variation in these parameters (FEV_1 approximately 30% under normal conditions, see e.g. Hruby and Butler 1975), small changes will not be noticeable as "discomfort". In general, a decrement in FEV_1 of 20 percent is required to elicit changes in biological function that are clinically significant and represent the threshold for notable discomfort that characterizes AEGL-1 level effects. Therefore, changes of 20% or higher in FEV_1 are considered relevant for AEGL-1. In the human volunteer studies, the changes in FEV_1 were typically within 20% of the pre-exposure values.

Symptoms

Symptoms of respiratory irritation were observed in many of the human volunteer studies. The most important symptoms in healthy subjects were cough, throat irritation, chest tightness, and burning sensations in the nose and chest. In addition to these symptoms, asthmatics sometimes also experienced wheeze and dispnea. The severity of symptoms in asthmatics observed in the study of Linn *et al*. (1989) necessitated subjects to stop exercise or exposure. All these symptoms noted in the volunteer studies are considered relevant for AEGL-1.

Mucociliary clearance

Results of effects of sulfuric acid on mucociliary clearance are not univocal. There are differences between and within studies: the clearance is sometimes enhanced, sometimes retarded. Study authors could only speculate about these differences, but were unable to elucidate a mechanism behind the observations. Besides, the effects on mucociliary clearance were already observed at levels that did not induce any symptoms or effects on lung function. Therefore, the effects on mucociliary clearance are considered as not relevant for the development of AEGLs.

2.2.3. Occupational / Epidemiological Studies

Ten Bruggen Cate (1968) examined dental erosion in 555 acid workers in different jobs and factories. He found that dental erosion was most prevalent in acid battery forming workers, and less among picklers. Exposure to acids included sulfuric acids and several other acids.

Thirty-two workers from two battery factories were tested for pulmonary function, salivary pH, and dental anomalies. The air samples (12 samples per day at various times, probably area samples) of sulfuric acid ranged from 26 to 35 mg/m^3 in one factory and averaged to approximately 13 mg/m^3 in the other. The samples were taken at 2 liters per minute through a bubbler containing 0.02 N NaOH and the concentration of H_2SO_4 was determined by the analysis of excess NaOH by standard H_2SO_4 (0.02 N) titration. The pH of the saliva was 7 before and 6.95 after the shift in controls, whereas in exposed workers the pH dropped from 6.9 to 6.7. The VC was not affected by exposure. The FEV_1 decreased by 82 ml (an estimated decrease of 2%) during the shift of exposed workers, but this is a small amount compared to the normal diurnal variation in FEV_1 of approximately 10% (Troyanov et al. 1994). Dental erosion was evident in exposed workers (El-Sadik *et al*. 1972).

Jones and Gamble (1984) measured sulfuric acid in five lead acid plants. The average of all personal samples for H_2SO_4 taken during the work shift was 0.18 mg/m^3 with a range of "non-detectable" to 1.7 mg/m^3. Highest levels of acid were found in the charging and forming areas of the plants. The MMAD of aerosols was 2.6-10 µm. The same group of investigators examined the acute health effects in 225 workers of these five lead acid battery plants (Gamble *et al*. 1984a). The workers were given a questionnaire and underwent spirometry. There were no exposure-related changes in symptoms or respiratory function.

Effects on the respiratory system and teeth were investigated in 248 workers in five lead acid battery plants. The workers were given a questionnaire, underwent spirometry, and had their teeth examined. Concentrations were estimated from personal samples for sulfuric acid taken in the same factory in another study (Jones and Gamble 1984, see above). Dental erosion was evident in exposed workers. Symptoms and respiratory function were unremarkable (Gamble *et al*. 1984b).

Grasel *et al* (2003) examined 52 workers from five anodizing plants exposed to sulfuric acid. The workers underwent a clinical examination, and ear, nose and throat examination including nasal endoscopy. A subgroup of 20 workers underwent a nasal biopsy. Matched controls underwent the same investigations. Area samples and personal samples (respiratory area) of sulfuric acid were taken during five workdays at several times over the 8-hour work shifts. Exposure concentrations were very different for each plant. The personal samples in the plant with the lowest exposure levels were in the range of 0.005-0.031 mg/m^3, and the area concentrations were in the range of 0.041-0.081 mg/m^3. No personal samples were taken in the plant with the highest area concentrations (1.52-2.78 mg/m^3). The highest personal exposures (0.45-0.87 mg/m^3) were recorded in a plant with area concentrations of 0.11-1.47 mg/m^3. Higher incidences in macroscopic and microscopic findings of the nasal mucosa were observed in exposed workers, and included squamous metaplasia, squamous atypia, thickness of nasal membrane, inflammatory infiltrate in lamina propria, and infiltration of neutrophils. There was no association between the effects and the exposure duration (4 months – 15 years).

In a storage battery plant, the exposure to sulfuric acid mist during the forming process varies from 3.0-16.6 mg/m^3 on a dry day and often exceeds 16 mg/m^3 on a cold humid day (area samples, duration not stated). During the charging process the exposure is in the range of <0.8 to 2.5 mg/m^3. The teeth of workers employed for several years were eroded to a varying degree, depending on length of exposure (etching starts at least after 3-4 months of exposure), “lip level” (people with short lips showed more erosion), and the concentration of sulfuric acid in the air (in the forming department, there were

more people with affected teeth and the degree of erosion was severe compared to the workers in the charging department) (Malcolm and Paul 1961).

In the forming department of a storage battery factory the mean sulfuric acid concentration in the air was 1.4 mg/m^3 (range: trace-6.1 mg/m^3, 38 observations on two days, duration of measurements not stated). Compared to controls, men in this department had a slight excess of spells of respiratory disease, particularly bronchitis, but not of other disease. Their ventilatory capacity was not different from that of controls (Williams, 1970).

Mustajbegovic *et al*. (2000) investigated ventilatory capacity and symptoms in 567 male and 135 female workers employed in two chemical plants, and in male and female unexposed workers. The workers were regularly exposed to sulfuric acid (0.02-0.09 mg/m^3), but because there was co-exposure to many other chemicals including hydrochloric acid, sodium hydroxide, and organic compounds, the results of this study can not be used for the establishment of AEGL values.

Anfield and Warner (1968) measured the sulfuric acid concentrations in five industrial departments including pickling, forming and acid recovery departments, that covered open and (partly) closed processes. Sulfuric acid was sampled using filters positioned approximately 5 ft above floor level. The flow rate was 20 l/min and the sampling period varied from half an hour up to several hours. The number of samples taken at each department ranged from 12 to 85, with a total of 225 samples for all five locations. The sulfuric acid concentration was above 1.0 mg/m^3 in 85 of the 225 samples (38%) for (according to the authors) “extended periods of time”. The lowest and highest overall average concentration of sulfuric acid in a department were 0.33 and 2.96 mg/m^3, respectively. In one department, 6 out of 85 samples contained a concentration above 10.0 mg/m^3, with an avarage of 14.4 mg/m^3. Health effects were not investigated in this study.

Morning and evening peak expiratory flow rates (PERF) and the presence of symptoms were recorded in 83 children in Pennsylvania during summer. Air pollution, including total sulfate particles, was also measured during that period. The mean total sulfate particle concentration was 147 nmol/m^3 (maximum 515 nmol/m^3). An increased concentration was associated with increased cough incidence and lower PERF (Neas *et al*. 1995).

Raizenne *et al*. (1989) studied the lung function of 112 girls in a summer camp in Canada and recorded the concentrations of O_3, H^+, and H_2SO_4. There were several episodes of pollution, of which the one with the highest concentrations (O_3: 143 ppb, H^+: 559 nmol/m^3, H_2SO_4: 47.7 µg/m^3) was associated with the largest changes in lung function (FEV_1: -66 ml, only in asthmatics, and PEF –57 ml/s in healthy girls and –143 ml/s in asthmatics).

In an analysis of 541 cases of acute occupational chemical injuries within a company in China, Xia *et al*. (1999) reported 9 cases of accidental exposure to sulfuric acid. The exposure concentrations and effects were not reported.

2.3. Neurotoxicity

No human data.

2.4. Developmental / Reproductive toxicity

No human data.

2.5. Genotoxicity

No human data.

2.6. Carcinogenicity

The IARC concluded in 1992 that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic to humans (group 1) (IARC monograph 54, 1992).

An epidemiological study into lung cancer mortality among workers in three steel-pickling factories was conducted by Beaumont *et al*. (1987). The lung cancer mortality ratio was 1.39, but restriction to the time 20 years and more from first employment in a job with probable daily sulfuric acid exposure resulted in a ratio of 1.93. Higher ratios were found for workers exposed to acids other than sulfuric acid. The exposure to sulfuric acid was measured in 1975-1979 and was on average 0.19 mg/m^3 for personal samples and 0.29 mg/m^3 for area samples. However, the investigators could not exclude the possibility that sulfuric acid mist exposures were higher prior to 1975.

In a review article about 16 studies into the association of sulfuric acid and cancer, Soskolne *et al*. (1989) concluded that there is an expanding body of evidence supporting such an association.

Sathiakumar *et al*. (1997) reviewed 25 epidemiological studies regarding the carcinogenicity of sulfuric acid mists. They concluded that there was little evidence in support of a causal relationship between exposure to sulfuric acid and lung cancer and that no adequate conclusions could be drawn about the relationship with nasal cancer. There was a moderate association of sulfuric acid exposure and larynx cancer, but the authors noted that many results of individual studies were imprecise and not adequately adjusted for confounders.

2.7. Summary of human data

There are no reports on lethal inhalation exposures to sulfuric acid. Case studies of accidental exposures are not suitable due to their lack of exposure estimates.

Many human volunteer studies with inhalation exposure concentrations of 0.01 to 39.4 mg/m^3 were available. Both healthy and asthmatic volunteers were involved. The studies were conducted with varying particle sizes, and exposures were given in environmental chambers or by using a mouth piece, a face mask, a head dome, or a nasal mask. In a number of studies, the subjects gargled with a juice containing citric acid to deplete oral ammonia. Most of the studies focussed on lung function and symptoms, some other studies also investigated effects on mucociliary clearance. Meaningful changes in lung function were limited: the change in FEV_1 was generally within 20%. The lowest level of notable irritation was 0.23 mg/m^3 for 120 minutes, as evidenced by the occurrence of symptoms of respiratory irritation.

A recent occupational study in different plants reported breathing zone exposure concentrations of up to 0.87 mg/m^3 and area concentrations of up to 2.78 mg/m^3. Older studies reported much higher are concentrations of up to 35 mg/m^3. Long term exposure of workers resulted in dental erosion, pathological changes of the nasal mucosa, and a slight increase in the incidence of bronchitis. In general, workers included in the occupational studies had a long exposure history, which make the studies less suitable for

the assessment of short-term effects. It was however clear that the concentrations in these studies would not impair the persons ability to escape or induce severe short-term toxic effects.

There was no human data on neurotoxicity, developmental / reproductive toxicity, and genotoxicity. The IARC classified strong-inorganic-acid mists as carcinogenic to humans.

3. ANIMAL TOXICITY DATA

The guinea pig has been frequently used as an animal model to study the effects of sulfuric acid inhalations. This animal species appeared to be far more sensitive than other animal species. In paragraph "4.3.2 Species variability in effects" is explained why the guinea pig is not a suitable species to use as a model for predicting effects in humans. For the reasons stated there, the studies with guinea pigs are not included in this TSD.

3.1. Acute lethality

3.1.1. Rats

Groups of two rats (strain and sex not given) were exposed (2.75-7 h/day, 1-5 days; whole body) to an actual concentration of 87-1610 mg/m^3 sulfuric acid mist generated from an aqueous solution of sulfuric acid (93-99%: <2 µm in diameter; many about 1 µm measured with a photograph of a slide after thermal precipitation) (Treon *et al.* 1950). The follow-up period after exposure was not stated but included at least 9 days after the last exposure. Animals survived a 3.5-h exposure to concentrations up to and including 718 mg/m^3. At 7 h of exposure, in general animals survived up to and including 461 mg/m^3. At 383 mg/m^3, however, one rat died during the first 7-h period of exposure (and the second rat during the second period), indicating that some variability in the response of rats might be present. At concentrations from 699 mg/m^3 and higher all animals died within 7 h of exposure. At non-lethal concentrations animals exhibited signs of intoxication by rubbing their noses, sneezing labored respiration. Lethal concentrations further induced signs of respiratory irritation, gasping and distress. In the lungs atelectasis, emphysema, swelling of septal cells, mucin and leukocytes in the lumen of bronchioles, epithelial cell degeneration (at all concentrations tested), hyperemia (≥218 mg/m^3), pulmonary hemorrhage and edema, engorgement of interlobular lymphatics and interstitial edema (at higher concentrations) preceded death. Half of the deaths among rats exposed on one occasion occurred during exposure, the remainder occurring within 17 hours to three days thereafter. The only exception was one rat that did not die until five days after exposure.

At repeated exposures, both animals survived a 5-days exposure of 203 mg/m^3 (7 h/day). At 670 and 839 mg/m^3 (7 h/day) the animals died after 2 and 3 days respectively, indicating that some variability in the response of rats might be present.

Groups of five male or female Sprague-Dawley rats were exposed for 1 h to fuming sulfuric acid in bell jars or large desiccators (Vernot *et al.* 1977). For males a 1-h LC_{50}-value of 420 (95% confidence limits: 397-444) ppm was found and for females a 1-h LC_{50}-value of 347 (95% confidence limits: 260-464) ppm. The SO_3 content of the fuming sulfuric acid was not given. It is not clear what exactly was measured (SO_3 or H_2SO_4 or both) and what methods were used to generate, control and monitor the exposure. Results are expressed in ppm. No information is provided on the particle size of the mist or on the follow-up period. For these reasons, the results can not be used for AEGL-development and are not included in Table 5.

Groups of ten male SPF-reared rats (Cpb:WU; Wistar random) were exposed (whole body) to sulfuric acid mist (airflow: 2 l/min; mean H_2O/H_2SO_4 ratio: 0.8; particle size not determined) at a temperature of 21 ± 1 °C (Zwart *et al*. 1984). Two groups were exposed for 60 min to an actual concentration of H_2SO_4 of 3940 ± 90 mg/m^3 and 3540 ± 30 g/m^3, one group for 105 min to 3870 ± 100 mg/m^3 and one group for 150 min to 3610 ± 130 mg/m^3. After exposure, survivors were observed for two weeks, followed by autopsy.

Most of the animals died on the day of exposure (day 0) or the day thereafter (day 1). The mortality on day 1 was 4/10 and 1/10 (60 min), 5/10 (105 min), and 5/10 (150 min). Only 9/40 animals survived the 14-d observation period. Unrest, irritation of the eyes, salivation, sniffing, mouth breathing (during exposure), labored respiration, and body weight loss (during exposure and consecutive days) was seen. Dead animals showed discharges around nares, eyes, mouth and anus, gas in stomach and/or intestines, gray spotted and red colored lungs or hemorrhages. Sacrificed animals (day 14) showed gray spotted lungs. The 1-h LC_{50} was calculated to be 3600 mg H_2SO_4/m^3 air (70% confidence limits: 3100-3700 mg/m^3).

Groups of 4 male and 4 female Fischer 344 rats were whole-body exposed for 1, 2, 4 or 8 hours to a sulfuric acid aerosol with a MMAD of 1.1 to 1.4 µm and concentrations of 240, 470, 730, 800, 1090 or 1080 mg/m^3 (Runkle and Hahn 1976). The aerosol was produced by mixing of SO_3 with humidified air. The sulfuric acid concentration was measured after collection on filters or on the stages of a mercer cascade impactor by two methods. The results of the rapid determination with a conductivity bridge usually agreed within 5% with the results using the barium chloranilate method of Barton. The relative humidity was maintained at 40%. The method for the determination of the particle size was not stated but probably involved the cascade impactor. Animals were held for 21 days at which time survivors were sacrificed.

The LC_{50} values were approximately 375 and 425 mg/m^3 for 4 and 8 hours exposure, respectively. The mortality in rats can be divided into rats dying during or shortly after exposure at high dose and or longer exposure periods or rats dying at several days after the exposure at lower concentrations or shorter exposure periods. These differences are also reflected in the lung pathology. In rats dying acutely, ulceration of turbinates, trachea and larynx was seen while in the other rats fibrosis of the larynx and bronchopneumonia associated with aspirated foreign material was seen.

3.1.2. Mice

Groups of five mice (strain and sex not given) were exposed (2.75-7 h/day, 1-5 days; whole body) to an actual concentration of 87-1610 mg/m^3 of sulfuric acid mist generated from an aqueous solution of sulfuric acid (93-99%: <2 µm in diameter; many about 1 µm measured with a photograph of a slide after thermal precipitation) (Treon *et al.* 1950). The follow-up period after exposure was not stated but included at least 9 days after the last exposure. All animals survived a 2.75-h exposure of 87 mg/m^3. At 7-h of exposure, all animals survived up to and including 461 mg/m^3. At concentrations from 549 mg/m^3 up to 1470 mg/m^3 two or three animals/group died during 3.5 h of exposure. The lower mortality found at 3.5 h of exposure to 1470 mg/m^3 (2/5) compared to 718 mg/m^3 (3/5) indicates that some variability in the response of mice might exist. Two or three deaths were also found after 7 h of exposure to 699 mg/m^3 and 1610 mg/m^3. The similar results at 3.5 h and 7 h of exposure indicate that this two times increase in exposure time did not influence mortality. Non-lethal exposure of 203 mg/m^3 induced labored respiration after 7 h. At lethal concentrations pawing of the nose, sneezing, labored respiration, grasping and distress were seen. In the lungs hemorrhage (at all concentrations tested), and edema (≥190 mg/m^3) preceded death. In the larynx and trachea epithelial cell degradation and small focal ulcers with inflammatory cell infiltration were seen accompanied by congestion of the mucosa and submucosa of the respiratory tract (≥190 mg/m^3).

Half of the deaths among mice exposed on one occasion occurred during exposure, the remainder occurring within 17 hours to three days thereafter.

At longer exposure times, all mice survived a 5-day exposure of 203 mg/m^3 (7 h/day). A 5-d exposure of 383 mg/m^3 (7 h/day) resulted in four dead animals, while a 2-day exposure of 670 mg/m^3 and 1160 mg/m^3 (7 h/day) resulted in five dead animals. At a 3-day exposure of 839 mg/m^3 (7 h/day) only three dead animals were found, indicating that some variability in the response of mice might exist.

Groups of 5-7 male and 5-7 female CD-1 mice were whole-body exposed for 1, 2, 4 or 8 hours to a sulfuric acid aerosol with a MMAD of 0.9 to 1.2 µm and concentrations of 270, 550, 730 or 1040 mg/m^3 (Runkle and Hahn 1976). The methods used to determine the concentration and the particle size were not described. Animals were held for 21 days at which time survivors were sacrificed.

The LC_{50} values were approximately 850 and 600 mg/m^3 for 4 and 8 hours exposure, respectively. Only two mice showed ulcerations of the turbinates or the trachea and non showed ulceration of the larynx. Approximately ten mice showed lung lesions resulting from pneumonia, which appeared to be associated with aspiration of foreign material.

3.1.3. Rabbits

Groups of two rabbits (strain and sex not given) were exposed (2.75-7 h/day, 1-5 days; whole body) to an actual concentration of 87-1610 mg/m^3 of sulfuric acid mist generated from an aqueous solution of sulfuric acid (93-99%: <2 µm in diameter; many about 1 µm measured with a photograph of a slide after thermal precipitation) (Treon *et al.* 1950). The follow-up period after exposure was not stated but included at least 9 days after the last exposure. All animals survived a 2.75-h exposure of 87 mg/m^3. At 3.5 h of exposure all animals survived up to and including 718 mg/m^3 and at 7 h of exposure up to and including 699 mg/m^3. One out of two rabbits died at 3.5 h exposure to 1470 mg/m^3 and at 7 h exposure to 1610 mg/m^3. These two rabbits succumbed 12 h after being exposed.

At non-lethal concentrations, the first sign of intoxication was rubbing of the nose, followed by sneezing. After 7 h of exposure to 839 mg/m^3 an audible rasping sound was heard in association with breathing of the rabbits. At lethal concentrations signs of respiratory irritation and distress were observed. In the lungs hemorrhage, edema, desquamation of epithelial cells, shreds of degenerating material (≥218 mg/m^3), atelectasis and emphysema (both with inflammatory cells) (≥461 mg/m^3) preceded death. The larynx and trachea showed cell degeneration and edema.

At longer exposure times, all rabbits survived a 5 days exposure of 203 mg/m^3 (7 h/day) and a 3-day exposure of 839 mg/m^3. Rabbits died after a 5 d exposure of 383 mg/m^3 (7 h/day) and a 4 days exposure of 1160 mg/m^3 (7 h/day). At 839 mg/m^3 first an audible rasping sound in association with breathing was heard, followed by signs of respiratory irritation and distress. Several days at 383 mg/m^3 or more induced pawing of the nose, sneezing, labored respiration and gasping.

3.1.4. Other species

One cat (strain and sex not given) was exposed (whole body) for 7 h to an actual concentration of 461 mg/m^3 sulfuric acid mist and survived (Treon *et al.* 1950). The cat showed salivation, a striking response of cats to irritant materials in air. Postmortem examination of the lungs showed numerous partially atelectatic alveoli, a few areas of definite emphysema, numerous small hemorrhages and severe congestion of the lungs. Shreds of desquamated epithelium were seen in the lumen of the bronchioles and

mucous degeneration of the cells lining the bronchi occurred. The trachea showed marked infiltration of polymorphonuclear granulocytes and there was edema of the vocal folds infiltrated with leukocytes.

In a study with monkeys (Schwartz *et al*. 1977; see description in the non-lethal section), concentrations of 502 mg/m^3 for 7 days did not result in mortality.

Table 5. Summary of Acute lethal Inhalation Data in Laboratory Animals

Species	Particle size	Duration	Dose (mg/m^3)	Mortality	Reference
Monkey	0.3 – 0.6 µm	7 days	502	0/2	Schwartz *et al*. 1977
Rat	93-99%: <2 µm	7 hours	1610	2/2	Treon *et al*. 1950
			699	2/2	
			461	0/2	
			218	0/2	
			190	0/2	
		3.5 hours	1470	2/2	
			718	0/2	
			549	0/2	
		2.75 hours	87	0/2	
		4 * 7 hours	1160	2/2 (within 7 hours)	
		2 * 7 hours	839	2/2	
		3 * 7 hours	670	2/2	
		5 * 7 hours	383	2/2 (within 7/14 hours)	
		5 * 7 hours	203	0/2	
Rat	Unknown	60 minutes	3940	9/10	Zwart 1984
		60 minutes	3540	5/10	
		105 minutes	3870	10/10	
		150 minutes	3610	7/10	
Rat	MMAD: 1.1 –1.4 µm	1 hour	240	0/8	Runkle and Hahn 1976
			470	1/8	
			730	1/8	
			800	0/8	
			1090	0/8	
		2 hours	240	0/8	
			470	0/8	
			730	3/8	
			800	5/8	
			1090	3/8	
		4 hours	240	0/8	
			470	5/8	
			730	5/8	
			800	6/8	
			1090	5/8	
			1080	7/8	
		8 hours	240	0/8	
			470	7/8	
			730	7/8	
			800	7/8	
			1080	8/8	

Species	Particle size	Duration	Dose (mg/m^3)	Mortality	Reference
Mouse	MMAD: 0.9 – 1.2 µm	1 hour	270	0/10	Runkle and Hahn 1976
			550	0/10	
			730	3/10	
			1040	4-5/12	
		2 hours	270	0/10	
			550	0/10	
			730	1/10	
			1040	8/14	
		4 hours	270	0-1/10	
			550	2/10	
			730	3/10	
			1040	11/14	
		8 hours	270	0/10	
			550	4/10	
			730	7/10	
Mouse	93-99%: <2 µm	7 hours	1610	3/5	Treon *et al*. 1950
			699	2/5	
			461	0/5	
			218	0/5	
			190	0/5	
		3.5 hours	1470	2/5	
			718	3/5	
			549	2/5	
		2.75 hours	87	0/5	
		4 * 7 hours¶	1160	5/5 (within 7/14 hours	
		3 * 7 hours¶	839	3/5	
		2 * 7 hours¶	670	5/5	
		5 * 7 hours¶	383	4/5	
		5 * 7 hours¶	203	0/5	
Rabbit	93-99%: <2 µm	7 hours	1610	1/2	Treon *et al*. 1950
			699	0/2	
			461	0/2	
			218	0/2	
			190	0/2	
		3.5 hours	1470	1/2	
			718	0/2	
			549	0/2	
		2.75 hours	87	0/2	
		4 * 7 hours¶	1160	2/2	
		3 * 7 hours¶	839	0/2	
		2 * 7 hours¶	670	0/2	
		5 * 7 hours¶	383	2/2	
		5 * 7 hours¶	203	0/2	
Cat	93-99%: <2 µm	7 hours	461	0/1	Treon *et al*. 1950

¶ Repeated dose study: duration refers to number of exposure days times number of hours per day.

3.2. Nonlethal toxicity

Mucous clearance and comparable effects such as ciliary beating frequency and infective models are not summarized because the response was variable in humans and it is unknown to what AEGL level these effects could lead.

3.2.1. Monkeys

Groups of nine cynomolgus monkeys (*Macaca iris*, strain not given, 5m/4f or 4m/5f) were exposed (whole body) for 78 weeks to 0 (control), 0.38 ± 0.18 (MMD: 2.15 ± 0.64 µm), 2.43 ± 0.80 (MMD: 3.60 ± 1.25 µm), 0.48 ± 0.19 (MMD: 0.54 ± 0.56 µm), and 4.79 ± 1.82 (MMD: 0.73 ± 0.38 µm) mg/m^3 H_2SO_4 mist (Alarie *et al*. 1973). Exposure was only interrupted for 20 minutes a day and for testing. There were no differences in body weight, body weight gain and mortality between the groups. Some statistical significant changes were seen in some mechanical properties of the lung especially in the high dose groups. The affected parameters were increased respiratory rate and increased distribution of ventilation. The high dose group with large particles also showed a reduction of the PaO_2 compared to the controls after 77 weeks of exposure. Microscopic examination showed no changes in the lungs of animals treated with the low dose and the small particles. In the animals treated with the low dose and the large particles, hyperplasia of the bronchiolar epithelium, slight thickening of the walls of the respiratory bronchioles and focal bronchial epithelial hyperplasia was seen in some animals. At the higher dose, both groups showed hyperplasia and hypertrophy of the bronchiolar epithelium and hyperplasia of the bronchial epithelium. The walls of the bronchioles were focally thickened and there was focal replacement of normal epithelium with cuboidal epithelium. Animals treated with large particles showed an increase in the thickness of the alveolar septa sometimes accompanied by hyperplasia and hypertrophy of the alveolar cells. Animals treated with small particles also showed an increase in the amount of connective tissue stroma and smooth muscle of the bronchioles.

Exposure of one monkey to 60 mg/m^3 SO_3 and 2-3 mg/m^3 HCl during 6 hours a day for 7 days resulted in lung damage only (Cameron 1954). Exposure of another monkey to 30 mg/m^3 SO_3 and 2 mg/m^3 HCl during 6 hours a day for 14 days did not resulted in an effect.

Groups of 2 female rhesus monkeys (Macaca mulatta) were whole body exposed to an aerosol of sulfuric acid at a concentration of 150 mg/m^3 for 3 days, 361 mg/m^3 for 7 days or 502 mg/m^3 for 7 days (Schwartz *et al*. 1977). The number of hours of exposure per day was not specified. There was no concurrent control group but controls from other studies were used . The MMAD or CMD was determined with a seven-stage impactor or optical particle counting at 0.3 to 0.6 µm. Sulfate concentrations were determined with the barium chloranilate procedure after collection on membrane filters with a pore size of 0.2 µm. Morphological alterations were not seen in the nasal septum, trachea, major bronchi, and terminal respiratory units. Changes in histochemical characteristics of airway mucosubstance were not observed.

3.2.2. Dogs

The tracheal mucus clearance was measured by using a radioactive protein in 8 Beagle dogs after a single one hour exposure to 0, 0.5 (0.9 µm MMAD), 1.0 (0.9 µm), 1.0 (0.3 µm) and 5.0 (0.3 µm) mg/m^3 H_2SO_4 (Wolff *et al*. 1981). Exposure to the 0.9 µm particles resulted in reddening of the pharyngeal, laryngeal and tracheal mucosa as seen directly after exposure. In the 0.3 µm group, mild mucosal reddening was seen in one animal only. There was a drift of baseline values towards slower tracheal mucus clearance over the course of all experiments. Statistical significant reductions were only seen at one week after exposure in dogs treated with 0.5 mg/m^3 (0.9 µm) and at 30 minutes, one day and 1 week

after treatment with 1.0 mg/m^3 (0.9 µm). Non significant increases were seen at 30 minutes and 1 day after treatment with 0.5 mg/m^3 (0.9 µm). All changes were reversible within 5 weeks.

A 7.5 minutes exposure of anesthetized Mongrel dogs (n=5) to 1 or 8 mg/m^3 H_2SO_4 (mean diameter 0.1 – 0.2 µm) with a orotracheal tube did not significantly affect respiratory resistance, functional residual capacity, lung compliance, specific lung compliance or specific respiratory conductance as measured up to 30 minutes after cessation of exposure (Sackner *et al*. 1978). A 4 hour exposure to 4 mg/m^3 (mean diameter 0.2 µm) did not affect total respiratory resistance, specific respiratory conductance, lung compliance, specific lung compliance, functional residual capacity, pulmonary and systemic arterial blood pressures, cardiac output, heart rate, stroke volume, or arterial blood gas tensions.

3.2.3. Rats

Exposure of 20 rats to 60 mg/m^3 SO_3 and 2-3 mg/m^3 HCl during 6 hours a day for 9 days and a preliminary exposure to 30 mg/m^3 did not result in mortality or lung damage (Cameron 1954). Exposure of 20 rats to 30 mg/m^3 SO_3 and 2 mg/m^3 HCl during 6 hours a day for 14 days resulted in a 10% mortality and lung damage in 40% of the animals. There was no control group.

Rats were treated with sulfuric acid mist or ozone or the combination. Only the results of the tests with sulfuric acid are summarized (Cavender *et al*. 1977a). Groups of 20 male Fischer rats were exposed for 2 or 7 days to sulfuric acid aerosol with a MMD of 0.9 µm at concentrations of 5 or 10 mg/m^3. The exposure period per day is unknown. No morphologic effects or effects on body weight gain, lung weight or lung/body weight ratio were seen. Groups of 20 rats were exposed for 5 days to sulfuric acid aerosol with a MMD of 0.8 µm at concentrations of 0, 10, 30 and 100 mg/m^3. No morphologic effects were seen in the lung, trachea and nasal cavity. An effect on the body weight of the higher doses was stated in the summary but not in the text.

Groups of 25 male Sprague-Dawley rats were exposed whole body for 82 days for 8 hours per day to sulfuric acid mist with a MMD between 0.2 and 0.4 µm and a concentration of 2 mg/m^3 (Juhos *et al*. 1978). Minimal evidence of hypertrophy of the epithelial lining cells, mainly at the ductal level was seen. There was no effect on body weight, lung weight, total lung capacity, filling time, hematocrit and hemoglobin. The number of red blood cells per ml was increased.

Groups of 10 female Wistar rats were exposed nose-only for 5 or 28 days, for 6 hours a day, for 5 days a week to an aerosol of sulfuric acid with a MMAD between 0.6 and 0.9 µm at concentrations of 0, 0.30, 1.38 or 5.52 mg/m^3 (Kilgour *et al*. 2002). Recovery groups of 5 animals were exposed for 28 days to 0 or 5.52 mg/m^3 and retained for 4 or 8 weeks after exposure. No effects on body weight and lung weight or adverse clinical effects were seen. No histopathological changes or changes in cell proliferation were seen in the lung or nasal cavity. A five day exposure to 1.38 and 5.52 mg/m^3 resulted in squamous metaplasia of the ventral epithelium at level 1 of the larynx. The severity was dose dependent and in the more severe cases the squamous epithelium was keratinized. A 28 day exposure to 1.38 and 5.52 mg/m^3 resulted in squamous metaplasia of the ventral epithelium at level 1 of the larynx. This effect was also evident at level 2 at the highest concentration. Parakeratosis was also seen in some animals at this level of the larynx. Minimal squamous metaplasia at level 1 was seen in some animals at 0.30 mg/m^3. Less severe squamous epithelial metaplasia was seen following 4 week recovery. However, no signs of further resolution were seen after 8 weeks of recovery. The proliferation of the cells at level 1 of the larynx was increased at the highest concentration after 5 and 28 days exposure.

Groups of 6 or 10 male Sprague-Dawley rats were exposed nose-only for 2 days for 4 hours per day to an aerosol of sulfuric acid with a MMD of 0.06 µm or 0.3 µm at a concentration of 0 or 0.5 mg/m^3

(Kimmel *et al*. 1997). Both particle sizes did not produce morphological changes of the lung, changes in proliferation of the pulmonary parenchyma and periacinar region, breathing pattern and some ventilatory parameters. Only the minute volume was decreased during the second exposure day to the 0.06 µm aerosol.

Groups of 6 male Sprague-Dawley rats were continuously or 12 hours a day exposed whole body for 30 or 90 days to sulfuric acid aerosol with a 0.4 to 0.8 µm diameter at concentrations of 0, 0.02, 0.10 or 0.15 mg/m^3 (Last and Pinkerton 1997). No biochemical or morphometrical changes of the lung were observed.

Groups of 6 female F344 rats were exposed whole body for four hours to an aerosol of sulfuric acid with a MMAD of 0.8 µm at a concentration of 94 mg/m^3 (Lee *et al*. 1999). There was no effect on lung lavage and surfactant parameters and no histopathological changes in the lungs.

Groups of 6 female f344 rats were exposed whole body for 4 hours to an aerosol of sulfuric acid with a MMAD of 0.8 µm at a concentration of 94 mg/m^3 (Lee *et al*. 1995). A several fold increase in the thickness of the mucous layer with exudation of protein-like material was seen. There was no effect on the surface tension of the mucous.

A group of 36 male F344 rats were nose-only exposed for 1 hour to sulfuric acid aerosols with an unknown MMAD at a concentration of 13 mg/m^3. This was the control group for an exposure to beryllium sulfate (Sendelbach *et al*. 1986). The labeling index and histopathological changes were determined in 4 animals at several days between day 1 and day 21 after exposure. No increases in the labeling index of the sulfuric acid exposed rats were stated. A few animals had rare foci with an increase in alveolar macrophages.

Groups of 30 F344/crl rats (sex unknown) were whole body exposed for 6 hours to an aerosol of sulfuric acid with a MMAD of 0.9 µm at a concentration of 0, 1.1, 11 or 96 mg/m^3 (Wolff *et al*. 1986). No changes in the mucociliary clearance or changes in some parameters of the bronchoalveolar lavage fluid were seen. Scanning electron micrographs showed a slight increase in the thickness of the trachea mucus at 11 mg/m^3 and a definite increase at 96 mg/m^3. Morphological changes were seen at an unknown period after exposure of rats to 96 mg/m^3 consisting of a loss of cilia in the airways and ulcerations of the larynx. No effects on the deep lung were seen.

Groups of 6 to 18 male Sprague-Dawley and Long-Evans rats were whole body exposed to an aerosol of sulfuric acid at a concentration of 45 mg/m^3 for 11 days, 68 mg/m^3 for 6 days or 172 mg/m^3 for 7 days (Schwartz *et al*. 1977). There was a concurrent control group. The MMAD or CMD was determined with a seven-stage impactor or optical particle counting at 0.3 to 0.6 µm. Sulfate concentrations were determined with the barium chloranilate procedure after collection on membrane filters with a pore size of 0.2 µm. Morphological alterations were not seen in the nasal septum, trachea, and pulmonary parenchyma. Examination of selected regions by SEM did not show differences between treated and control animals.

3.2.4. Mice

Exposure of 20 mice to 60 mg/m^3 SO_3 and 2-3 mg/m^3 HCl during 6 hours a day for 7 days did not resulted in mortality or lung damage (Cameron 1954). Exposure of 20 mice to 30 mg/m^3 SO_3 and 2 mg/m^3 HCl during 6 hours a day for 14 days resulted in a 10% mortality and lung damage in 10% of the animals. There was no control group.

Exposure of mice for 4 hours to a sulfuric aerosol with a count median diameter of 3.2 µm and a concentration of 15 mg/m^3 did not result in lesions of the nasal and pulmonary epithelium (Fairchild *et al*. 1975).

Exposure of mice to a sulfuric acid aerosol at a concentration of 1 mg/m^3 did not increase the levels of allergic lung sensitization towards an aerosolized ovalbumin (Osebold *et al*. 1980).

A group of 36 male BALB/c mice were nose-only exposed for 1 hour to an aerosol of sulfuric acid with an unknown MMAD at a concentration of 13 mg/m^3. This was the control group for an exposure to beryllium sulfate. The labeling index and histopathological changes were determined in 4 animals at several days between day 1 and day 21 after exposure. A small increase in the labeling index of the alveolar parenchymal cells was seen around day 9 in the sulfuric acid exposed mice. No histopathological changes were reported.

Groups of 8 to 45 male Swiss-Webster mice were whole body exposed to an aerosol of sulfuric acid at a concentration of 140 mg/m^3 for 14 days, or 170 mg/m^3 for 10 days (Schwartz *et al*. 1977). There was a concurrent control group. The MMAD was determined with a seven-stage impactor at 0.3 to 0.6 µm. Sulfate concentrations were determined with the barium chloranilate procedure after collection on membrane filters with a pore size of 0.2 µm. Lesions were only observed within the larynx and upper trachea and generally confined to the posterior and ventral portion of the larynx and extended no further than 2-3 mm into the trachea. The surface epithelium was ulcerated and the adjoining connective tissue stroma was edematous and heavily infiltrated with neutrophils. Adjacent cartilage did not appear to be affected. This focal necrotizing laryngitis was observed as early as 24 hr after the initial acid exposure and persisted throughout a 7-day exposure period. Cellular components of the inflammatory response became spindloid and fibrous in character with increasing length of exposure, but regions of ulceration persisted. Lesions within the upper trachea were similar in nature to those of the larynx and were characterized by ulceration, accumulation of cellular debris, and inflammatory cell infiltrates.

3.2.5. Rabbits

Groups of 5 new Zealand White rabbits were exposed for 3 hours to an aerosol (MMD: 0.3 µm) at a concentration of 0, 0.050 or 0.125 mg/m^3 (Chen *et al*. 1995). The internal pH of the macrophages obtained by lung lavage was decreased after exposure to 0.125 mg/m^3 but not after exposure to 0.050 mg/m^3. Exposure to 0.050 mg/m^3 reduced the ability of the macrophages to extrude H^+ after temporary acidification.

Groups of 4 male New Zealand white rabbits were exposed nose only during 1 hr a day, 5 days a week for 4, 8 or 12 months to an aerosol of sulfuric acid at a concentration of 0 or 0.25 mg/m^3 with a MMD of 0.3 µm (Gearhart and Schlesinger 1986). The treatment did not affect the pulmonary resistance, dynamic compliance and respiratory rate before the challenge with acetylcholine. The treatment with sulfuric acid during 4, 8 and 12 months reduced the amount of acetylcholine necessary for a 50% increase in pulmonary resistance. The changes of the dynamic compliance and respiratory rate to challenge with acetylcholine were not affected by the treatment with sulfuric acid.

3.2.6. Other species

Exposure of 4 donkeys to 0.1 mg/m^3 H_2SO_4 (MMAD: 0.5 µm) for 1 hr/day, 5 days/week for 6 months resulted in erratic bronchial clearance of radioactive ferric oxide during the first week of exposure and sustained impairment in two animals towards the end of the exposure period and in a 3 months follow up period (Schlesinger *et al*. 1979).

Exposure of 4 donkeys to 1.4 mg/m^3 H_2SO_4 (MMAD: 0.4 µm) and below for 1 hour did not result in changes of the pulmonary resistance, the dynamic compliance and regional deposition of ferric oxide aerosol (Schlesinger *et al*. 1978). The tracheobronchial clearance was temporarily reduced in 3 out of 4 donkeys after exposure to 0.2 to 1.4 mg/m^3 and more persistently reduced in 2 out of 4 animals.

Exposure of two goats to 60 mg/m^3 SO_3 and 2-3 mg/m^3 HCl during 6 hours a day for 9 days did not resulted in a effect (Cameron 1954). Exposure of two goats to 30 mg/m^3 SO_3 and 2 mg/m^3 HCl during 6 hours a day for 14 days resulted in mild lung damage in one of the goats.

A 20 minutes exposure of sheep (n=6) to 1, 8 or 14 mg/m^3 H_2SO_4 (mean diameter 0.1 – 0.2 µm) did not significantly affect the tracheal mucous velocity, respiratory frequency, tidal volume, and minute ventilation (Sackner *et al*. 1978). A 4 hour exposure to 4 mg/m^3 (mean diameter 0.2 µm) did not affect the tracheal mucous velocity.

Table 6. Non lethal toxicity

Species	Dose	Particle size	Duration	Effect	Assessment	Reference
Monkey	0.4 – 0.5 mg/m^3	0.5 or 2 µm	24 hr/day, 78 weeks	Minimal adaptive microscopic changes of the lung	No effect level	Alarie *et al*. 1973
Monkey	2.4 –4.8 mg/m^3	0.7 or 2 µm	24 hr/day, 78 weeks	Adaptive microscopic changes of the lung and mechanical lung changes	Minimal effect level	Alarie *et al*. 1973
Monkey	30 mg/m^3	Unknown	6 hr/day, 14 days	None	No effect level	Cameron 1954
Monkey	60 mg/m^3	Unknown	6 hr/day, 7 days	Changes of the lung	Minimal effect level	Cameron 1954
Monkey	502 mg/m^3	0.3 to 0.6 µm	7 days	No histological changes	No effect level	Schwartz *et al*. 1977
Dog	0.5 mg/m^3	0.9 µm	1 hour	Changes in tracheal mucus clearance, reversible	Minimal effect level	Wolff *et al*. 1981
Dog	1.0 mg/m^3	0.9 µm	1 hour	Changes in tracheal mucus clearance, reversible	Minimal effect level	Wolff *et al*. 1981
Dog	1.0 mg/m^3	0.3 µm	1 hour	No changes	No effect level	Wolff *et al*. 1981
Dog	5.0 mg/m^3	0.3 µm	1 hour	No changes	No effect level	Wolff *et al*. 1981
Dog	8 mg/m^3	0.1-0.2 µm	7.5 minutes	None	No effect level	Sackner *et al*. 1978
Dog	4 mg/m^3	0.2 µm	4 hours	None	No effect level	Sackner *et al*. 1978
Donkey	0.1 mg/m^3	0.5 µm	1 hr/day, 5 days/week, 6 months	Changes in lung particle clearance, non reversible	Minimal effect level	Schlesinger *et al*. 1979
Donkey	0.2 to 1.4 mg/m^3	0.4 µm	1 hr	Changes in tracheobronchial clearance	Minimal effect level	Schlesinger *et al*. 1978
Goat	30 mg/m^3	Unknown	6 hr/day, 14 days	Mild lung changes	Minimal effect level	Cameron 1954
Goat	60 mg/m^3	Unknown	6 hr/day, 9 days	None	No effect level	Cameron 1954
Goat	14 mg/m^3	0.1-0.2 µm	20 minutes	None	No effect level	Sackner *et al*. 1978
Goat	4 mg/m^3	0.2 µm	4 hours	None	No effect level	Sackner *et al*. 1978

Species	Dose	Particle size	Duration	Effect	Assessment	Reference
Rabbit	0.125 mg/m^3	0.3 µm	3 hours	Decreased internal pH	Minimal effect level	Chen *et al*. 1995
Rabbit	0.05 mg/m^3	0.3 µm	3 hours	Reduced pH regulation	Minimal effect level	Chen *et al*. 1995
Rabbit	0.25 mg/m^3	0.3 µm	1 hour/day, 5 days/week, 4, 8 or 12 months	Increased sensitivity to acetylcholine challenge	Minimal effect level	Gearhart and Schlesinger 1986
Rabbit	87 – 218 mg/m^3	93-99% < 2 µm	2.75 to 7 hr	Occasional rubbing of their noses with their forefeet	Minimal effect level	Treon *et al*. 1950
	461 mg/m^3	93-99% < 2 µm	7 hr	sneezing	Minimal effect level	
	840 mg/m^3 and above	93-99% < 2 µm	7 hr	Signs of respiratory irritation and distress and an audible rasping (but also mortality)	Severe effect level	
	87 – 190 mg/m^3 and above	93-99% < 2 µm	2.75 – 7 hr	Several effects including slight hyperemia and edema of sectors of the tracheas, larynges and nose	Severe effect level	
	218 mg/m^3 and above	93-99% < 2 µm	7 hr	Focal areas of hemorrhage and edema in the peripheral portions of the lung and desquamation of the bronchiolar epithelial cells	Severe effect level	
	416 mg/m^3 and above	93-99% < 2 µm	7 hr	Extensive patches of complete atelectasis and emphysema of the aerated portions of the lungs. Ulcer on the larynx	Severe effect level	
Rat	30 mg/m^3	Unknown	6 hr/day, 14 days	10% mortality and 40% lung damage	Severe effect level	Cameron 1954
Rat	60 mg/m^3	Unknown	6 hr/day, 9 days	None	No effect level	Cameron 1954
Rat	5 mg/m^3	0.9 µm	2 and 7 days	No effects	No effect level	Cavender *et al*. 1977a
Rat	10 mg/m^3	0.9 µm	2, 5 and 7 days	No effects	No effect level	Cavender *et al*. 1977a
Rat	30 mg/m^3	0.9 µm	5 days	No effects or body weight reduction	Unknown	Cavender *et al*. 1977a
Rat	100 mg/m^3	0.9 µm	5 days	No effects or body weight reduction	Unknown	Cavender *et al*. 1977a
Rat	2 mg/m^3	0.2 – 0.4 µm	8 hr/day, 82 days	Increase RBC	No effect level	Juhos *et al*. 1978
Rat	0.30 mg/m^3	0.6 µm	5 days, 6 hour per day	No effects	No effect level	Kilgour *et al*. 2002
	1.38 mg/m^3	0.8 µm		Histopathological changes of the larynx	Effect level	
	5.52 mg/m^3	0.9 µm		Histopathological changes of the larynx with increased proliferation	Effect level	
Rat	0.30 mg/m^3	0.6 µm	28 days, 5 days a week, 6 hours a day	Minimal histopathological changes of the larynx	Minimal effect level	

Species	Dose	Particle size	Duration	Effect	Assessment	Reference
	1.38 mg/m^3	0.8 µm		Histopathological changes of the larynx	Effect level	
	5.52 mg/m^3	0.9 µm		Histopathological changes of the larynx with increased proliferation, only partial reversible	Irreversible effects	
Rat	0.5 mg/m^3	0.06 µm	2 days, 4 hours a day	Reduction in minute volume	Minimal effect level	Kimmel *et al.* 1997
		0.3 µm		No effects	No effect level	
Rat	0.02 – 0.50 mg/m^3	0.2 – 0.4 µm	Continuously or 12 hours a day for 30 or 90 days	No biochemical or morphometrical effects on the lung	No effect level.	Last and Pinkerton 1997
Rat	94 mg/m^3	0.8 µm	4 hours	No effects	No effect level	Lee *et al.* 1999
Rat	94 mg/m^3	0.8 µm	4 hours	Increase in the thickness of the mucous layer.	Minimal effect level	Lee *et al.* 1995
Rat	13 mg/m^3	Unknown	1 hour	No effects	No effect level	Sendelbach *et al.* 1986
Rat	1.1 mg/m^3	0.9 µm	6 hours	No effects	No effect level	Wolff *et al.* 1986
	11 mg/m^3	0.9 µm	6 hours	slight increase in the thickness of the trachea mucus	Minimal effect level	
	96 mg/m^3	0.9 µm	6 hours	increase in the thickness of the trachea mucus, loss of cilia in the airways and ulcerations of the larynx	Severe effect level	
Rat	172 mg/m^3	0.3 to 0.6 µm	7 days	No histological changes	No effect level	Schwartz *et al.* 1977
Rat	87 – 218 mg/m^3	93-99% < 2 µm	2.75 to 7 hr	Occasional rubbing of their noses with their forefeet	Minimal effect level	Treon *et al.* 1950
	461 mg/m^3	93-99% < 2 µm	7 hr	sneezing	Minimal effect level	
	840 mg/m^3 and above	93-99% < 2 µm	7 hr	Signs of respiratory irritation and distress (but also mortality)	Severe effect level	
	87 mg/m^3	93-99% < 2 µm	2.75 hr and longer	Focal atelectasis of some lobules and emphysema of others, swelling of septal cells	Minimal effect level	
	218 mg/m^3 and above	93-99% < 2 µm	3.5 hr and longer	Extensive hyperemia of the lungs with areas of pulmonary hemorrhage	Severe effect level	
Mouse	203 mg/m^3	93-99% < 2 µm	7 hr	Labored respiration	Minimal effect level	Treon *et al.* 1950
	840 mg/m^3 and above	93-99% < 2 µm	7 hr	Signs of respiratory irritation and distress (but also mortality)	Severe effect level	
	87 mg/m^3 and above	93-99% < 2 µm	3.5 hr and longer	Focal hemorrhages of the lung	Minimal effect level	
	190 mg/m^3 and above	93-99% < 2 µm	3.5 hr and longer	Small amounts of edema in the in the peritruncal tissues and alveoli	Severe effect level	

Species	Dose	Particle size	Duration	Effect	Assessment	Reference
	1160 mg/m^3 and above	93-99% < 2 µm	3.5 hr and longer	Impressive degenerative changes in the cells lining the larynges and trachea with occasional small focal ulcers, infiltration of the ulcerated areas with polymorphonuclear granulocytes and congestion of the mucosa and submucosa of the respiratory tract.	Severe effect level	
Mouse	30 mg/m^3	Unknown	6 hr/day, 14 days	10% mortality and 10% lung damage	Severe effect level	Cameron 1954
Mouse	60 mg/m^3	Unknown	6 hr/day, 9 days	None	No effect level	Cameron 1954
Mouse	15 mg/m^3	3.2 µm	4 hours	No lesions of nasal and pulmonary epithelium	No effect level	Fairchild *et al*. 1975
Mouse	1 mg/m^3	0.04 µm				
Mouse	13 mg/m^3	Unknown	1 hour	Small increase in alveolar parenchymal cells	Minimal effect level	Sendelbach *et al*. 1986
Mouse	140-170 mg/m^3	0.3 to 0.6 µm	10 - 14 days	Ulceration of the epithelium of the larynx and upper trachea	Severe effect level	Schwartz *et al*. 1977
Hamster	300 mg/m^3	2.6 µm	6 hours	Nasal and eye irritation, slight dispnea, body weight loss, partial etelectasis, focal emphysema and slight thickening of the alveolar septa.	Effect level	Laskin and Sellakumar 1978
Hamster	100 mg/m^3	2.6 µm	6 hours, 5 days a week, 30 days	Slight increase in the incidence of laryngeal hyperplasia and squamous metaplasia	Effect level	Laskin and Sellakumar 1978

3.3. Developmental / Reproductive toxicity

Groups of 35 or 40 pregnant mice were whole body exposed for 7 hours a day from day 6 to 15 to sulfuric acid aerosol with a CMD of 1.6 or 2.4 µm at a concentration of 0, 5.7 or 19.3 mg/m^3 (Murray *et al*. 1979). There were no effects on maternal appearance, incidence of pregnancy, body weight gain and gross and microscopic appearance of the nasal turbinates, trachea and lungs. The food consumption was reduced during the first days and the liver weight was reduced at the highest concentration. There was no embryo- and fetotoxicity and no significant increases in malformations.

Groups of 20 pregnant rabbits were whole body exposed for 7 hours a day from day 6 to 18 to sulfuric acid aerosol with a CMD of 1.6 or 2.4 µm at a concentration of 0, 5.7 or 19.3 mg/m^3 (Murray *et al*. 1979). There were no effects on maternal appearance, incidence of pregnancy and liver weight. The body weight gain was reduced during the first days at the highest concentration. A dose related increase was found of the incidence of subacute rhinitis and tracheitis but no changes in the lung. There was no embryo- and fetotoxicity and no significant increases in malformations. There was only a statistical significant increase in the incidence of small non-ossified areas in the skull bones (a minor variation in skeletal development).

3.4. Genotoxicity

The genetic and related effects of sulfuric acid and other inorganic acids are summarized by the IARC (1992):

"4.4.2 Experimental systems

Genotoxicity under extreme conditions of culture, including pH, has been reviewed (Scott et al., 1991). No data were available on the genetic and related effects of exposures to acid mist in experimental systems; however, the effects of pH reduction have been investigated.

Low pH enhances the level of depurination of isolated DNA (Singer & Grunberger, 1983), and the fidelity of DNA replication and repair enzymes may be reduced by extremes of pH (Brusick, 1986). Low pH did not affect the frequency of point mutations in Salmonella typhimurium (with or without S9), Escherichia coli, Neurospora crassa or Saccharomyces cerevisiae, but it induced gene conversion in S. cerevisiae, chromosomal aberrations in Vicia faba root tips and a variety of mitotic abnormalities in sea urchin embryos and in offspring after treatment of sperm.

In mammalian systems, the genotoxic effects of low pH appear to be strongly enhanced by the presence of S9. Brusick (1986) reported that low pH induced chromosomal aberrations in Chinese hamster ovary cells only in the presence of S9. Morita et al. (1989), however, showed that in the same cells at low pH (5.5 or less) aberrations were also induced in the absence of S9, although S9 greatly enhanced the effect. No chromosomal effect was observed in rat lymphocytes incubated at pH 5.1, either with or without S9. Mutations have been reported in mouse lymphoma L5178Y cells exposed to low pH, both with and without S9, although the effect was only marginal (1.9 fold at pH 6.3) in the absence of S9. Reduction in pH from 7.35 to 6.70, achieved by lowering the concentration of sodium bicarbonate in the medium, resulted in increased transformation frequency in Syrian hamster embryo cells."

3.5. Carcinogenicity

The IARC concluded in 1992 that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic to humans (group 1) (IARC 1992).

A range-finding study was performed in which groups of 10 male hamsters (Syrian golden) were whole body exposed for 6 hours to a mist of sulfuric acid with a MMD of 2.6 µm at a concentration of 0, 300 or 500 mg/m^3 (Laskin and Sellakumar 1978). There was no increase in mortality. The initial responses of the animals were nasal and eye irritation, slight dispnea and a body weight loss of 3 to 4 g for approximately one week. Two animals from each group were sacrificed on day 15. One animal of each group showed partial atelectasis and focal emphysema. All animals showed slight thickening of the alveolar septa on day 30 but no abnormality of the bronchial epithelium.

A range-finding study was performed in which groups of 20 (control) or 40 male hamsters (Syrian golden) were whole body exposed for 30 days, 5 days a week and 6 hours a day to a mist of sulfuric acid with a MMD of 2.6 µm at a concentration of 0 or 100 mg/m^3 (Laskin and Sellakumar 1978). The follow-up period was 92 weeks. The mortality in the treated animals was reduced over the whole follow-up period compared to the control animals which showed a 33% mortality after 24 weeks compared to a mortality of 6% in the treated animals. During the first two weeks the treated animals showed slight respiratory irritation but appeared to be adapted thereafter. A depression of weight gain was seen during the first week in the treated animals. Histopathological examination of the lungs of 5 animals at the interim sacrifice on day 57 did not show exposure-related abnormalities. The major exposure related findings in the terminal sacrifice appeared to be congestion, hemorrhage and edema (data not shown). The treatment also induced a small increase in the incidence of laryngeal hyperplasia and squamous metaplasia.

A initiation-promotion study was performed with 60 male Syrian golden hamsters per group using a single intratracheal exposure to 10 or 40 mg benzo[a]pyrene as initiator and lifetime exposure to 100 mg/m^3 sulfuric acid mist (MMD: 2.6 µm) for 6 hours a day and 5 days a week as promotor (Laskin and Sellakumar 1978). Treatment with sulfuric acid increased the incidence of laryngeal and tracheal hyperplasia but not of tumors of the larynx, trachea or lung. There was no promotor effect of sulfuric acid.

A combination study was performed with 60 male Syrian golden hamsters per group using repeated (15) intratracheal exposure to 10 or 40 mg benzo[a]pyrene and lifetime exposure to 100 mg/m^3 sulfuric acid mist (MMD: 2.6 µm) for 6 hours a day and 5 days a week (Laskin and Sellakumar 1978). The major histological findings in the lungs appeared to be hemorrhage and edema (data not shown). Treatment with sulfuric acid alone did not increase the incidence of laryngeal and tracheal hyperplasia or of tumors of the larynx, trachea or lung. Animals receiving only sulfuric acid showed a moderate hyperplasia of the lining epithelium of the bronchi and mucoid degenerative changes. Diffused septal edema, congestion and areas of thickness of the alveolar septa were seen in a moderate number of animals. Interstitial tissues sometimes developed a high cellular activity containing a mixture of cells with pyknotic nuclei and small mononuclear cells resembling lymphocytes. Crystalline pigment laden macrophages were seen in the alveolar, peribronchial and perivascular areas. Animals dying at later stages developed atelectasis and emphysema (data not shown). There was no synergistic effect of sulfuric acid.

Limited studies on the carcinogenicity of inorganic acid mists does not show a carcinogenic effect according to a review by Swenberg and Beauchamp (1997).

Groups of 30 male and 30 female Wistar rats were treated with: Group 1: 0.5 ml 0.6% sulfuric acid once a week for life by gastric intubations, Group 2: 0.3 ml 0.6% sulfuric acid twice a month for 12 months by intratracheal intubations, Group 3: 0.3 ml 0.6% sulfuric acid twice a month for 12 months by intratracheal intubations and 5 mg benzo[a]pyrene/rat mixed with India black-ink powder in saline twice a month for 2 months intratracheal, Group 4: 5 mg benzo[a]pyrene/rat mixed with India black-ink powder in saline twice a month for 2 months intratracheal, Group 5: untreated control and Group 6: 5 mg India black-ink powder in saline twice a month for 12 months intratracheal in 15 female rats (Uleckiene and Griciute 1997). The animals were observed for their entire life. Gastric intubation of sulfuric acid induced a small increase in benign forestomach tumors ($p<0.1$). Intratracheal exposure to sulfuric acid increased the incidence of malignant tumors and animals with multiple tumors significantly, but the number of respiratory tract tumors increased only from 0/57 in the control rats to 3/56 in the treated animals. Combination of sulfuric acid with benzo[a]pyrene or benzo[a]pyrene alone resulted in 6/52 and 3/49 respiratory tract tumors respectively.

Groups of 30 male and 22 to 27 female CBAxC57Bl mice were treated with: Group 1: 0.2 ml 0.2% sulfuric acid once a week for life by gastric intubations, Group 2: 10 mg urethane/mouse i.p., twice a week, total 10 injections and 0.2 ml 0.2% sulfuric acid once a week for life by gastric intubations, Group 3: 10 mg urethane/mouse i.p., twice a week, total 10 injections, Group 4: untreated controls (Uleckiene and Griciute 1997). Gavage treatment with sulfuric acid only did not increase the number of lung adenomas. Treatment with urethane and urethane plus sulfuric acid resulted in the formation of lung adenomas in all mice. Treatment with sulfuric acid did not significantly increase the number of forestomach papillomas.

3.6. Summary of animal data

Lethality

In rats, a 1 hour LC_{50} of 3600 mg/m^3 (Zwart 1984), a 4 hour LC_{50} of 375 mg/m^3 (Runkle and Hahn 1976) and a 8 hour LC_{50} of 425 mg/m^3 (Runkle and Hahn 1976) were reported. In mice, LC_{50} values for 4 and 8 hour exposures of 600 and 850 mg/m^3, respectively, were reported by Runkle and Hahn (1976). Delayed mortality was seen in several studies and was associated with fibrosis of the larynx and bronchopneumonia with aspirated foreign material in the study on rats by Runkle and Hahn (1976).

The highest concentrations in rats without mortality was 240 mg/m^3 in experiments with 1, 4 and 8 hour exposures (Runckle and Hahn 1976). However, there is some doubt on the 1 hour value. This value is based on the mortality of 1 out of 8 animals at 470 mg/m^3, but higher concentrations did not cause mortality in this one hour study and exposure to 470 mg/m^3 for 2 hours did also not result in mortality. The highest concentrations in mice without mortality were 550 mg/m^3 and 270 mg/m^3 in experiments with 1 and 8 hour exposures (Runckle and Hahn 1976). No level without mortality could be determined for the 4 hour exposure.

In hamsters, no mortality was seen after a 6 hour exposure to 500 mg/m^3 (Laskin and Sellakumar 1978).

Exposure of rhesus monkeys to 502 mg/m^3 for 7 days, of rats for 7 days to 152 mg/m^3 and mice for 10 days to 170 mg/m^3 did not induce mortality (Schwartz *et al*. 1977).

Irritation

Exposure of rats and rabbits to concentrations of 87 mg/m^3 to 218 mg/m^3 showed only occasional rubbing of their noses with their forefeet in the early period of their exposure. A seven hour exposure to 203 mg/m^3 resulted in labored respiration in some mice. Sneezing was observed among rats and rabbits exposed to 461 mg/m^3. Exposure to 840 mg/m^3 and higher induced signs of respiratory irritation in several species (Treon, 1950). A level without effects could not be determined.

Eye and nasal irritation was seen in hamsters at 300 mg/m^3 after a 6 hour exposure (Laskin and Sellakumar 1978). A lower level was not tested.

Slight respiratory irritation was seen during the first two weeks of an exposure of hamsters to 100 mg/m^3 during 6 hours a day and 5 days a week (Laskin and Sellakumar 1978)

All rats exposed to 3500 mg/m^3 and above showed unrest, irritation of the eyes, salivation, sniffing, mouth breathing (during exposure), and labored respiration (Zwart 1984).

Pulmonary function changes

Exposure of dogs up to 8 mg/m^3 for 7.5 minutes or to 4 mg/m^3 for 4 hours did not induce pulmonary function changes (Sackner *et al*. 1978). Exposure of sheep up to 14 mg/m^3 for 20 minutes did not induce pulmonary function changes. Exposure of rats for 2 days during 4 hours a day to 0.5 mg/m^3 (MMD: 0.06 μm) reduced the minute volume.

Pathologic changes of the respiratory tract

Pathological changes of the lung were seen in several species even at the lowest tested concentration of 87 mg/m^3 (2.75 hours) and the changes increased with the concentration (Treon *et al*. 1950). Pulmonary hemorrhage was seen above 218 mg/m^3 in rats. All exposed mice had hemorrhages.

All rats exposed to 3500 mg/m^3 and above showed gray spotted and red colored lungs or hemorrhages (Zwart 1984).

Exposure to 100 mg/m^3 and below for 2 or 7 days did not result in histopathological changes of the lung, trachea and nasal cavity of rats (Cavender *et al*. 1977a).

Exposure of rats to 1.38 or 5.52 mg/m^3 for 5 days induced no histopathological changes of the lung or nasal cavity but did induce squamous metaplasia of the ventral epithelium at level 1 of the larynx. This was only slowly reversible after prolonged exposure (Kilgour *et al*. 2002).

Ulceration of the larynx and loss of cilia in airways was seen in rats after a 6 hours exposure to 96 mg/m^3 (MMAD: 0.9 µm) but not at 11 mg/m^3 (Wolff *et al*. 1986).

No histological effects were seen in the respiratory tract of rats after a 7 day exposure to 152 mg/m^3 nor in monkeys after a 7 day exposure to 502 mg/m^3 (Schwartz *et al*. 1977). In mice, ulceration of the larynx and the upper trachea was seen after exposure to 140 mg/m^3.

Partial atelectasis and focal emphysema was seen in one out of 2 hamsters on day 15 after a single 6 hour exposure to 300 and 500 mg/m^3 (Laskin and Sellakumar 1978). On day 30 all animals showed slight thickening of the alveolar septa.

A slight increase in the incidence of laryngeal hyperplasia and squamous metaplasia was seen in hamster at 88 weeks after a 30 days exposure to 100 mg/m^3 for 6 hours a day and 5 days a week (Laskin and Sellakumar 1978).

Short-term exposure (2.75 – 7 hours) of mice, rats and rabbits to sulfuric acid aerosol at concentration of 87 mg/m^3 and above resulted in a dose-dependent increase in clinical effects and morphological changes in the lungs (Treon *et al*. 1950).

Developmental toxicity

Exposure of mice and rabbits to 5.7 or 19.3 mg/m^3 sulfuric acid for 6 hours a day during the period of major organogenesis did not induce embryo- or fetotoxicity or teratogenicity (Murray *et al*. 1979).

Genotoxicity

There is some information indicating a genetic effect of low pH in *in vitro* systems but no information on the effects in *in vivo* systems (IARC 1992).

Carcinogenicity

Chronic exposure of hamsters to 100 mg/m^3 for 6 hours a day and 5 days a week did not induce tumor formation (Laskin and Sellakumar 1978).

Intratracheal instillation of rats with 0.3 ml 0.6% sulfuric acid twice a month for 12 months induced a small increase in the incidence of respiratory tract tumors (Uleckiene and Griciute 1997).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Very little data on absorption, distribution, metabolism, or excretion are available. Such data are also considered as less relevant because the toxicity in humans and animals is the result of local irritation.

The clearance of radioactive sulfuric acid was measured in male F344 rats after instillation and inhalation exposure (Dahl *et al*. 1983). Five minutes after nasal instillation, 97.1% of the radioactivity was present in the head and 2.9% in the body. Clearance of the lung after inhalation exposure resulted in a $t_{1/2}$ of 170 seconds.

The clearance of radioactive sulfuric acid was measured in male Beagle dogs after instillation and inhalation exposure (Dahl *et al*. 1983b). Deeper instillation (2 cm behind the nares versus second and seventh generation bronchus) resulted in a quicker uptake of the sulfuric acid in the blood (n=1). Clearance of the lung after inhalation exposure resulted in a $t_{1/2}$ of 261 ± 108 seconds.

4.2. Mechanism of Toxicity

All available data indicate that the main short term effects of sulfuric acid inhalation result directly from the local irritation of the respiratory tract. The titratable acidity (i.e. the amount of dissociated H^+ ions) of a dose is most determinative for the effect sizes (Fine *et al*. 1987). Mucus pH and respiratory ammonia are the most important defenses against the reaction of H^+ with the epithelial lung cells (Holma 1989, Hunt *et al*. 2002).

4.3. Other relevant information

4.3.1. Hygroscopy and species variability in deposition

Sulfuric acid is a very hygroscopic compound (Loerting and Liedl 2000). The reaction with ambient water is ultrafast and the resulting droplet sizes will depend on the relative humidity. Carabine and Maddock (1976) found that at a RH of 20%, the mass median diameter will be approximately 0.38 µm, whereas at 60% RH, the MMD will be approximately 0.48 µm. Also $(NH_4)_2SO_4$, the reaction product of the neutralization of sulfuric acid by respiratory ammonia (see paragraph 4.3.3), is very hygroscopic (Gysel *et al*. 2002).

It is well known that respiratory flow, the size of aerosols and the variation of that size determines the total aerosol deposition in the lungs, as well as the regional distribution of this deposition (EPA, 1996). The total deposition in the human respiratory tract is lowest for particles with a diameter 0.5 µm, and higher for particles with smaller and larger diameters. The larger particles are predominantly deposited in the extrathoratic region, whereas smaller particles are mainly deposited in the tracheobronchial and alveolar regions (Hiller 1991, Kim 2000).

Due to the high humidity in the respiratory tract, hygroscopic particles will grow following inhalation. Because inhaled dry air will be progressively humidified until it reaches the upper parts of the lung, the droplet growth will continue up to that time. The growth of the particles will change the amounts and sites of particle deposition (Morrow 1986). The consequence of hygroscopic growth of particles in the respiratory tract is, according to Carabine and Maddock (1976), that originally small droplets have greater probability of deposition than (a) inert particles of the same size, on account of their growth, and (b) inert particles of the same diameter as the grown droplets, on account of their greater penetration. Another consequence of hygroscopic growth in the respiratory tract is that inhaled droplets of submicrometer size will reach the human lung with substantial dilution. Naturally, the different deposition of hygroscopic particles compared to inert particles will influence the toxicity (Cavender *et al*. 1977).

The growth of hygroscopic particles in the human airways as described above is mainly based on expectations and model calculation. Models have been developed to predict the size of hygroscopic aerosol particles as a function of the humidity of the air, which could be applied to the situation in the human respiratory tract to predict the deposition patterns (Broday *et al*. 2001, Ferron 1977, Martonen *et al*. 1982, Scherer *et al*. 1979). In addition, *in vivo* SPECT-analysis of the deposition of radioaerosols in human airways confirmed the expected differences between hygroscopic and non-hygroscopic particles (Chan *et al*. 2002), and matched well with model calculations (Finlay *et al*. 1996). Specific models have been developed for sulfuric acid aerosol deposition in the respiratory tract of adults and children (Cocks and Fernando 1982, Cocks and McElroy 1984, Larson 1989, Martonen and Patel 1981, Martonen *et al*. 1985, Martonen and Zhang 1993, Sarangapani and Wexler 1996). These models take account of hygroscopic growth and in most cases also neutralization by respiratory ammonia.

Very little is known about the species differences in aerosol deposition of sulfuric acid in the lungs. Martonen and Schroeter (2003a, 2003b) validated a human deposition model with human data and modeled lung deposition of particles in rats by plugging algorithms for rat morphologies and ventilatory parameters into the validated model. The results showed that the deposition fraction of a dose was generally higher in humans as compared to rats for all particle sizes, and that hygroscopic growth of particles >1 µm increased deposition in humans but not in rats. However, the mass per surface area unit was much greater for rats than for humans, in particular for the first ten airway generations.

4.3.2. Species variability in effects

Guinea pigs are much more susceptible to sulfuric acid mist than other laboratory animals. For example, the 8 hour LC_{50} values as determined by Runkle and Hahn (1976) in rats and mice were 425 and 600 mg/m^3, respectively, are much higher than the value of 31 mg/m^3 for guinea pigs as stated in the same reference. This findings are confirmed by the results of Treon (1950). Comparison of the levels with some mortality in guinea pigs (12 mg/m^3 for 8 hours, Treon 1952) with levels to which humans are exposed (8-hour TLV is 1 mg/m^3, occupational exposures up to 35 mg/m^3 were reported), also indicate that guinea pigs are far more susceptible than humans.

Reflex airway constriction observed in guinea pigs is mediated by the parasympathetic nervous system (Amdur *et al.* 1952a). Other effects, in particular desquamation of terminal bronchiolar epithelium in guinea pigs, are related to these parasympathetic reflexes (Brownstein 1980). Schwartz *et al*. (1977) found that guinea pigs are far more sensitive to pulmonary damage by sulfuric acid inhalation than other species (mice, rats, monkeys). The total deposition of sulfuric acid aerosols >0.4 µm is larger in rats than in guinea pigs (Dahl and Griffith 1983), whereas the rat is a less sensitive animal species (Treon *et al*. 1950). Lee *et al*. (1999) found that sulfuric acid strongly affects the alveolar surface tension in guinea pigs but not in rats, and they suggest that neurogenic inflammation could be involved which may also lead to a potent bronchoconstrictive response.

For the reasons stated above, the guinea pig is considered as no suitable animal model to predict the acute health effects of sulfuric acid inhalation in humans. Therefore, the results of the studies in guinea pigs were not included in section 3 of this TSD.

Lippmann and Schlesinger (1984) reported that effects of sulfuric acid on mucociliary clearance was comparable in mice, rats, rabbits, donkeys, and humans.

4.3.3. Intraspecies variability / Susceptible populations

Neutralization by ammonia

Larson *et al*. (1977) hypothesized that exhaled ammonia was capable of neutralizing sulfuric acid aerosols to $(NH_4)_2SO_4$, a nearly neutral salt. In humans exposed for 60 minutes to 1200 µg/m^3 sulfuric acid, equimolar mixtures of NH_4HSO_4 and H_2SO_4 were found in exhaled air, whereas human exposure to 600 µg/m^3 sulfuric acid for 60 minutes resulted in the presence of NH_4HSO_4 and $(NH_4)_2SO_4$ in exhaled air.

Larson *et al*. (1980, 1982) confirmed the neutralization of sulfuric acid by respiratory ammonia in anaesthetized dogs. The extent of neutralization was dependent on the ammonia concentration as well as the particle size of the acid aerosols: smaller aerosols are neutralized more than larger ones.

McMurray *et al*. (1983) studied the reaction rate of sulfuric acid aerosols and ammonia gas. They found that the extent of neutralization of sulfuric acid was dependent on ammonia concentration, reaction time, and particle size. Small particles were relatively more neutralized that larger ones.

An ex-vivo investigation into the rate of neutralization of sulfuric acid aerosols by ammonia gas showed a dependency to the concentration of both compounds. A sulfuric acid concentration of 2.0 mg/m^3 (MMD 0.13 µm; 25°C, RH 95%) could be neutralized to approximately 90% of the amount of H^+ by 200 ppb ammonia, whereas after reaction with 400 ppb ammonia approximately 80% of the amount of H^+ remained. The ten-fold lower concentration of sulfuric acid of 0.2 mg/m^3 (MMD 0.23 µm; 25°C, RH 95%) was reduced to approximately 45% and 35% of the amount of H^+ following reaction with 200 and 400 ppb ammonia, respectively (Schlesinger and Chen, 1994).

Diskin *et al.* (2003) quantified ammonia in the breath of five human subjects using a SIFT-MS technique. The concentrations of ammonia ranged from 400 to 2400 ppb. Hunt and Williams (1977) measured ammonia levels in breath of 330-3170 ppb by spectrometry. Larson *et al*. (1977) measured ammonia concentrations of 10-744 ppb in human exhaled air. The variation between individuals was large but was small within individuals. Senthilmohan *et al*. (2000) reported ammonia concentrations in breath in the range of 50-500 ppb during exercise, and they found that the ammonia time profile with exercise showed both decreasing and increasing patterns for different subjects. Ament *et al*. (1999) found that respiratory ammonia output increased exponentially with the increasing workload of a bicycle exercise of human subjects. A few minutes post-exercise the amount of respiratory ammonia decreased to pre-exercise levels (0.45-2.36 µmol/min.). Breathing zone ammonia concentration from eight healthy male volunteers at rest was 80-180 ppb (Clarck *et al.* 1995). Increasing wind speed (from 0 to 16 km/h) resulted in decreasing average ammonia concentrations in the breathing zone (from 155 to 27 ppb) during 30 minutes of exercise.

In rats, the concentration of ammonia in exhaled air was in the range of 10 to 353 ppb (Barrow and Steinhagen 1980). Ammonia concentrations in exhaled air of rabbits were in the range of 14-1084 ppb (Vollmuth and Schlesinger 1984).

Clarck *et al*. 1995 concluded that a sulfuric acid chamber exposure of 0.100 mg/m^3 will lead to a personal exposure of approximately 0.075 mg/m^3 due to neutralization by exhaled ammonia. This effect will be less pronounced outdoors where there are higher wind speeds.

Norwood *et al*. (1992) showed that an acidic oral rinse (pH 2.5) gives an immediate 90% reduction of the oral ammonia levels. The oral ammonia levels returned to 50% of their baseline levels within 1 hour after the rinse.

Utell *et al.* (1989) showed that gargling with citric acid may reduce oral ammonia levels with approximately a factor 5 (from 500 to 100 ppm). The change in FEV_1 in asthmatics following exercise and exposure to 0.350 mg/m^3 sulfuric acid aerosols (MMAD 0.8 µm, GSD 1.7; RH 20-25%) was more than 2 times greater in subjects with depleted oral ammonia.

Asthmatics

High molecular fractions in the airway mucus are most responsible for the H^+ ion absorption capacity of the mucus in the respiratory tract, and form a protection against penetration of H^+ to surrounding tissues. Following saturation of this buffer capacity, the H^+ will react with epithelial tissue (Holma 1989). Acidic mucus or mucus with low protein concentration, as in some asthmatics (Holma 1985), constitutes a base for enhanced risks from inhalation exposure to acids.

Median ammonia levels in breath condensate of asthmatics were low (30 µM) compared to those of healthy subjects (327 µM), and correlated well with condensate pH (Hunt *et al*. 2002). The authors revealed that glutaminase expression and activity in epithelial cells determine the ammonia production and pH. The glutaminase activity of human lung epithelial cells increased in relation to acidic stress *in vitro*, improved culture medium pH, and improved cell survival. Interferon-γ and tumor-necrosis-factor-α, inflammatory cytokines known to be elevated in asthma, downregulated glutaminase expression and ammonia production in tissue culture. Open lung biopsies revealed expression of glutaminase in epithelial cells *in vivo* in a healthy subject, but dramatically less in an asthmatic subject.

4.3.4. Irritation and Sensibilisation

Sulfuric acid is a strong acid (pK_a values of <0 and 1.92 for the dissociation of the first and second hydrogen ion, IARC 1992) and is corrosive.

4.3.5. Concurrent Exposure Issues

Exposure to sulfuric acid and ozone

Frampton *et al*. (1995) reported small alterations of the response of asthmatic volunteers to ozone due to pre-exposure by sulfuric acid. Linn *et al*. (1994) exposed normal and asthmatic subjects to ozone, sulfuric acid, and their combination, and found a slight but insignificantly larger change in mean lung function and bronchial reactivity with the combination. This appeared to be the result of the substantially greater decline in lung function of a minority of asthmatic and healthy volunteers, which was reproducible but not in a quantitative way.

Study results of Horvath *et al*. (1987) showed no enhanced response to the combination of sulfuric acid and ozone following exposure to humans at the TLV levels. Also Kulle *et al*. (1982) found no enhanced effects of sequential exposure to ozone and sulfuric acid.

Background exposure to sulfuric acid

Industrial pollution has led to the generation of acidic aerosols, of which sulfuric acid is the most important. Twenty-four hour average concentrations in some states of the USA exceeded 20 µg/m^3 while peak concentrations reached 100 µg/m^3 (Spengler *et al.* 1989).

Ambient concentrations of sulfur trioxide were reported in the range of 8 µg/m^3 (Arizona, USA) to 12 µg/m^3 (North Carolina, USA) (Kikuchi 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of human data relevant to AEGL-1

Many human volunteer studies were performed involving over a thousand healthy and asthmatic persons. The results of these studies were fairly consistent.

Symptoms of respiratory irritation and changes in lung function are the primary effects of exposure to sulfuric acid that may lead to notable discomfort. Symptoms of respiratory irritation appeared to be the most sensitive effects (see 5.3). In the study of Horvath *et al*. (1982) three out of eleven healthy male exercising volunteers showed signs of respiratory irritation following exposure to sulfuric acid at concentrations of 0.23 mg/m^3 and higher for 120 minutes. At the same exposure duration, Avol *et al*. (1979) found no signs of irritation in 6 healthy and 6 asthmatic exercising volunteers at a concentration of 0.1 mg/m^3.

5.2. Summary of animal data relevant to AEGL-1

Respiratory irritation and lung function changes were also the main effects relevant to AEGL-1 in animals (Laskin and Sellakumar 1978, Zwart 1984, Sackner *et al*. 1978). Considering the large database in humans on these effects, the animal data are not further discussed.

5.3. Derivation of AEGL-1

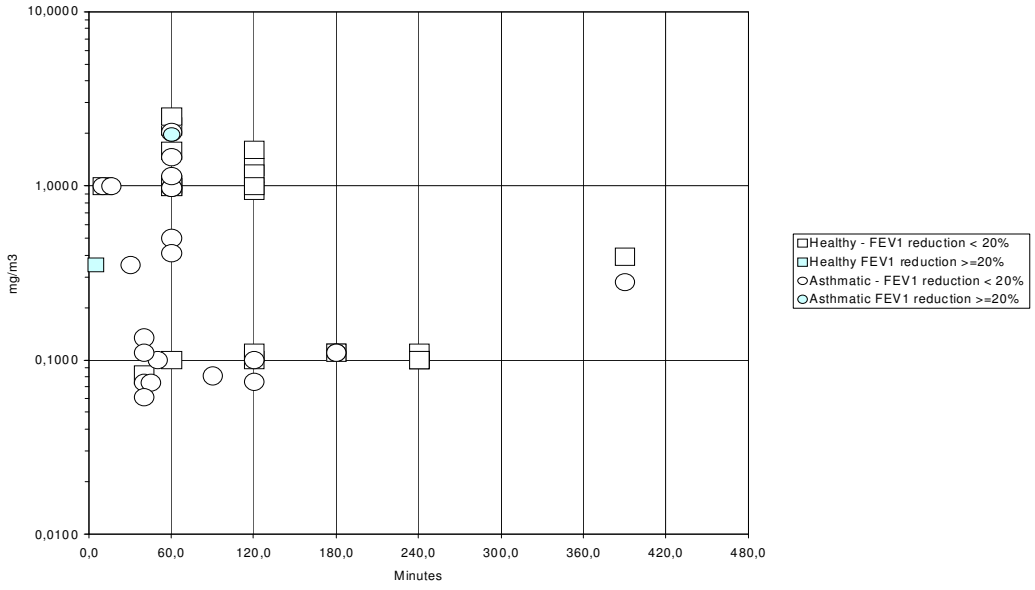
Since appropriate human data exist for exposure to sulfuric acid, they will be utilized to derive values for AEGL-1. Symptoms of respiratory irritation and changes in lung function are the primary effects of exposure to sulfuric acid that may lead to notable discomfort. Given the large database regarding these effects in humans, two category plots from the human volunteer studies are presented (Figure 1 and Figure 2): one for lung function changes (a decrease of 20% in FEV_1 is usually considered as a critical effect size for AEGL-1 derivation) and one for other symptoms (mainly respiratory irritation). It can be seen that the latter symptoms occur at lower exposure concentrations than effects on the lung function parameter FEV_1. Therefore (irritation) symptoms by H_2SO_4 exposure are considered as the most sensitive end-point for AEGL-1.

All the results of the human volunteer studies (with a total of 610 subjects tested for symptoms) showed fairly consistent results. Both healthy and asthmatic exercising volunteers were tested.

The results of various studies clearly indicate that the first signs of respiratory irritation that can be characterized as notable discomfort occur at concentrations higher than 0.2 mg/m^3 (e.g. 0.23 mg/m^3, Horvath *et al*. 1982). It is therefore concluded that the concentration of 0.2 mg/m^3 can be used as the point of departure for AEGL-1. Since the test subjects included exercising asthmatics, the most sensitive subpopulation, an intraspecies uncertainty factor of 1 is considered sufficient.

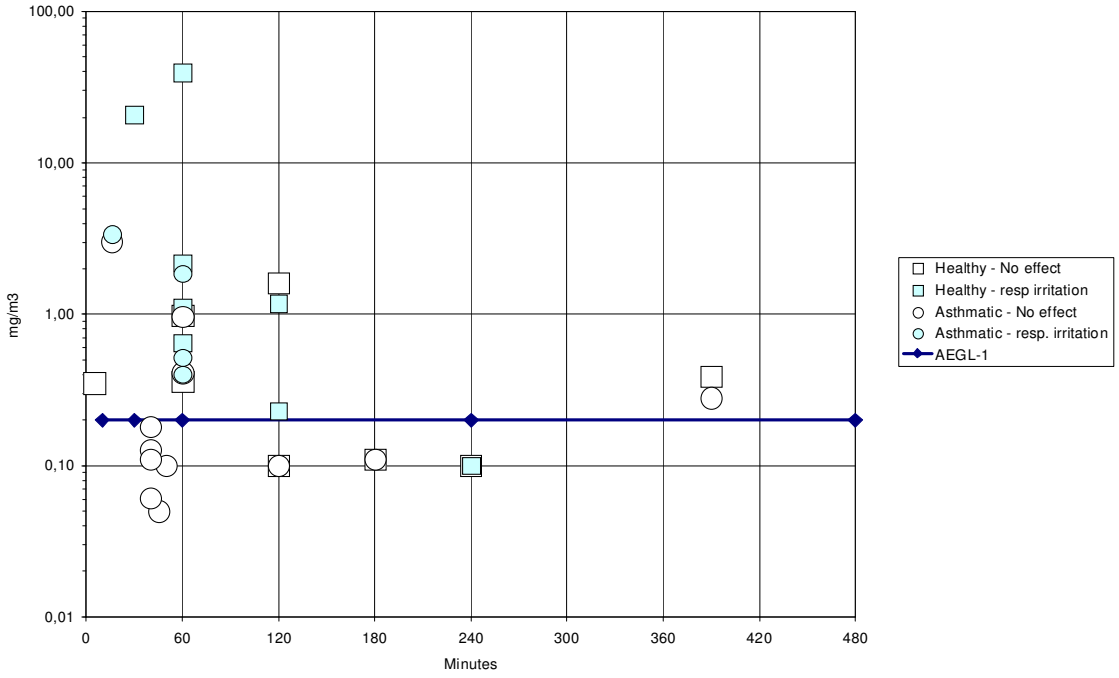
There are no good data to establish a time-concentration effect (there are no data beyond 120 minutes where concentrations higher than 0.39 mg/m^3 were tested). Considering the data up to 120 minutes of exposure and the type of effect (local irritation) the value of 0.2 mg/m^3 was flat-lined across the 10- and 30-minute, and the 1-, 4-, and 8-hour exposure time points. This approach was considered appropriate because mild irritant effects generally do not vary greatly over time, and is in line with the derivation of AEGL-1 values for other respiratory irritants. The resulting AEGL-1 values are shown in Figure 2 and listed in Table 7.

Figure 1. Effects of sulfuric acid on the changes in FEV_1 in healthy and asthmatic volunteers



Note: The colored square in this figure (0.35 mg/m^3, 5 min) is Amdur *et al.* 1952b. The significance of the effect ("expiratory flow" rather than FEV_1) is unclear. The study is old and limitedly described and the results do not correspond well to those of other (later and well-performed) studies. The colored circle (2 mg/m^3, 60 min) is Linn *et al* 1989 who found that FEV_1 in asthmatics decreased 21-24% following exercise (this was 14-19% in controls) and 60 min exposure to 1.86-2.27 mg sulfuric acid/m^3.

Figure 2. Effects of sulfuric acid on symptoms of respiratory irritation in healthy and asthmatic volunteers



Note: The lowest effect concentration (0.1 mg/m^3, 240 min.) in Figure 2 is observed by Kulle *et al*. 1982, where 1/12 healthy exercising volunteers reported mild throat irritation. The method of recording the symptoms was not given and the study has been limitedly reported. This observation does not correspond with the results of Kerr *et al*. (1981) who found no effects in 28 exercising healthy adults at the same exposure concentration and duration. Also Frampton *et al*. 1995 (n=30 healthy and n=30 asthmatic exercising subjects) detected no symptoms at nearly the same concentration (0.11 mg/m^3) for 180 minutes. Moreover, Linn *et al*. 1994 (n=15 healthy and n=30 asthmatic exercising subjects) could not detect any symptoms at exposures of 0.28-0.39 mg/m^3 at 2 x 390 minutes on subsequent days.

Table 7. AEGL-1 Values for Sulfuric acid[1]

10-minute	30-minute	1-hour	4-hour	8-hour
0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3

[1] For accidents with sulfur trioxide or oleum, the actual ambient exposure is to sulfuric acid mist. Therefore the sulfuric acid AEGLs should apply in such situations.

The AEGL-1 values derived for sulfuric acid were compared to those of hydrogen chloride and nitric acid. For this purpose, the values were transposed to µmoles/m^3. It should be noted that each mole of sulfuric acid delivers 2 moles of H^+ ions, while each mole of hydrogen chloride or nitric acid only delivers 1 mole of H^+ ions.

Table 8. AEGL-1 comparison of sulfuric acid, nitric acid, and hydrogen chloride

	10-minute	30-minute	1-hour	4-hour	8-hour	endpoint
sulfuric acid	2.04 µmoles/m^3	2.04 µmoles/m^3	2.04 µmoles/m^3	2.04 µmoles/m^3	2.04 µmoles/m^3	respiratory irritation in healthy and asthmatic humans
nitric acid	8.41 µmoles/m^3	8.41 µmoles/m^3	8.41 µmoles/m^3	8.41 µmoles/m^3	8.41 µmoles/m^3	change in pulmonary function in humans
hydrogen chloride	49.4 µmoles/m^3	49.4 µmoles/m^3	49.4 µmoles/m^3	49.4 µmoles/m^3	49.4 µmoles/m^3	NOAEL in exercising human asthmatics

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of human data relevant to AEGL-2

A large number of human volunteer studies are available. In one of these studies (Linn *et al*. 1989) a subgroup of asthmatics, 4/19 persons had to terminate exercise or exposure due to "lung function and severe symptoms" (see Table 4; exposure 1.86-2.27 mg/m^3 for 60 minutes; average exposure concentrations was 2.0 mg/m^3). The effects were observed in a sensitive subpopulation exposed under worst case conditions (exercising asthmatics who were withheld regular medication and who gargled citric acid to deplete oral ammonia). However, this termination does not necessarily reflect an impaired ability to escape and the symptoms of these subjects were relieved by a normal dose of their medication.

Besides, occupational data indicate that workers can complete their normal work shifts at sulfuric acid concentrations of 26-35 mg/m^3 (El-Sadik *et al*. 1972).

6.2. Summary of animal data relevant to AEGL-2

Serious effects of exposure to sulfuric acid in animals were reported by Treon *et al*. (1950), Kilgour *et al*. (2002), Wolff *et al*., and Schwartz *et al*. (1977). These effects included pulmonary laryngal edema in rabbits (87-190 mg/m^3 and above) and mice (190 mg/m^3 and above), pulmonary hemorrhages in rabbits and in rats (218 mg/m^3 and above), desquamation of the bronchiolar epithelial cells in rabbits (218 mg/m^3 and above), atelectasis and emphysema in rabbits (416 mg/m^3 and above), ulcers on the larynx in rabbits (416 mg/m^3 and above) and in rats (96 mg/m^3) and mice (140-170 mg/m^3), and partly reversible histopathological changes of the larynx with increased proliferation in rats (5.52 mg/m^3 for 28 days).

Remarkably, no serious effects were observed in several studies with monkeys that included histopathological examination, using exposure concentrations up to 502 mg /m^3 for an unknown daily exposure period on 7 consecutive days (Schwartz et al. 1977). Overall, exposures of 8 hours or less did not result in severe effects at concentrations up to 60 mg/m^3 in any of the animal species.

Given the large differences in aerosol deposition between (small) animals and humans, in particular for very hygroscopic substances such as sulfuric acid, it is very difficult to extrapolate the results from animals studies (concentrations and effects) to humans, and hence, the animal data are considered of much less value than the human data. Of the animal data, the primate data are considered to be the most relevant. Since sufficient adequate human data are available, the animal data will not be used for the derivation of the AEGL-2 values.

6.3. Derivation of AEGL-2

In the human volunteer studies with exposures up to 3.37 mg/m^3 (more than a thousand subjects, including exercising asthmatics), no effects were observed that are relevant for AEGL-2. The results of the study by Linn *et al*. (1989) do not provide an adequate point of departure for AEGL-2 because of the worst case exposure conditions and because the termination by some of the subjects was due to sub-AEGL-2 effects. Further, the 8-hour TLVs of 1.0 mg/m^3 represent a common actual exposure in industrial practice with no reported short-term effects (see studies in paragraph 2.2.3). Occupational studies indicate that no irreversible or other serious health effects or an impaired ability to escape are to be expected from single exposures to concentrations of up to 35 mg/m^3.

The reported lower concentration of 26.0 mg/m^3 (8-hour exposure) from the study of El-Sadik *et al*. (1972) can be used as the point of departure for AEGL-2. Under these exposure conditions workers were perfectly able to complete their work shift. An intraspecies uncertainty factor of 3 is needed to account for sensitive subpopulations. This results in an 8-hour AEGL-2 value of 8.7 mg/m^3. This AEGL-2 level is considered to be rather conservative because no irreversible or disabling effects were observed following acute exposure to sulfuric acid in any of the relevant human volunteer studies.

There are no good data to establish a time-concentration effect. The level of 8.7 mg/m^3 was flat-lined across the 10- and 30-minute, and the 1-, 4-, and 8-hour exposure time points. This approach was considered appropriate because the main effects of sulfuric acid are local effects on the respiratory tract. Local irritant effects generally do not vary greatly over time. This approach is in line with the derivation of AEGL-2 values for other locally acting substances previously evaluated by the Committee. The resulting AEGL-2 values are shown in Figure 3 and listed in Table 9.

Figure 3. Disabling effects in healthy and asthmatic subjects following exposure to sulfuric acid

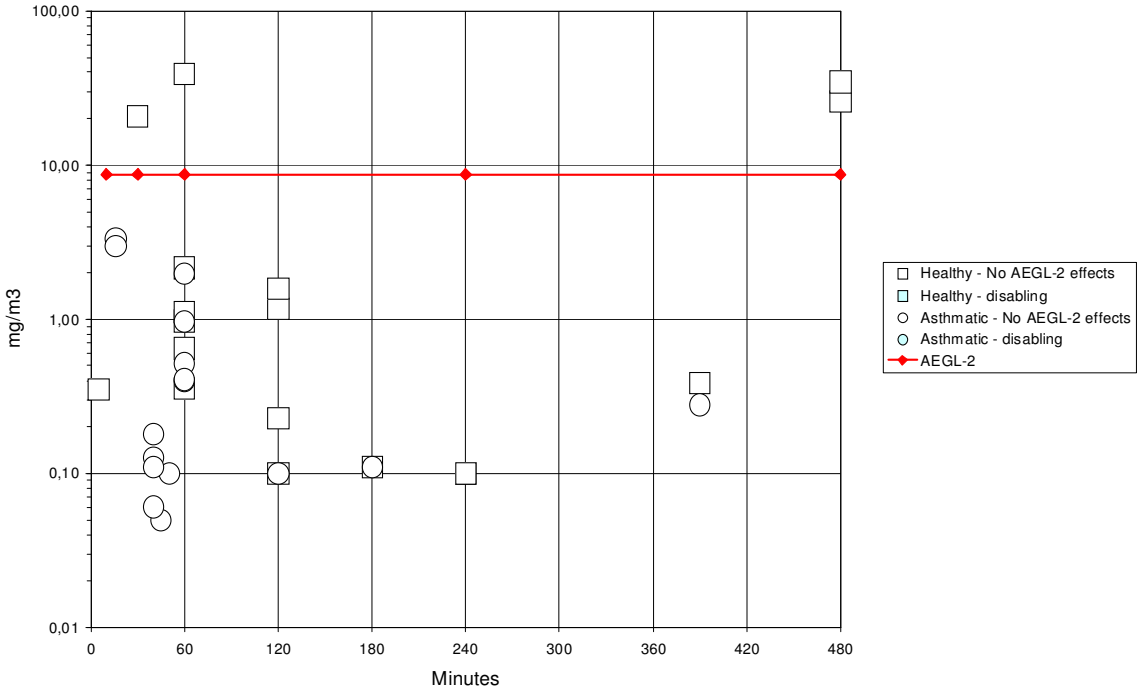


Table 9. AEGL-2 Values for Sulfuric acid[1]

10-minute	30-minute	1-hour	4-hour	8-hour
8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3

[1] For accidents with sulfur trioxide or oleum, the actual ambient exposure is to sulfuric acid. Therefore the sulfuric acid AEGLs should apply in such situations.

The AEGL-2 values derived for sulfuric acid were compared to those of hydrogen chloride and nitric acid. For this purpose, the values were transposed to µmoles/m^3. It should be noted that each mole of sulfuric acid delivers 2 moles of H^+ ions, while each mole of hydrogen chloride or nitric acid only delivers 1 mole of H^+ ions.

Table 10. AEGL-2 comparison of sulfuric acid, nitric acid, and hydrogen chloride

	10-minute	30-minute	1-hour	4-hour	8-hour	endpoint
sulfuric acid	88.7 µmoles/m^3	88.7 µmoles/m^3	88.7 µmoles/m^3	88.7 µmoles/m^3	88.7 µmoles/m^3	Absence of AEGL-2 effects in workers
nitric acid	106 µmoles/m^3	77.8 µmoles/m^3	63.5 µmoles/m^3	42.8 µmoles/m^3	34.9 µmoles/m^3	Irritation with cough; burning of eyes and skin; lacrymation and salivation
hydrogen chloride	2742 µmoles/m^3	1179 µmoles/m^3	603 µmoles/m^3	148 µmoles/m^3	74 µmoles/m^3	Mouse RD_{50}; histopath in rats

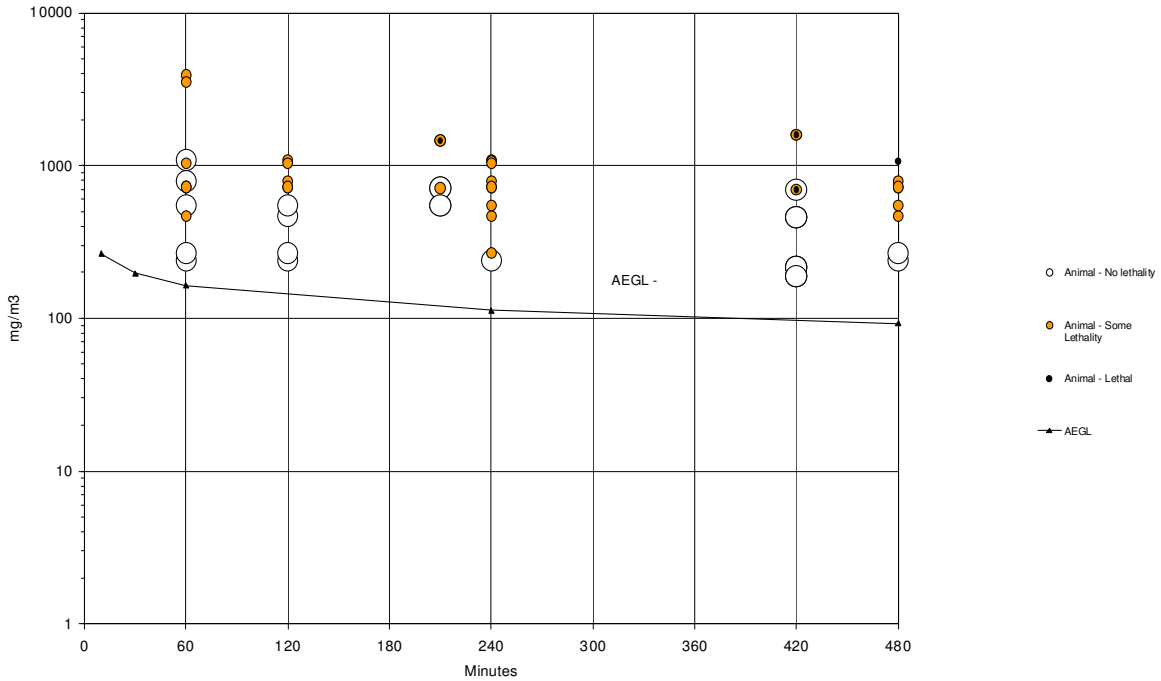
7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of human data relevant to AEGL-3

No adequate data on lethality in humans are available.

7.2. Summary of animal data relevant to AEGL-3

Figure 4. Category plot of animal lethality data for sulfuric acid



Lethality data were available in guinea pigs, rats, mice, and rabbits. Figure 4 shows a category plot of the most relevant lethality data in animals (rabbits, rats and mice). As explained in paragraph 4.3.2, guinea pigs are considered not suitable as an animal model to predict the acute health effects of sulfuric acid in humans. Studies in rats and mice provide adequate data on lethality (Runckle and Hahn 1976). In this study the effects of time and concentration were investigated. The results are given in Table 5. The 4-hour LC_{50}'s for rats and mice were 375 and 600 mg/m^3, respectively.

7.3. Derivation of AEGL-3

The study of Runckle and Hahn (1976) is used to develop values for AEGL-3. Because the authors studied both time and concentration effects, it was possible to perform a multivariate probit-analysis including time and concentration on these data. The input data were taken from Table 5. The results of the probit-analysis are listed in Table 11.

Table 11. Probit-analysis results: estimated LC_{01} with 95%-confidence intervals for rats and mice at the AEGL time points

Exposure duration	RATS		MICE	
	LC_{01} (mg/m^3)	95% confidence limits (mg/m^3)	LC_{01} (mg/m^3)	95% confidence limits (mg/m^3)
10 minutes	1751	897 – 3620	796	475 – 1158
30 minutes	740	436 – 1132	592	379 – 770
1 hour	430	252 – 595	491	319 – 613
4 hours	145	63.8 – 217	338	206 – 426
8 hours	84.0	29.7 – 142	280	160 – 368

The probit LC_{01} method was used because it allows to determine the combined effect of both concentration and time with all data included in the analysis simultaneously. No $BMDL_{05}$ was calculated because the BMD software does not allow to develop benchmark concentrations for multivariate situations, and the available software for multivariate analysis does not allow to calculate benchmark concentrations.

The lethality data of rats used in this analysis appear not to be very suitable for this purpose, given the steep and sometimes irregular response versus concentration (see Table 5). This is also reflected in the large confidence intervals of the probit analysis (table 11). Moreover, the predicted LC_{01} of rats is not very consistent with the input data itself, and neither with other data from rats: Cavender *et al*. 1977a reported a NOEL of 100 mg/m^3 for a 5-days exposure, Schwartz *et al*. 1977 reported a NOEL of 172 mg/m^3 for a 7-days exposure, and Treon *et al*. 1950 reported 461 mg/m^3 (7 hr) as a minimal effect level. In this respect, the lethality data in mice appear to be far more suitable for a probit analysis, and the results of this analysis are in line with the input data and the results of other studies in mice (Schwartz *et al*. 1977, Treon *et al*. 1950).

For the reasons stated above, the calculated LC_{01} values for mice will be used as a point of departure for the AEGL-3. No uncertainty factor is applied for the extrapolation from animals to humans, considering that (1) mice are more sensitive to sulfuric acid exposure than rats and rabbits (Treon *et al.* 1950), (2) monkeys did not die and showed no serious effects up to 502 mg/m^3 for an unknown exposure duration per day for 7 days, and (3) occupational concentrations up to 35 mg/m^3 were tolerated during work shifts without significant acute health effects. An uncertainty factor of 3 is applied to account for variation in sensitivity among humans. The resulting AEGL-3 values are listed in Table 12.

The values were time-scaled across all time intervals with the n-value calculated from the data, because the data span a range of exposure periods ranging from 1 - 8 hours.

Table 12. AEGL-3 Values for Sulfuric acid[1]

10-minute	30-minute	1-hour	4-hour	8-hour
270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3

[1] For accidents with sulfur trioxide or oleum, the actual ambient exposure is to sulfuric acid. Therefore the sulfuric acid AEGLs should apply in such situations.

The AEGL-3 values derived for sulfuric acid were compared to those of hydrogen chloride and nitric acid. For this purpose, the values were transposed to µmoles/m^3. It should be noted that each mole of sulfuric acid delivers 2 moles of H^+ ions, while each mole of hydrogen cholride or nitric acid only delivers 1 mole of H^+ ions.

Table 13. AEGL-3 comparison of sulfuric acid, nitric acid, and hydrogen chloride

	10-minute	30-minute	1-hour	4-hour	8-hour	endpoint
sulfuric acid	2702 µmoles/m^3	2009 µmoles/m^3	1672 µmoles/m^3	1152 µmoles/m^3	948 µmoles/m^3	LC_{01} in mice
nitric acid	587 µmoles/m^3	428 µmoles/m^3	349 µmoles/m^3	238 µmoles/m^3	190 µmoles/m^3	LC_{50} in rats
hydrogen chloride	17004 µmoles/m^3	5760 µmoles/m^3	2743 µmoles/m^3	713 µmoles/m^3	357 µmoles/m^3	NOEL for death in rats

8. SUMMARY OF AEGLS

8.1. AEGL values and toxicity endpoints

Table 14. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3
AEGL-2 (Disabling)	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3
AEGL-3 (Lethal)	270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3

8.2. Comparison with other standards and guidelines

AEGL-1 values are only 20% of the 8-hour occupational limits of 1 mg/m^3. The AEGL-2 values are above the occupational limits. The AEGL-3 values are well above the occupational limits, as expected.

Table 15. Extant Standards and Guidelines for Sulfuric acid

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3
AEGL-2	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3
AEGL-3	270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3
ERPG-1 (AIHA)[a]			2 mg/m^3		
ERPG-2 (AIHA)			10 mg/m^3		
ERPG-3 (AIHA)			30 mg/m^3		
EEGL (NRC)[b]	5 mg/m^3	2 mg/m^3	1 mg/m^3		
PEL-TWA (OSHA)[c]					1 mg/m^3
PEL-STEL (OSHA)[d]					1 mg/m^3
IDLH (NIOSH)[e]		15 mg/m^3			
REL-TWA (NIOSH)[f]					1 mg/m^3
REL-STEL (NIOSH)[g]	3 mg/m^3 (15 minutes)				
TLV-TWA (ACGIH)[h]					1 mg/m^3
TLV-STEL (ACGIH)[i]	3 mg/m^3				
MAK (Germany)[j]					1 mg/m^3
MAK Peak Limit (Germany)[k]		-			
MAC (The Netherlands)[l]					1 mg/m^3

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association**
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual=s ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**EEGL (Emergency Exposure Guidance Levels, National Research Council**
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** is defined analogous to the ACGIH-TLV-STEL.

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA.

[g]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** is defined analogous to the ACGIH TLV-STEL.

[h]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average**)?) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** is defined as a 15-minute TWA exposure, which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[j]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association]) is defined analogous to the ACGIH-TLV-TWA.

[k]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2000) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[l]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands) is defined analogous to the ACGIH-TLV-TWA.

8.3. Data quality and research needs

A very comprehensive database on the health effects of sulfuric acid inhalation exposure is available, including numerous healthy and asthmatic human volunteer studies and experimental studies in a wide variety of animal species. The study reports cover a time period from the early fifties until 2003, and are of varying quality and completeness. Starting values for AEGLs were taken from studies with a reasonable quality and are supported by the results of many other studies. Data on disabling effects were scarce, so only a conservative estimate for AEGL-2 could be made.

9. REFERENCES

Alarie, Y., W.M. Busey, A.A. Krumm, and C.E. Ulrich. 1973. Long-term continuous exposure to sulfuric acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 16-24

Allott, C.P., D.P. Evans, and P.W. Marshall. 1980. A model of irritant-induced bronchoconstriction in the spontaneously breathing guinea pig. Br. J. Pharmacol. 71: 165-168

Amdur, M.O. 1954. Effect of a combination of SO_2 and H_2SO_4 on guinea pigs. Public Health Rep. 69: 503-506

Amdur, M.O. 1958. The respiratory response of guinea pigs to sulfuric acid mist. A.M.A. Arch. Industr. Health 18: 407-414

Amdur, M.O. 1959. The physiological response of guinea pigs to atmospheric pollutants. Int. J. Air Poll. 1: 170-183

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

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

Amdur, M.O., R.Z. Schulz, and P. Drinker. 1952a. Toxicity of sulfuric acid mist to guinea pigs. Ind. Hyg. Occ. Med. 5: 318-329

Amdur, M.O., L. Silverman, and P. Drinker. 1952b. Inhalation of sulfuric mist by human subjects. Ind. Hyg. Occ. Med. 6: 305-313

Amdur, M.O., M. Dubriel, and D.A. Creasia. 1978. Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423

Amdur, M.O., and L.C. Chen. 1989. Furnace-generated acid aerosols: speciation and pulmonary effects. Environ Health Persp. 79: 147-150

Ament, W., J.R. Huizenga, E. Kort, T.W. van der Mark, R.G. Grevink, and G.J. Verkerke. 1999. Respiratory ammonia output and blood ammonia concentration during incremental exercise. Int. J. Sports Med. 20: 71-77

Anderson, K.R., E.L. Avol, S.A. Edwards, D.A. Shamoo, R.-C. Peng, W.S. Linn, and J.D. Hackney. 1992. Controlled exposures of volunteers to respirable carbon and sulfuric acid. J. Air Waste Manage. Assoc. 42:770-776

Anfield, B.D., and C.G. Warner. 1968. A study of industrial mists containing sulphuric acid. Ann. Occup. Hyg. 11: 185-194

Aris, R., D. Christian, D. Sheppard, and J.R. Balmes. 1991. Lack of bronchoconstrictor response to sulfuric acid aerosols and fogs. Am. Rev. Respir. Dis. 143: 744-750

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. Toxicological Profile for sulfur trioxide and sulfuric acid. U.S. Public Health Service. December, 1998

Avol EL, Jones MP, Bailey RM, Chang NM, Kleinman MT, Linn WS, Bell KA, Hackney JD. 1979. Controlled exposures of human volunteers to sulfate aerosols. Health effects and aerosol characterization. Am Rev Respir Dis. 120(2):319-27.

Avol, E.L., W.S. Linn, L.H. Whiteman, J.D., J.D. Whynot, K.R. Anderson, and J.D. Hackney. 1988a. Short-term respiratory effects of sulfuric acid in fog: a laboratory study of healthy and asthmatic volunteers. JAPCA 38: 258-263

Avol, E.L., W.S. Linn, J.D. Whynot, K.R. Anderson, D.A. Shamoo, L.M. Valencia, D.E. Little, and J.D. Hackney. 1988b. Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. Toxicol. Ind. Health 4(2): 173-184

Avol, E.L., W.S. Linn, D.A. Shamoo, K.R. Anderson, R.-C. Peng, and J.D. Hackney. 1990. Respiratory responses of young asthmatic volunteers in controlled exposures to sulfuric acid aerosol. Am. Rev. Respir. Dis. 142: 343-348

Barrow, C.S. and W.H. Steinhagen. 1980. NH_3 concentrations in the expired air of the rat: importance to inhalation toxicology. Toxicol. Appl. Pharmacol. 53: 116-121

Bauer, M.A., M.J. Utell, D.M. Speers, F.R. Gibbs, and P.E. Morrow. 1988. Effects of near ambient levels of sulfuric acid aerosol on lung function in exercising subjects with asthma and COPD. Am. Rev. Respir. Dis. 137: 167

Beaumont, J.J., J. Leveton, K. Knox, T. Bloom, T. McQuiston, M. Young, R. Goldsmith, N.K. Steenland, D.P. Brown, and W.E. Halperin. 1987. Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. JNCI 79(5): 911-921

Boulet, L.-P. 1988. Increases in airway responsiveness following acute exposure to respiratory irritants. Chest 94: 476-481

Bowes, S.M., M. Francis, B.L. Laube, and R. Frank. 1995. Acute exposure to acid fog: Influence of breathing pattern on effective dose. Am. Ind. Hyg. Assoc. J. 56:143-150

Broday, D.M., and P.G. Georgopoulos. 2001. Growth and deposition of hygroscopic particulate matter in the human lungs. Aerosol Sci. Technol. 34: 144-159

Brownstein, D.G. 1980. Reflex-mediated desquamation of bronchiolar epithelium in guinea pigs exposed acutely to sulfuric acid aerosol. Am. J. Pathol. 98: 577-590

Bruggen Cate Ten, H.J. 1968. Dental erosion in industry. Brit. J. Indust. Med. 25: 249-266

Cameron, G.R. 1954. Toxicity of chlorsulphonic acid-sulphur trioxide mixture smoke clouds. J. Path. Bact. 68: 197-204

Carabine, M.D., and J.E.L. Maddock. 1976. The growth of sulfuric acid aerosol particles when contacted with water vapour. Atmos. Environ. 10: 735-742

Cavender, F.L., W.H. Steinhagen, C.E. Ulrich, W.M. Busey, B.Y. Cockrell, J.K. Haseman, M.D. Hogan, and R.T. Drew. 1977a. Effects in rats and guinea pigs of short-term exposures to sulfuric acid mist, ozone, and their combination. J. Toxicol. Environ. Health 3: 521-533

Cavender FL, Williams JL, Steinhagen WH, Woods D. 1977b. Thermodynamics and toxicity of sulfuric acid mists. J. Toxicol. Environ. Health 2: 1147-1159

Chan, H.K., S. Eberl, E. Daviskas, C. Constable, and I. Young. 2002. Changes in lung deposition of aerosols due to hygroscopic growth: a fast SPECT study. J. Aerosol Med. 15: 307-311

Chaney, S., W. Blomquist, K. Muller, and P. DeWitt. 1980a. Biochemical effects of sulfuric acid mist inhalation by human subjects while at rest. Arch. Environ. Health 35: 270-275

Chaney, S., W. Blomquist, K. Muller, and G. Goldstein. 1980b. Biochemical changes in humans upon exposure to sulfuric acid aerosol and exercise. Arch. Environ. Health 35: 211-216

Chen, L.C., J.M. Fine, Q.-S. Qu, M.O. Amdur, and T. Gordon. 1992a. 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

Chen, L.C., P.D. Miller, M.O. Amdur, and T. Gordon. 1992b. Airway hyperresponsiveness in guinea pigs exposed to acid-coated ultrafine particles. J. Toxicol. Environ. Health 35: 165-174

Chen, L.C., Q. Qu, M.O. Amdur, and R.B. Schlesinger. 1995. Alteration of pulmonary macrophage intracellular pH following inhalation exposure to sulfuric acid/ozone mixtures. Exp. Lung Res. 21: 113-128

Clark, K.W., K.R. Anderson, W.S. Linn, and H. Gong Jr. 1995. Influence of breathing-zone ammonia on human exposures to acid aerosol pollution. J. Air Waste Manag. Assoc. 45: 923-925

Cockrell BY, Busey WM, Cavender FL. 1978. Respiratory tract lesions in guinea pigs exposed to sulfuric acid mist. J. Toxicol. Environ. Health. 4: 835-44

Cocks, A.T., and R.P Fernando. 1982. The growth of sulphate aerosols in the human airways. J. Aerosol Sci. 13: 9-19

Cocks, A.T., and W.J. McElroy. 1984. Modeling studies of the concurrent growth and neutralization of sulfuric acid aerosols under conditions in the human airways. Environ. Res. 35: 79-96

Conner, M.W., W.H. Flood, A.E. Rogers, and M.O. Amdur. 1989. Changes in the pulmonary lavage fluid of guinea pigs exposed to ultrafine zinc oxide with adsorbed sulfuric acid. J. Toxicol. Environ. Health. 1989. 26: 223-234

Couling, S.B., K.J. Sully, and A.B. Horn. 2003. Experimental study of the heterogeneous interaction of SO_3 and H_2O: formation of condensed phase molecular sulfuric acid hydrates. J. Am. Chem. Soc. 125: 1994-2003

Culp, D.J., L.R. Latchney, M.W. Frampton, M.R. Jahnke, P.E. Morrow, and M.J. Utell. 1995. Composition of human airway mucins and effects after inhalation of acid aerosol. Am. J. Physiol. 269: L358-370

Dahl, A.R., and W.C. Griffith. 1983. Deposition of sulfuric acid mist in the respiratory tracts of guinea pigs and rats. J Toxicol. Environ. Health 12: 371-383

Dahl, A.R., S.A. Felicetti, and B.A. Muggenburg. 1983a. Clearance of sulfuric acid-introduced 35S from the respiratory tracts of rats, guinea pigs and dogs following inhalation or instillation. Fund. Appl. Toxicol. 3: 293-297

Dahl, A.R., M.B. Snipes, B.A. Muggenburg, and T.C. Young. 1983b. Deposition of sulfuric acid mists in the respiratory tract of beagle dogs. J. Toxicol. Environ. Health 11:141-149

Daisley, H, and V. Simmons. 1999. Forensic Analysis of acute fatal poisonings in the southern districts of Trinidad. Vet. Human Toxicol. 41(1): 23-25

Diskin, A.M., P. Spanel, and D. Smith. 2003. Time variation of ammonia, acetone, isoprene and ethanol in breath: a quantitative SIFT-MS study over 30 days. Physiol. Meas. 24: 107-119

El-Fawal, H.A.N., and R.B. Schlesinger. 1994. Nonspecific airway hyperresponsiveness induced by inhalation exposure to sulfuric acid aerosol: an in vitro assessment. Toxicol. Appl. Pharmacol. 125: 70-76

El-Fawal, H.A.N., T. McGovern, and R.B. Schlesinger. 1995. Nonspecific bronchial responsiveness assessed in vitro following acute inhalation exposure to ozone and ozone/sulfuric acid mixtures. Exp. Lung Res. 21: 129-139

El-Sadik, Y.M., H.A. Osman, and R.M. El-Gazzar. 1972. Exposure to sulfuric acid in manufacture of storage batteries. JOM 14(3): 224-226

EPA (Environmental Protection Agency). 1996. Air Quality Criteria for Particulate Matter.

Fairchild, G.A., Kane, P., Adams, B, Coffin, D. 1975. Sulfuric acid and Streptococci clearance from respiratory tracts of mice. Arch. Environ. Health 30: 538-545

Ferron, G.A. 1977. The size of soluble aerosol particles as a function of the humidity of the air: application to the human respiratory tract. J. Aerosol Sci. 8: 251-267

Fine, J.M., T. Gordon, J.E. Thompson, and D. Sheppard. 1987. The role of titratable acidity in acid-induced bronchoconstriction. Am. Rev. Respir. Dis. 135: 826-830

Finlay, W.H., K.W. Stapelton, H.K. Chan, P. Zuberbuhler, and I. Gonda. 1996. Regional deposition of inhaled hygroscopic aerosols: in vivo SPECT compared with mathematic modeling. J. Appl. Physiol. 81: 374-383

Folinsbee, L.J. 1989. Human health effects of exposure to airborne acid. Environ. Health Persp. 79: 195-9

Frampton, M.W., N.J. Roberts, D.J. Culp, P.E. Morrow, and M.J. Utell. 19??. Effects of exposure to H2SO4 aerosol on alveolar cell populations in humans. Am. Rev. Respir. Dis. 141 (4 part 2), A76

Frampton, M.W., K.Z. Voter, P.E. Morrow, N.J. Roberts, D.J. Culp, C. Cox, and M.J. Utell. 1992. Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. Am. Rev. Respir. Dis. 146: 626-632

Frampton, M.W., P.E. Morrow, C. Cox, P.C. Levi, J.J. Condemi, D. Speers, F.R. Gibb, and M.J. Utell. 1995. Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. Environ. Res. 69: 1-14

Fujimaki, H., N. Katayama, and K. Wakamori. 1992. Enhanced histamine release from lung mast cells of guinea pigs exposed to sulfuric acid aerosols. Environ. Res. 58: 117-123

Gamble, J., W. Jones, and J. Hancock. 1984a. Epidemiological – environmental study of lead acid battery workers. II. Acute effects of sulfuric acid on the respiratory system. Environ. Res. 35: 11-29

Gamble, J., W. Jones, J. Hancock, and R.L. Meckstroth. 1984b. Epidemiological – environmental study of lead acid battery workers. III. Chronic effects of sulfuric acid on the respiratory system and teeth. Environ. Res. 35: 30-52

Gearhart, J.M., and R.B. Schlesinger. 1986. Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7: 681-689

Gearhart, J.M., and R.B. 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

Gearhart, J.M., and R.B. Schlesinger. 1989. Sulfuric acid-induced changes in physiology and structure of the tracheobronchial airways. Environ. Health Persp. 79: 127-137

Goldman, A., and W.T. Hill. 1953. Chronic bronchopulmonary disease due to inhalation of sulfuric acid fumes. Arch. Indust. Hyg. Occ. Med. 8(3): 205-211

Grasel, S.S., V.A.F. Alves, C.S. da Silva, O.L.M. Cruz, E.R. Almeida, and E. de Oliveira. 2003. Clinical and histopathological changes of the nasal mucosa induced by occupational exposure to sulphuric acid mist. Occup. Environ. Med. 60: 395-402

Grose, E.C., J.H. Richards, J.W. Illing, F.J. Miller, D.W. Davies, J.A. Graham, and D.E. Gardner. 1982. Pulmonary host defense responses to inhalation of sulfuric acid and ozone. J. Toxicol. Environ. Health 10: 351-362

Gysel, M., E. Weingartner, and U. Baltensperger. 2002. Hygroscopicity of aerosol particles at low temperatures. 2. Theoretical and experimental properties of laboratory generated aerosols. Environ. Sci. Technol. 36: 63-68

Hackney, J.D., W.S. Linn, and E.L. Avol. 1985. Potential risks to human respiratory health from “acid fog”: evidence from experimental studies of volunteers. Environ. Health Persp. 63: 57-61

Hackney, J.D., W.S. Linn, and E.L. Avol. 1989. Acid fog: effects on respiratory function and symptoms in healthy and asthmatic volunteers. Environ. Health Persp. 79: 159-162

Hanley, Q.S., J.Q. Koenig, T.V. Larson, T.L. Anderson, G. Van Belle, V. Rebolledo, D.S. Covert, and W.E. Pierson. 1992. Response of young asthmatic patients to inhaled sulfuric acid. Am. Rev. Respir. Dis. 145: 326-331

Hiller, F.C. 1991. Health implications of hygroscopic growth in the human respiratory tract. J. Aerosol Med. 4: 1-23

Hirano, S., S. Adachi, M. Ono, H. Nitta, I. Kaneko, and I. Wakisaka. 1985. Respiratory response to sulfuric acid and sulfate salts mist. Jpn. J. Hyg. 39: 905-913 (*Japanese article, abstract in English*)

Holma, B. 1985. Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. Sci. Total Environ. 41: 101-123

Holma, B. 1989. Effects of inhaled acids on airway mucus and its consequences for health. Environ. Health Persp. 79: 109-113

Holma B, Lindegren M, Andersen JM. 1977. pH effects on ciliomotility and morphology of respiratory mucosa. Arch Environ Health. 32(5):216-26.

Horstman, D., M. Hazucha, E. Haak, and R. Stacy. 1982. Effects of submicronic sulfuric acid aerosol on human pulmonary function. Arch. Environ. Health 37: 136-141

Horvath, S.M., L.J. Folinsbee, and J.F. Bedi. 1982. Effects of large (0.9 micrometers) sulfuric acid aerosols on human pulmonary function. Environ Res. 28: 123-130

Horvath, S.M., L.J. Folinsbee, and J.F. Bedi. 1987. Combined effect of ozone and sulfuric acid on pulmonary function in man. Am. Ind. Hyg. Assoc. J. 48(2): 94-98

Hruby, J., and J. Butler. 1975. Variability of routine pulmonary function tests. Thorax 30: 548-553

Hunt, R.D., and D.T. Williams. 1977. Spectrometric measurements on ammonia in normal human breath. Am. Lab. 9: 10-23

Hunt, J.F., E. Erwin, L. Palmer, J. Vaughan, N. Malhotra, T.A.E. Platts-Mills, and B. Gaston. 2002. Expression and activity of pH-regulatory glutaminase in the human airway epithelium. Am. J. Respir. Crit. Care Med. 165: 101-107

IARC (International Agency for Research on Cance). 1992. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 54. Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals. World Health Organization, UK.

Jones, W., and J. Gamble. 1984. Epidemiological-environmental study of lead acid battery workers. I. Environmental study of five lead acid battery plants. Environ. Res. 35: 1-10

Juhos, L.T., M.J. Evans, R. Mussenden-Harvey, N.H. Furiosi, C.E. Lapple, and G. Freeman. 1978. Limited exposure of rats to H_2SO_4 with and without O_3. J. Environ. Sci. Health C. 13: 33-47

Kapias, T., and R.F. Griffiths. 1999. Dispersion and thermodynamics of clouds generated from spills of SO_3 and oleum. J. Hazard. Materials A67: 9-40

Kerr, H.D., T.J. Kulle, B.P. Farrell, L.R. Sauder, J.L. Young, D.L. Swift, and R.M. Borushok. 1981. Effects of sulfuric acid aerosol on pulmonary function in human subjects: an environmental chamber study. Environ. Res. 26: 42-50

Kikuchi, R. 2001. Environmental management of sulfur trioxide emission: impact of SO_3 on human health. Environ. Manage. 27: 837-844

Kilgour, J.D., F. Foster, A. Soames, D.G. Farrar, and P.M. Hext. 2002. Responses in the respiratory tract of rats following exposure to sulphuric acid aerosols for 5 or 28 days. J. Appl. Toxicol. 22: 387-395

Kim, C.S. 2000. Methods of calculating lung delivery and deposition of aerosol particles. Respir. Care 45: 695-711

Kimmel, T.A., L.C. Chen, M.C. Bosland, and C. Nadziejko. 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

Kleinman MT, Bailey RM, Chang YT, Clark KW, Jones MP, Linn WS, Hackney JD. 1981. Exposures of human volunteers to a controlled atmospheric mixture of ozone, sulfur dioxide and sulfuric acid. Am Ind Hyg Assoc J. 42(1):61-9.

Knapp, M.J., W.B. Bunn, and G.M. Stave. 1991. Adult respiratory distress syndrome from sulfuric acid fume inhalation. Southern Med. J. 84(8): 1031-1033

Kobayashi, T., and Y. Shinozaki. 1993. Effects of sulfuric acid-aerosol on airway responsiveness in guinea pigs: concentration and time dependency. J. Toxicol. Environ. Health 39: 261-272

Koenig, J.Q., W.E. Pierson, and M. Horike. 1983. The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. Am. Rev. Respir. Dis. 128: 221-225

Koenig, J.Q., M.S. Morgan, M. Horike, and W.E. Pierson. 1985. The effects of sulfur oxides on nasal and lung function in adolescents with extrinsic asthma. Allergy Clin. Immunol. 76: 813-818

Koenig, J.Q., D.S. Covert, and W.E. Pierson. 1989. Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. Environ. Health Persp. 79: 173-178

Koenig, J.Q., D.S. Covert, T.V. Larson, and W.E. Pierson. 1992. The effect of duration of exposure on sulfuric acid-induced pulmonary function changes in asthmatic adolescent subjects: a dose-response study. Toxicol. Indust. Health 8(5): 285-296

Koenig, J.Q., K. Dumler, V. Rebolledo, P.V. Williams, and W.E. Pierson. 1993. Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics. Arch. Environ. Health 48(3): 171-175

Kulle, T.J., H.D. Kerr, B.P. Farell, L.R. Sauder, and M.S. Bermel. 1982. Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. Am. Rev. Respir. Dis. 126: 996-1000

Larson, T.V. 1989. The influence of chemical and physical forms of ambient air acids on airway doses. Environ. Health Persp. 79: 7-13

Larson, T.V., D.S. Covert, R. Frank, and R.J. Charlson. 1977. Ammonia in the human airways: neutralization of acid sulfate aerosols. Science (Washington DC) 197: 161-163

Larson, T., R. Frank, D. Covert, D. Holub, and M. Morgan. 1980. The chemical neutralization of inhaled sulfuric acid aerosol. Am. J. Ind. Med. 1: 449-452

Larson, T.V., R. Frank, D.S. Covert, D. Holub, and M.S. Morgan. 1982. Measurements of respiratory ammonia and the chemical neutralization of inhaled sulfuric acid aerosol in anesthetized dogs. Am. Rev. Respir. Dis. 125: 502-506

Larson, T.V., Q.S. Hanley, J.Q. Koenig, and O. Bernstein. 1993. Calculation of acid aerosol dose. In: Mohr, U., ed. Advances in controlled clinical inhalation studies. Berlin. Federal Republic of Germany: Springer-Verlag; 109-121

Laskin, S., and A.R. Sellakumar. 1978. Comparison of pulmonary carcinogenicity of known carcinogens with and without added H_2SO_4 mists, airborne respirable particles, and gases. Final Report of the Institute of Environmental Medicine, New York University Medical Center, Project No. 68-02-1750

Last, J.A., and K.E. Pinkerton. 1997. Chronic exposure of rats to ozone and sulfuric acid aerosol: biochemical and structural responses. Toxicology 166: 133-146

Laube, B.L., S.M. Bowes, L.M. Links, K.K. Thomas, and R. Frank. 1993. Acute exposure to acid fog. Effects on mucociliary clearance. Am. Rev. Respir. Dis. 147: 1105-1111

Leduc, D. S. Fally, P. de Vuyst, R. Wollast, and J.-C. Yernault. 1995. Acute exposure to realistic acid fog: effects on respiratory function and airway responsiveness in asthmatics. Environ. Res. 71: 89-98

Lee, M.M., S. Schürch, S.H. Roth, X. Jiang, S. Cheng, S. Bjarnason, and F.H.Y. Green. 1995. Effects of acid aerosol exposure on the surface properties of airway mucus. Exp. Lung Res. 21: 835-851

Lee, M.M., F.H.Y. Green, S.H. Roth, A. Karkhanis, S.G. Bjarnason, and S. Schürch. 1999. Sulfuric acid aerosol induces changes in alveolar surface tension in the guinea pig but not in the rat. Exp. Lung Res. 25: 229-244

Leikauf, G., D.B. Yeates, K.A. Wales, D. Spektor, R.E. Albert, and M. Lippmann. 1981. Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. Am. Ind. Hyg. Assoc. J. 42: 273-282

Leikauf, G.D., D.M. Spektor, R.E. Albert, and M. Lippmann. 1984. Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. Am. Ind. Hyg. Assoc. J. 45(5): 285-292

Linn, W.S., E.L. Avol, D.A. Shamoo, J.D. Whynot, K.R. Anderson, and J.D. Hackney. 1986. Respiratory responses of exercising asthmatic volunteers exposed to sulfuric acid aerosol. J. Air Poll. Contr. Assoc. 36(12): 1323-1328

Linn, W.S., E.L. Avol, K.R. Anderson, D.A. Shamoo, R.-C. Peng, and J.D. Hackney. 1989. Effect of droplet size on respiratory responses to inhaled sulfuric acid in normal and asthmatic volunteers. Am. Rev. Respir. Dis. 140: 161-166

Linn, W.S., D.A. Shamoo, K.R. Anderson, R.-C. Peng, E.L. Avol, and J.D. Hackney. 1994. Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. Am. J. Respir. Crit. Care Med. 150: 431-440

Linn, W.S., K.R. Anderson, D.A. Shamoo, S.A. Edwards, T.L. Webb, J.D. Hackney, and H. Gong. 1995. Controlled exposures of young asthmatics to mixed oxidant gases and acid aerosol. Am. J. Respir. Crit. Care Med. 152: 885-891

Linn, W.S., H. Gong, D.A. Shamoo, K.R. Anderson, and E.L. Avol. 1997. Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. Arch. Environ. Health 52(3): 179-187

Lippmann, M., R.B. Schlesinger, and G. Leikauf. 1980. Effects of sulfuric acid aerosol inhalations. Am. J. Ind. Med. 1: 375-381

Lippmann, M., G. Leikauf, D. Spektor, R.B. Schlesinger, and R.E. Albert. 1981. The effects of irritant aerosols on mucus clearance from large and small conductive airways. Chest 80: 873-877

Lippmann, M., R.B. Schlesinger, G. Leikauf, D. Spektor, and R.E. Albert. 1982. Effects of sulphuric acid aerosols on respiratory tract airways. Ann. Occup. Hyg. 26: 677-690

Lippmann, M., and R.B. Schlesinger. 1984. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. J. Toxicol. Environ. Health 13: 441-469

Loerting, T., and K.R. Liedl. 2000. Toward elimination of discrepancies between theory and experiment: the rate constant of the atmospheric conversion of SO_3 to H_2SO_4. PNAS 97:8874-8878

Malcolm, D., and E. Paul. 1961. Erosion of the teeth due to sulfuric acid in the battery industry. Brit. J. Industr. Med. 18: 63-69

Martonen, T.B., and M. Patel. 1981. Modeling the dose distribution of H_2SO_4 aerosol in the human tracheobronchial tree. Am. Ind. Hyg. Assoc. J. 42: 453-460

Martonen, T.B., K.A. Bell, R.F. Phalen, A.F. Wilson, and A. Ho. 1982. Growth rate measurements and deposition modelling of hygroscopic aerosols in human tracheobronchial models. Ann. Occup. Hyg. 26: 93-108

Martonen, T.B., A.E. Barnett, and F.J. Miller. 1985. Ambient sulfur aerosol deposition in man: modeling the influence of hygroscopy. Environ. Health Persp. 63: 11-24

Martonen, T.B., and Z. Zhang. 1993. Deposition of sulfate acid aerosols in the developing human lung. Inhal. Toxicol. 5: 165-187

Martonen, T.B., and J.D. Schroeter. 2003a. Risk assessment dosimetry model for inhaled particulate matter: I. Human subjects. Toxicol. Lett. 138: 119-132

Martonen, T.B., and J.D. Schroeter. 2003b. Risk assessment dosimetry model for inhaled particulate matter: II. Laboratory surrogates (rat). Toxicol. Lett. 138: 133-142

McMurray, P.H., H. Takano, and G.R. Anderson. 1983. Study of the ammonia (gas) – sulfuric acid (aerosol) reaction rate. Environ. Sci. Technol. 17: 347-351

Morrow, P.E. 1986. Factors determining hygroscopic aerosol deposition in airways. Physiol. Rev. 66: 330-376

Murray, F.J., Schwetz, B.A., Nitschke, K.D., Crawford, A.A., Quast, J.F., and R.E. Staples. 1979. Embryotoxicity of inhaled sulfuric acid aerosol in mice and rabbits. J. Environ. Sci. Health C13: 251-266

Mustajbegovic, J., E. Zuskin, E.N. Schachter, J. Kern, K. Vitale, Z. Ebling, and M. Vrcic-Keglevic. 2000. Respiratory findings in chemical workers exposed to low concentrations of organic and inorganic air pollutants. Am. J. Ind. Med. 38: 431-440

Naumann, B.D., and R.B. Schlesinger. 1986. Assessment of early alveolar particle clearance and macrophage function following acute inhalation of sulfuric acid mist. Exp. Lung Res. 11: 13-33

Neas, L.M., D.W. Dockery, P. Koutrakis, D.J. Tollerud, and F.E. Speizer. 1995. The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122

Newhouse, M.T., M. Dolovich, G. Obminski, and R.K. Wolff. 1978. Effect of TLV levels of SO2 and H2SO4 on bronchial clearance in exercising man. Arch. Environ. Health ??:24-32

NIOSH. 1974. Criteria for a recommended standard. Occupational exposure to sulfuric acid. U.S. Department of Health, Education, and Welfare; Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health.

Norwood, D.M., T. Wainman, P.J. Lioy, and J.M. Waldman. 1992. Breath ammonia depletion and its relevance to acidic aerosol exposure studies. Arch. Environ. Health 47: 309-313

Osebold JW, Gershwin LJ, Zee YC. 1980. Studies on the enhancement of allergic lung sensitization by inhalation of ozone and sulfuric acid aerosol. J Environ Pathol Toxicol. 1980 Jun-Jul;3(5-6):221-34.

Pattle, R.E., F. Burgess, and H. Cullumbine. 1956. The effects of a cold environment and of ammonia on the toxicity of sulfuric acid mist to guinea pigs. J. Path. Bact. 72: 219-232

Phalen, R.F., J.L. Kenoyer, T.T. Crocker, T.R. McClure. 1980. Effects of sulfate aerosols in combination with ozone on elimination of tracer particles by rats. J. Toxicol. Environ. Health 6: 797-810

Qu, Q.-S., L.C. Chen, T. Gordon, M. Amdur, and J.M. Fine. 1993. Alteration of pulmonary macrophage intracellular pH regulation by sulfuric acid aerosol exposures. Toxicol. Appl. Pharmacol. 121: 138-143

Raizenne, M.E., R.T. Burnett, B. Stern, C.A. Franklin, and J.D. Spengler. 1989. Acute lung function responses to ambient acid aerosol exposures in children. Environ. Health Persp. 79: 179-185

Roth, S.H., S.G. Bjarnason, G.T. De Sanctis, F. Feroah, X. Jiang, A. Karkhanis, and F.H.Y. Geen. 1998. Ventilatory responses in awake guinea pigs exposed to acid aerosols. J. Toxicol. Environ. Health 54: 261-283

Runckle, B.K., and F.F. Hahn. 1976. The toxicity of H_2SO_4 aerosols to CD-1 mice and Fisher-344 rats. Ann. Rep. Inhal. Toxicol. Res. Inst. 435-439

Sackner, M.A., Ford, D., Fernandez, J., Cipley, J., Perez, D., Kwoka, M., Reinhart, M., Michaelson, E.D., Schreck, R., and A. Wanner. 1978. Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep and humans. Am. Rev. Resp. Dis. 118: 497

Sarangapani, R., and A.S. Wexler. 1996. Growth and neutralization of sulfate aerosols in human airways. J. Appl. Physiol. 81: 480-490

Sathiakumar, N., E. Delzell, Y. Amoateng-Adjepong, R. Larson, and P. Cole. 1997. Epidemiologic evidence on the relationship between mists containing sulfuric acid and respiratory tract cancer. Crit. Rev. Toxicol. 27(3): 233-251

Schaper, M., and Y. Alarie. 1985. The effects of aerosols of carbamylcholine, serotonin and propanolol on the ventilatory response to CO_2 in guinea pigs and comparison with the effects of histamine and sulfuric acid. Acta Pharmacol. Toxicol. 56: 244-249

Scherer, P.W., F.R. Haselton, L.M. Hanna, and D.R. Stone. 1979. Growth of hygroscopic aerosols in a model of bronchial airways. J. Appl. Physiol. 47: 544-550

Schlesinger, R.B. 1987a. Functional assessment of rabbit alveolar macrophages following intermittent inhalation exposures to sulfuric acid mist. Fund. Appl. Toxicol. 8: 328-334

Schlesinger, R.B. 1987b. Effects of intermittent inhalation exposures to mixed atmospheres of NO_2 and H_2SO_4 on rabbit alveolar macrophages. J. Toxicol. Environ. Health 22: 301-312

Schlesinger, R.B. 1989. Factors affecting the response of lung clearance systems to acidic aerosols: role of exposure concentration, exposure time, and relative acidity. Environ. Health Perspect. 79: 121-126

Schlesinger, R.B. 1990. Exposure-response pattern for sulfuric acid-induced effects on particle clearance from the respiratory region of rabbits lungs. Inhal. Toxicol. 2: 21-27

Schlesinger, R.B., Lippmann, M, Albert, R. 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

Schlesinger, R.B., M. Halpern, R.E. Albert, and M. Lippmann. 1979. Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. J. Environ. Pathol. Toxicol. 2: 1351-1367

Schlesinger, R.B., Naumann, B.D., Chen, L.D. 1983. Physiological and histological alterations in the bronchial mucociliary clearance in rabbits following intermittent oral or nasal inhalation of sulfuric acid mist. J. Toxicol. Environ. Health 12: 441

Schlesinger, R.B., L.C. Cheng, and K.E. Driscoll. 1984. Exposure-response relationship of bronchial mucociliary clearance in rabbits following acute inhalations of sulfuric acid mist. Toxicology Letters 22: 249-254

Schlesinger, R.B., and J.M. Gearhart. 1986. Early alveolar clearance in rabbits intermittently exposed to sulfuric acid mist. J. Toxicol. Environ. Health 17: 213-220

Schlesinger, R.B., L.C. Chen, I. Finkelstein, and J.T. Zelikoff. 1990a. Comparative potency of inhaled acidic sulfates: speciation and the role of hydrogen ion. Environ. Res. 52: 210-224

Schlesinger, R.B., A.F. Gunnison, and J.T. Zelikoff. 1990b. Modulation of pulmonary eicosanoid metabolism following exposure to sulfuric acid. Fundam. Appl. Toxicol. 15: 151-162

Schlesinger, R.B., J.M. Fine, and L.C. Chen. 1992a. Interspecies differences in the phagocytic activity of pulmonary macrophages subjected to acidic challenge. Fundam. Appl. Toxicol. 19: 584-589

Schlesinger, R.B., J.E. Gorczynski, J. Dennison, L. Richards, P.L. Kinney, and M.C. Bosland. 1992b. Long-term intermittent exposure to sulfuric acid aerosol, ozone, and their combination: alterations in tracheobronchial mucociliary clearance and epithelial secretory cells. Exp. Lung Res. 18: 505-534

Schlesinger, R.B., J.T. Zelikoff, L.C. Chen, and P.L. Kinney. 1992c. Assessment of toxicologic interactions resulting from acute inhalation exposure to sulfuric acid and ozone mixtures. Toxicol. Appl. Pharmacol. 115: 183-190

Schlesinger, R.B., and L.C. Chen. 1994. Comparative biological potency of acidic sulfate aerosols: implications for the interpretation of laboratory and field studies. Environ. Res. 65: 69-85

Schwartz, L.W., Moore, P.F., Chang, P.D., Tarkington, B.K.,Dungworth, D.L. and W.S. Tyler. 1977. Short-term effects of sulfuric acid aerosols on the respiratory tract. A morphological study in guinea pigs, mice, rats and monkeys. In: Biochemical effects of environmental pollutants, Lee, D.S. (ed.) Ann Arbor Science Publishers: Michigan; 257-271.

Sendelbach, L.E., H.P. Witschi, and A.F. Tryka. 1986. Acute pulmonary toxicity of berillium sulfate inhalation in rats and mice: cell kinetics and histopathology. Toxicol. Appl. Pharmacol. 85: 248-256

Senthilmohan, S.T., D.B. Milligan, M.J. McEwan, C.G. Freeman, and P.F. Wilson. 2000. Quantitative analysis of trace gases of breath during exercise using the new SIFT-MS technique. Redox Rep. 5: 151-153

Silbaugh, S.A., R.K. Wolff, W.K. Johnson, J.L. Mauderly, and C.A. Macken. 1981a. Effects of sulfuric acid aerosols on pulmonary function of guinea pigs. J. Toxicol. Environ. Health 7: 339-352

Silbaugh, S.A., J.L. Mauderly, and C.A. Macken. 1981b. Effects of sulfuric acid and nitrogen dioxide on airway responsiveness of the guinea pig. J. Toxicol. Environ. Health 7: 31-45

Sim, V.M., and R.E. Pattle. 1957. Effect of possible smog irritants on human subjects. J.A.M.A. 165(15): 1908-1957

Soskolne, C.L., G. Pagano, M. Cipollaro, J.J. Beaumont, and G.G. Giordano. 1989. Epidemiologic and Toxicologic evidence for chronic health effects and the underlying biologic mechanisms involved in sub-lethal exposures to acidic pollutants. Arch. Environ. Health 44(3): 180-191

Spektor, D.M., G.D. Leikauf, R.E. Albert, and M. Lippmann. 1985. Effects of submicrometer sulfuric acid aerosols on mucociliary transport and respiratory mechanics in asymptomatic asthmatics. Environ Res. 37(1):174-91

Spektor, D., B.M. Yen, and M. Lippmann. 1989. Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. Environ. Health Persp. 79: 167-172

Spengler, J.D., G.J. Keeler, P. Koutrakis, P.B. Ryan, M. Raizenne, C.A. Franklin. 1989. Exposures to acidic aerosols. Environ. Health Persp. 79: 43-51

Stengel, P.W., A.M. Bendele, S.L. Cockerham, and S.A. Silbaugh. 1993. Sulfuric acid induces airway hyperresponsiveness to substance P in the guinea pig. Agents Actions 39: C128-C139

Stueven, H.A., P. Coogan, and V. Valley. 1993. A hazardous material episode: sulfur trioxide. Vet. Hum. Toxicol. 35(1): 37-38

Suresh, B. (2003) Commodity Report. ISM eDigest: Chemicals 1: 1-4 (http://www.ism.ws/AboutISM/eDigest_Chemicals/newsletter112003.cfm)

Swenberg, J.A., and R.O. Beauchamp Jr. 1997. A review of the chronic toxicity, carcinogenicity, and possible mechanisms of action of inorganic acid mists in animals. Crit. Rev. Toxicol. 27: 253-259

Teramoto, S., H. Tanaka, S. Kaneko, and S. Abe. 2000. Neurokinin-1 receptor antagonist inhibits short-term sulfuric-acid-induced airway hyperresponsiveness in sensitized guinea pigs. Int. Arch. Allergy Immunol. 121: 53-56

Treon, J.F., F.R. Dutra, J. Cappel, H. Sigmon, and W. Younker. 1950. Toxicity of sulfuric acid mist. Ind. Hyg. Occ. Med. 2: 716-734

Troyanov, S., H. Ghezzo, A. Cartier, and J.L. Malo. 1994. Comparison of circadian variations using FEV1 and peak expiratory flow rates among normal and asthmatic subjects. Thorax 49: 775-780

Tunncliffe, W.S., D.E. Evans, D. Mark, R.M. Harrison, and J.G. Ayres. 2001. The effect of exposure to sulphuric acid on the early asthmatic response to inhaled grass pollen allergen. Eur. Respir. J. 18: 640-646

Uleckiene, S., and L. Griciute. 1997. Carcinogenicity of sulfuric acid in rats and mice. Pathol. Oncol. Res. 3: 38-43

Utell, M.J., P.E. Morrow, D.M. Speers, J. Darling, and R.W. Hyde. 1983. Airway responses to sulfate and sulfuric acid aerosols in asthmatics. An exposure-response relationship. Am. Rev. Respir. Dis. 128: 444-450

Utell, M.J., J.A. Mariglio, P.E. Morrow, F.R. Gibb, and D.M. Speers. 1989. Effects of inhaled acid aerosols on respiratory function: the role of endogenous ammonia. J. Aerosol Med. 2(2): 141-147

Utell, M.J., M.W. Frampton, and P.E. Morrow. 1991. Air pollution and asthma: clinical studies with sulfuric acid aerosols. Allergy Proc. 12: 385-388

Utell, M.J., M.W. Frampton, P.E. Morrow, C. Cox, P.C. Levy, D.M. Speers, and F.R. Gibb. 1994. Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. Res. Rep. Health Eff. Inst. 70: 37-93

Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423

Vollmuth, T.A. and R.B. Schlesinger. 1984. Measurement of respiratory tract ammonia in the rabbit and implications to sulfuric acid inhalation studies. Fundam. Appl. Toxicol. 4: 455-464

Williams, M.K. 1970. Sickness absence and ventilatory capacity of workers exposed to sulfuric acid mist. Brit. J. Industr. Med. 27: 61-66

Wolff, R.K., S.A. Silbaugh, D.G. Brownstein, R.L. Carpenter, and J.L. Mauderly. 1979. Toxicity of 0.4- and 0.8-µm sulfuric acid aerosols in the guinea pig. J. Toxicol. Environ. Health 5: 1037-1047

Wolff, R.R., Muggenburg, B.A., Silbauch, S.A. 1981. Effects of 0.3 and 0.9 µm sulfuric acid aerosols on tracheal mucous clearance in beagle dogs. Am. Rev. Resp. Dis. 123: 291

Wolff, R.K., R.F. Henderson, R.H. Gray, R.L. Carpenter, F.F. Hahn. 1986. Effects of sulfuric acid mist inhalation on mucous clearance and on airway fluids of rats and guinea pigs. J. Toxicol. Environ. Health 17: 129-142

Xia, Z.-L., S.-X. Jin, Y.-L. Zhou, J.-L. Zhu, F.-S. Jin, S.-L. Hu, H. Fu, T.-Y. Jin, and D.C. Christiani. 1999. Analysis of 541 cases of occupational acute chemical injuries in a large petrochemical company in China. Int. Occup. Environ. Health 5: 262-266

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

Zelikoff, J.T., M.P. Sisco, Z. Yang, M.D. Cohen, R.B. Schlesinger. 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

Zwart, A. 1984. Acute inhalation toxicity study of sulfuric acid mist in rats. TNO, Netherlands organisation for applied scientific research, unpublished report no. V 84.411/240540. Submitted by TNO with agreement of the sponsor.

APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key study:	various human volunteer studies
Toxicity Endpoint:	respiratory irritation in exercising asthmatics A weight-of-evidence approach based on the results of various studies clearly indicated that the first signs of respiratory irritation that can be characterized as notable discomfort occur at concentrations higher than 0.2 mg/m^3.
Time scaling:	Flatlined.
Uncertainty factors:	Since the test subjects included exercising asthmatics, the most sensitive subpopulation, an intraspecies uncertainty factor of 1 is considered sufficient.
Calculations:	n.a.
10-minute AEGL-1	0.2 mg/m^3
30-minute AEGL-1	0.2 mg/m^3
1-hour AEGL-1	0.2 mg/m^3
4-hour AEGL-1	0.2 mg/m^3
8-hour AEGL-1	0.2 mg/m^3

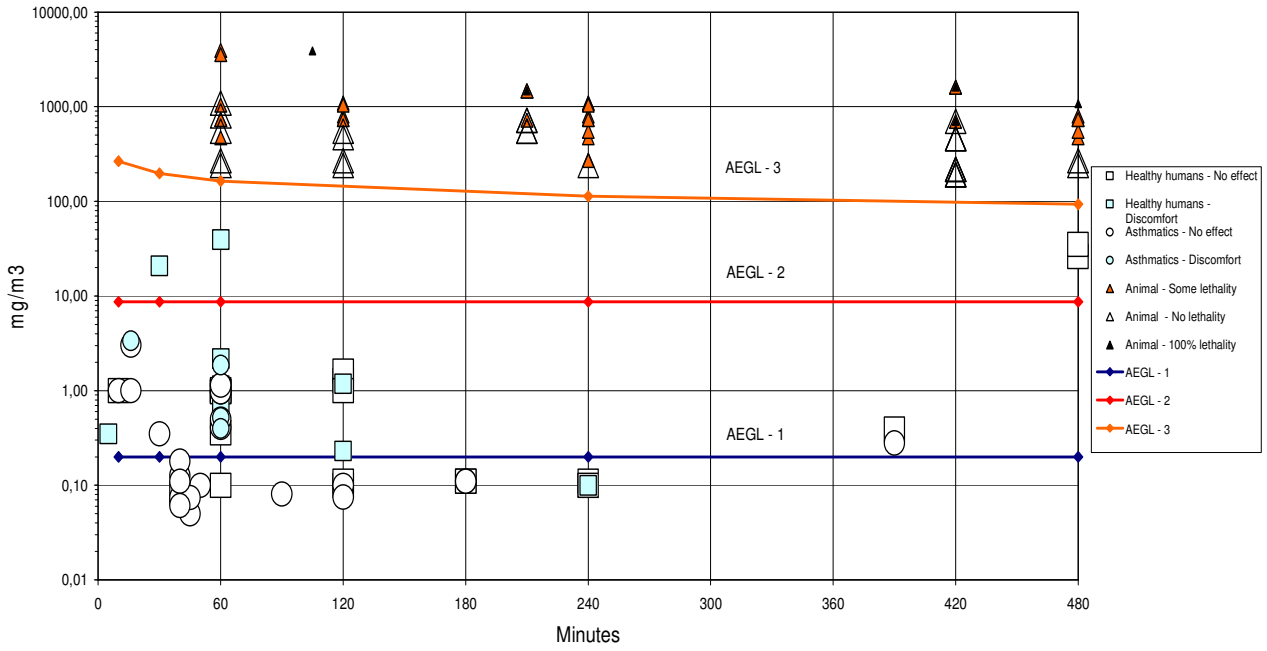
Derivation of AEGL-2

Key study:	El-Sadik *et al.* 1972
Toxicity Endpoint:	Absence of severe acute or disabling effects in humans at 26.0 mg/m^3 (8-hour exposure)
Time scaling:	Flatlined
Uncertainty factors:	3 for intraspecies
Calculations:	n.a.
10-minute AEGL-2	8.7 mg/m^3 (similar to 8-hour value)
30-minute AEGL-2	8.7 mg/m^3 (similar to 8-hour value)
1-hour AEGL-2	8.7 mg/m^3 (similar to 8-hour value)
4-hour AEGL-2	8.7 mg/m^3 (similar to 8-hour value)
8-hour AEGL-2	(POD) 26.0 mg/m^3 /3 = 8.7 mg/m^3

Derivation of AEGL-3

Key study:	Runckle and Hahn 1976
Toxicity Endpoint:	Lethality in mice
Time scaling:	data derived (LC_{01} values for each time point was calculated as POD by probit analysis according to Ten Berge)
Uncertainty factors:	1 for interspecies and 3 for intraspecies
Calculations:	probit analysis
10-minute AEGL-3	(LC_{01}: 796 mg/m^3 /3 =) 270 mg/m^3
30-minute AEGL-3	(LC_{01}: 592 mg/m^3 /3 =) 200 mg/m^3
1-hour AEGL-3	(LC_{01}: 491 mg/m^3 /3 =) 160 mg/m^3
4-hour AEGL-3	(LC_{01}: 338 mg/m^3 /3 =) 110 mg/m^3
8-hour AEGL-3	(LC_{01}: 280 mg/m^3 /3 =) 93 mg/m^3

APPENDIX B: Category Plot



This category plot is a combination of Figures 1, 2, 3 and 4. The following notes apply to this category plot:

1. No adequate human data that address the level of effects defined by the AEGL-2 were available. Therefore, no human data points relating to 'disablity' are presented. Further, animal data points addressing 'discomfort' and 'disability' are not shown because many human studies are available and provide an adequate data base for derivation of AEGL-1 and AEGL-2 values.
2. The most left situated colored square in this figure (datapoint: 0.35 mg/m^3, 5 min) is from Amdur *et al.* 1952b. The significance of the effect ("expiratory flow") is unclear. The study is old and limitedly described and the results do not correspond well to those of other (later and well-performed) studies.
3. The lowest (discomfort) effect concentration (0.1 mg/m^3, 240 min.) in figure 2 is observed by Kulle *et al*. 1982, where 1/12 healthy exercising volunteers reported mild throat irritation. The method of recording the symptoms was not given and the study has been limitedly reported. This observation does not correspond with the results of other studies in exercising healthy adults and asthmatics exposed under comparable conditions.

APPENDIX C: Derivation Summary for Sulfuric acid and sulfur trioxide AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFURIC ACID AND SULFUR TRIOXIDE (CAS Reg. No. 7664-93-9, 7446-11-9, 8014-95-7) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3	0.2 mg/m^3
Key Reference: various studies				
Test Species/Strain/Number: humans				
Exposure Route/Concentrations/Durations: inhalation // 0.01-39.4 mg/m^3 // up to 390 minutes				
Effects: respiratory irritation above 0.2 mg/m^3				
Endpoint/Concentration/Rationale: respiratory irritation // 0.2 mg/m^3 // all human data (more than 600 volunteers tested for irritation) of healthy and asthmatic subjects were combined and showed that some respiratory irritation started at levels above 0.2 mg/m^3.				
Uncertainty Factors/Rationale: 1 // There was a very large database of controlled human experiments with exercising asthmatics Total uncertainty factor: 1 Interspecies: n.a. Intraspecies: 1				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: n.a.				
Time Scaling: none Data Adequacy: very good				

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3
Key Reference: El-Sadik *et al*. 1972				
Test Species/Strain/Number: human (workers)				
Exposure Route/Concentrations/Durations: inhalation // 26-35 mg/m^3 // 8-h workshifts for a long period				
Effects: typical long term effects like tooth erosion. No acute effects relevant to AEGL-2				
Endpoint/Concentration/Rationale: Absence of acute severe or disabling effects // 26 mg/m^3 // Human data were used because the human database was large (n>1000) and animal to human extrapolation was difficult due to complex factors of deposition.				
Uncertainty Factors/Rationale: intraspecies 3 // to account for human variation in susceptibility Total uncertainty factor: 3 Interspecies: n.a. Intraspecies: 3				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: n.a.				
Time Scaling: none Data Adequacy: quantity very good, usefulness for AEGL-2 poor				

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3
Key Reference: Runckle and Hahn 1976				
Test Species/Strain/Number: mouse // CD-1 // 10-14 per dosing group and per time point				
Exposure Route/Concentrations/Durations: inhalation // 270-550-730-1040 mg/m^3 // 1-2-4-8 hours				
Effects: death				
Endpoint/Concentration/Rationale: lethality // LC01 // according to SOP				
Uncertainty Factors/Rationale: standard Total uncertainty factor: 3 Interspecies: 1 Intraspecies: 3				
Modifying Factor: none				
Animal to Human Dosimetric Adjustment: none				
Time Scaling: data derived, using probit-analysis according to Ten Berge Data Adequacy: very good				