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The Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals

140. Sulphuric, hydrochloric, nitric and phosphoric acids

Marianne van der Hagen
Jill Järnberg

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances.

For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed.

Whereas NEG adopts the documents by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document were made by Cand. Scient Marianne van der Hagen at the Norwegian Pollution Control Authority, and Dr. Jill Järnberg at the Swedish Work Environment Authority. The draft document was discussed within the group and the final version was accepted by NEG on April 1, 2008 as its document. The following individuals participated in the elaboration of the document:

Gunnar Johanson	Institute of Environmental Medicine, Karolinska Institutet, Sweden (chairman)
Maria Albin	Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden (former NEG expert)
Karin Sørig Hougaard	National Research Centre for the Working Environment, Denmark (former NEG expert)
Kristina Kjærheim	Cancer Registry of Norway (NEG expert)
Tiina Santonen	Finnish Institute of Occupational Health, Finland (NEG expert)
Vidar Skaug	National Institute of Occupational Health, Norway (NEG expert)
Jill Järnberg and Anna-Karin Alexandrie	Swedish Work Environment Authority, Sweden (NEG secretariat)

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All criteria document produced by NEG may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ARDS	acute (or adult) respiratory distress syndrome
ATSDR	Agency for Toxic Substances and Disease Registry
CI	confidence interval
DECOS	Dutch Expert Committee on Occupational Safety
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
FEF_x	forced expiratory flow at x % of FVC
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
IARC	International Agency for Research on Cancer
IOM	Institute of Occupational Medicine, Edinburgh, United Kingdom
IPCS	International Programme on Chemical Safety
LC_{50}	lethal concentration for 50 % of the exposed animals at single exposure
LOAEL	lowest observed adverse effect level
MD	median diameter
MMAD	mass median aerodynamic diameter
MMD	mass median diameter
NEG	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NIOSH	National Institute for Occupational Safety and Health (United States)
NOAEL	no observed adverse effect level
OR	odds ratio
PM_x	particulate matter with aerodynamic diameter up to x µm
RADS	reactive airways dysfunction syndrome
RD_{50}	air concentration associated with a 50 % decrease in the respiratory rate of animals
RR	relative risk (risk ratio)
SCOEL	Scientific Committee on Occupational Exposure Limits (European Union)
SG_{aw}	specific airway conductance
SIR	standardised incidence ratio
SMR	standard mortality ratio
STEL	short-term exposure limit
TNFα	tumour necrosis factor alpha
TWA	time-weighted average
VMD	volume median diameter
WHO	World Health Organization

1. Introduction

Inorganic acids are of prime importance in the chemical and metal industries. They are used as raw materials in the manufacture of a wide range of chemicals, as well as in refining, electrolysis and extraction in chemical processes. Inorganic acids are widely used in the pickling processes of electroplating, in vehicle production plants and in steel producing plants.

The present document concerns the effects of four inorganic acids: sulphuric acid (H_2SO_4), hydrochloric acid (HCl), nitric acid (HNO_3) and phosphoric acid (H_3PO_4). It does not consider sulphur dioxide, nitrous gases, or phosphorous compounds such as phosphorous pentoxide and red phosphorus, which may be converted to phosphoric acid.

A previous NEG document published in 1993 described the effects of aerosols of these four acids (142). The biological effects of H_2SO_4 are relatively well investigated, whereas the documentation concerning the effects of the other three acids, discussed in this document, is limited.

Acid concentrations are given in mg/m^3. Data originally reported in units of ppm have been converted to units of mg/m^3 by using the conversion factors given in Table 2. Occasionally, the originally reported ppm values are also given.

2. Substance identification

Substance identification data for the inorganic acids dealt with in this document are given in Table 1.

Although anhydrous *sulphuric* and *nitric acids* can be produced, the chemical names usually refer to aqueous solutions of the compounds.

Hydrochloric acid is the aqueous solution of hydrogen chloride gas. In this document, the chemical formula HCl may denote hydrochloric acid as well as hydrogen chloride gas.

Table 1. Substance identification data of the inorganic acids (142).

Common name	CAS No.	Synonyms	Molecular formula	Molecular weight
Sulphuric acid	7664-93-9	Battery acid, dipping acid, electrolyte acid, fertiliser acid, hydrogen sulphate, matting acid, Nordhausen acid, oil of vitriol, spirit of sulphur, sulfuric acid	H_2SO_4	98.08
Hydrochloric acid	7647-01-0	Hydrogen chloride, chlorohydric acid, hydrochloride, muriatic acid, spirits of salt	HCl	36.46
Nitric acid	7697-37-2	Aqua fortis, azotic acid, hydrogen nitrate	HNO_3	63.02
Phosphoric acid	7664-38-2	Orthophosphoric acid	H_3PO_4	98.00

Phosphoric acid, when pure, is a solid at room temperature and normal pressure. However, an aqueous solution of 85 % H_3PO_4 is a viscous liquid. In this document, H_3PO_4 refers to aqueous solutions of the solid compound.

3. Physical and chemical properties

Data on physical and chemical properties are presented in Table 2. H_2SO_4, HCl and HNO_3 are all strong acids, and dissociate completely in water at moderate concentrations. HCl is the strongest acid (indicated by the lowest pK_a) followed by H_2SO_4 and HNO_3. H_3PO_4 is the weakest of the acids. All four acids are hygroscopic (attract water molecules from the surrounding environment) and corrosive to (destroy or irreversibly damage) living tissue. HNO_3 and concentrated H_2SO are strong oxidising agents.

Solutions of the acids are not flammable in themselves. However, contact with metals may release flammable and explosive hydrogen gas (H_2).

The physical state of the acids in workplace air ranges from primarily liquid aerosols for the non-volatile H_2SO_4 and H_3PO_4 to liquid aerosols and vapours for the more volatile HCl and HNO_3 (37). There are a number of definitions of aerosols that are used in a wide variety of contexts. IUPAC defines an *aerosol* as a mixture of small (diameter 0.01-100 µm) solid or liquid particles and a carrier gas (usually air). A *droplet* is defined as a small liquid particle and a *mist* as a suspension of droplets in a gas. Also *fog* is used as a general term applied to a suspension of droplets in a gas (119). Other kinds of aerosols are *dust, fume, smoke, haze,* and *smog* (190).

In the present document the original wording regarding aerosols in the cited papers is retained.

Sulphuric acid

H_2SO_4 is a colourless (when pure) to dark brown, oily liquid. It is odourless unless heated (then pungent). Cold H_2SO_4 reacts with most metals and the reactivity increases upon heating. The acid can release flammable hydrogen gas when in contact with metals. H_2SO_4 is highly corrosive, a property accentuated by its highly exothermic (generates heat) reaction with water. H_2SO_4 is an excellent dehydrating agent. Its affinity for water is sufficiently strong to remove hydrogen and oxygen atoms from other compounds. Fuming H_2SO_4 (oleum) is a solution of the anhydride sulphur trioxide (SO_3) in anhydrous H_2SO_4. In air, sulphur trioxide vapour is rapidly converted to a stable mist of droplets of the acid by reacting with atmospheric moisture (6, 96, 110, 180).

Hydrochloric acid

HCl is a colourless fuming liquid with a pungent irritating odour. The mixture of HCl gas and water has a constant-boiling azeotrope at 20 % HCl. It is a very stable compound but decomposes at high temperatures into hydrogen and chlorine. HCl reacts violently with bases and is corrosive. It also reacts violently with oxidants

Table 2. Physical and chemical properties of the inorganic acids (3-6, 19, 74, 75, 129, 142, 143, 188).

Property	Sulphuric acid (H_2SO_4)	Hydrochloric acid (HCl)	Nitric acid (HNO_3)	Phosphoric acid (H_3PO_4)
Description	Colourless (pure) to dark brown, oily liquid; odourless unless heated, then pungent	Colourless to slightly yellow, fuming liquid; pungent irritating odour	Clear, colourless liquid; suffocating odour	Clear, colourless, syrupy liquid (<85 %); odourless
Boiling point (°C)	338 (98 %, aqueous solution)	110 (20 %) -85 (gas)	121 (70 %) 86 (100 %, decomposes)	158 (85 %) 261 (solid)
Melting point (°C)	10 (100 %)	- 85 (25 %) -114 (gas)	- 42 (70 %)	21 (85 %) 42 (solid)
Vapour pressure (kPa) at 20 °C	< 0.04	1.5	1.2	0.3
Vapour density (air=1)	3.4	1.3	1.4	3.4
Density (g/ml) at 25 ˚C	1.84 (100 %)	1.19 (38 %)	1.41 (70 %)	1.71 (85 %) 1.86 (solid)
Solubility in water	Complete	Complete	Complete	Complete
Solubility in organic solvents	Soluble in ethanol	Very soluble in alcohols, soluble in ether and benzene, insoluble in hydrocarbons	No data on solubility in ethanol, soluble in ether	Soluble in ethanol
Octanol/water partition coefficient (log P_{ow}) [a]	-2.20 (estimated)	0.54 (estimated)	0.21 (estimated)	-0.77 (estimated)
pK_a-value [b, c]	-3.0, 1.99	-8.0	-1.3	2.12, 7.21, 12.32
Odour threshold (mg/m^3)	> 1	Range 1-50	0.75-2.50	No odour
Conversion factors in air (25 °C, 101.3 kPa)	1 mg/m^3 = 0.25 ppm 1 ppm = 4.0 mg/m^3	1 mg/m^3 = 0.7 ppm 1 ppm = 1.4 mg/m^3	1 mg/m^3 = 0.4 ppm 1 ppm = 2.5 mg/m^3	1 mg/m^3 = 0.25 ppm 1 ppm = 4.0 mg/m^3

[a] Data from Syracuse Research Corporation's LogKow (KowWin) Program.

[b] Data from Harvard University, Evans Group, substrate H_2O. Values < 0 were extrapolated.

[c] H_2SO_4: Two pKa-values as it releases two hydrogen ions. H_3PO_4: Three pKa-values as it releases three hydrogen ions.

forming toxic chlorine. On contact with air it emits corrosive fumes. HCl attacks nearly all metals under release of hydrogen gas. A mixture of concentrated HCl and a strong oxidising agent dissolves gold, e.g. *aqua regia*, which is a 3:1 (v/v) mixture of concentrated HCl and HNO_3 (96, 110).

Nitric acid
Pure anhydrous HNO_3 is a transparent, colourless liquid with a characteristic choking odour and in moist air a white fuming liquid. In the presence of light or by heating, HNO_3 readily decomposes. The vapours formed are a mixture of HNO_3 and decomposition products such as nitrogen oxides (NO_x), oxygen and water. Nitrogen dioxide (NO_2) accounts for the red-brownish (yellow at low concentrations) colour that develops in the acid on standing. HNO_3 is highly corrosive and attacks most substances and all metals except the noble ones and certain alloys. Reactions with metals may produce nitrous gases and ammonia. Hydrogen gas is rarely formed. HNO_3 forms a constant boiling mixture with water. Concentrated HNO_3 (~70 %) is a powerful oxidising agent and reacts with combustible, organic and readily oxidisable materials. The reactions are often highly exothermic and explosive. Aqueous solutions of > 45 % HNO_3 may spontaneously ignite organic materials such as wood and straw (3, 96, 110, 129, 209).

Phosphoric acid
Pure anhydrous H_3PO_4 is an odourless white solid that melts at 42 °C to form a clear, colourless, viscous liquid. At room temperature, an 85 % aqueous solution of H_3PO_4 is likewise a clear, colourless, viscous liquid. Besides its acidic behaviour, H_3PO_4 is relatively unreactive at room temperature (74).

4. Occurrence, production and use

The four inorganic acids in this document are all important industrial chemicals used in a wide variety of industries/trades and products.

Sulphuric acid
H_2SO_4 is made as a by-product of other operations or directly from elemental sulphur, spent (contaminated and diluted) H_2SO_4, and hydrogen sulphide. Elemental sulphur is by far the most widely used raw material. Concentrated H_2SO_4 is ca 96-98 % (w/w) (18 M). Battery acid used in lead-acid batteries is 33.5 %, chamber or fertiliser acid 62-68 %. Fuming H_2SO_4, also called oleum, is a solution of sulphur trioxide in anhydrous H_2SO_4. H_2SO_4 is used in batteries, pH-regulation agents, electroplating agents, process regulators, cleaning/washing agents, complexing agents, and in surface treatment and laboratory chemicals. H_2SO_4 is also used in the manufacture of chemicals (e.g. titanium dioxide pigments), fertilisers, basic metals, pulp and paper, metal products, food products and beverages, electrical machinery and apparatuses, and in purification of water

and treatment of sewage. H_2SO_4 is the main air contaminant at anodising plants (6, 59, 129, 222).

Hydrochloric acid
HCl is produced in various processes, such as in the reaction between NaCl and H_2SO_4, or by direct synthesis from H_2 and Cl_2. HCl is also a major by-product in chemical processes when organic compounds are synthesised. It is produced in solutions up to 38 % (w/w) (concentrated grade) equivalent to 12 M (pH -1.1). HCl is used in the manufacture of chemicals, pulp and paper (although substituted in most enterprises by now), metal products, food products and beverages and in the extraction of crude petroleum and natural gas, in purification of water and treatment of sewage, and as a general disinfectant (5, 129, 222, 242).

Nitric acid
HNO_3 is difficult to manufacture as a pure substance due to its tendency to decompose. Virtually all HNO_3 manufacture is by oxidation of ammonia. The concentrated acid is an aqueous solution containing 70 % (w/w) (16 M) HNO_3 (azeotropic mixture). "White" fuming HNO_3 is a highly concentrated acid, typically > 90 %, containing 0.1-0.4 % nitrogen dioxide. "Red" fuming HNO_3 contains 8-17 % dissolved nitrogen dioxide. In practice, HNO_3 is usually found in conjunction with NO_x, and vapours of HNO_3 are always a mixture of acid, NO_x, oxygen and water whose composition is determined by factors such as temperature and humidity. HNO_3 is used in the manufacture of chemicals such as fertilisers and explosives, food products, beverages, metal products, in surface treatment and pH-regulation agents. It is also a component in laboratory chemicals and in cleaning/washing agents (3, 12, 66, 129, 209, 222).

Phosphoric acid
H_3PO_4 is produced commercially by either the wet process or the electric furnace process. In the wet process, H_3PO_4 is produced by reacting H_2SO_4 with naturally occurring phosphate rock in a reactor. Reagent grade H_3PO_4 is usually 85 % (w/w). H_3PO_4 is used in fertilisers, cleaning/washing agents, surface treatment, laboratory chemicals, colouring agents, pH-regulation agents, process regulators, food/feedstuff, flavourings and nutrients, non-agricultural pesticides and preservatives, and corrosion inhibitors. H_3PO_4 is also used in the manufacture of beverages, chemicals, metal products, pulp and paper, rubber and plastics, textiles, purification of water and treatment of sewage, and in the extraction of crude petroleum and natural gas (4, 114, 129, 222).

Table 3. Annual total use (kilotonnes) of inorganic acids in the Nordic countries (222).

Acid/	Year				
Country	2002	2003	2004	2005	2006
Sulphuric acid					
Denmark [a]	2	4	16	18	10
Finland	1 474	1 182	1 567	928	998
Norway	207	220	238	248	72
Sweden	240	253	240	316	324
Hydrochloric acid					
Denmark [a]	4	9	33	40	28
Finland [b]	<<1	23	58	<1	<1
Norway	34	41	34	39	40
Sweden	84	75	54	47	55
Nitric acid					
Denmark [a]	3	<1	25	26	27
Finland	273	212	513	277	279
Norway	1 217	1 254	1 260	1 253	1 176
Sweden	10	10	16	27	39
Phosphoric acid					
Denmark [a]	3	3	5	5	4
Finland	219	204	798	307	325
Norway	4	4	5	6	5
Sweden	49	49	53	41	50

[a] The large increase in volume in 2004 is due to new regulations for declaration.
[b] The amounts are for HCl, water free (index no. 017-002-00-2).

Uses in the Nordic countries

Table 3 shows the annual use of the four inorganic acids in question in Denmark, Finland, Norway, and Sweden in the years 2002-2006 (222). The large variations of tonnage between the countries are explained by national differences in type of industries. For example, Norway is a large producer of fertilisers, hence the large tonnage for HNO_3.

5. Measurements and analysis of workplace exposure

Data on particle size distribution of acid mists are limited, and sampling methods have generally not differentiated between liquid and gaseous forms of acid (180). The droplet size of acid aerosols is reported differently by various authors. Usually it is described as mass median aerodynamic diameter[1] (MMAD), mass median diameter (MMD) or volume median diameter (VMD). MMAD entails not only size and shape but also density of droplets. MMD describes the aerodynamic behaviour of spherical and unit density particles, so for such droplets MMAD equals MMD. When the aerosol density is approaching 1, VMD equals MMAD.

[1] Aerodynamic diameter: The diameter of a unit-density sphere having the same terminal settling velocity as the particle in question. It is used to predict where in the respiratory tract such particles will deposit.

The occupational exposure limits for the four acids in the Nordic countries (Appendix 1) applies to the *inhalable* fraction (particles with aerodynamic diameter ≤ 100 μm) of the airborne particles according to European standard EN 481:1993 (77). Poorly volatile acids such as H_2SO_4 and H_3PO_4 are typically sampled as inhalable aerosols on filters, whilst volatile acids such as HCl and HNO_3 are collected on sorbent tubes or alkali-impregnated filters. Analysis is usually carried out by ion chromatography (37, 92).

When comparing published exposure data, one must consider the sampling technique used. The IOM sampler[1], the Respicon impactor and the Millipore sampler measure different particle size fractions. The IOM sampler is assumed to come closer to the health-related inhalable fraction of aerosols, especially for aerosols with an aerodynamic diameter above 20 μm (40, 155). It is assumed that the Millipore sampler underestimates the H_2SO_4 concentration by a factor 1.5 compared to the IOM cassette. The detection limit for the Occupational Safety and Health Administration (OSHA) method ID-113 corresponds to 0.5 μg sulphate on the filter (40, 182).

In the year 2000, the former National Institute for Working Life in Sweden recommended sampling of these four inorganic acids on silica tubes and analysis by ion chromatography, with reference to the United States National Institute for Occupational Safety and Health (NIOSH) method no. 7903 (153). The NIOSH method provides total acid mist concentration, but no size-related information (113).

The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union acknowledged in 2007 that the reliable measurement of H_2SO_4 concentrations at and around the recommended limit values (8-hour time-weighted average (TWA) 0.05 mg/m^3, short-term exposure limit (STEL) 0.1 mg/m^3) was challenging. In some circumstances, there might be interference from sulphate salts also present in the atmosphere. It was concluded unproblematic to measure 8-hour shift concentrations in workplaces with exclusively H_2SO_4 mist, but impossible to monitor a 15-minute period with the necessary limit of detection. However, from the most recent evidence presented to SCOEL, it appears that there are, or soon will be, measurement techniques available that are compatible with the proposed limits (210). Interference may also be from oxidisable inorganic compounds such as sulphur dioxide and sulphites, and organic sulphuric compounds (144).

Interference from salts may be a challenge also for measurements and analysis of the other three acids (179).

[1] IOM sampler = personal sampler developed by the Institute of Occupational Medicine (IOM) in Edinburgh, United Kingdom. The sampler was developed to fit the curve for inhalable dust according to the European Committee for Standardization (CEN) standard EN 481:1993.

6. Occupational exposure data

Contrary to the wide industrial use of the four acids, published contemporary exposure data are limited and are almost exclusively air measurements of H_2SO_4 (Table 4). The Norwegian occupational exposure database EXPO contains data from all samples analysed at the National Institute of Occupational Health in Norway since 1984 (Table 5). Most of these samples have been collected as a result of requests from different enterprises to control their exposures and are likely to represent "worst case measurements" in many cases (189). From published data and data in EXPO it is difficult to describe the exposure levels in Nordic industry today.

Sulphuric acid

Occupational exposure data from various occupational settings are summarised in Table 4. Droplet size distributions are usually not given but industrial aerosols can have MMADs as large as 14 µm (160). In a study of lead acid battery plants, MMADs were in the range 2.6-10 µm (122). Most of the available exposure data comes from the pickling and plating industries (116). In a review, pre 1970s H_2SO_4 mist potential exposures were judged: a) high for workers in H_2SO_4 and isopropanol production, and in metal pickling (>1 mg/m^3, 8-hour TWA); b) judged moderate for workers in soap and detergent, HNO_3 and ethanol production (0.1-1 mg/m^3); and c) low for workers in copper and zinc refining and in phosphate fertiliser and lead battery production (< 0.1 mg/m^3) (197). Since then, substitution and other measures have reduced the levels considerably.

In 1990-1993, approximately 700 000 workers including 4 000 in Denmark, 2 000 in Finland and 8 000 in Sweden were exposed to strong inorganic mists containing H_2SO_4, as registered in the CAREX database (125). The CAREX database contains estimates of the numbers of workers occupationally exposed to carcinogens in the 15 member states of the European Union at the time (exposure data from 1990-1993) and in four of the ten countries that joined the European Union in 2004 (exposure data from 1997).

In conference proceedings from the Australian Institute of Occupational Hygienists (AIOH) 1996, Foster *et al* reported exposure levels of H_2SO_4 mist in several branches of industry. All measurements were expressed as total sulphate. In some cases this included sulphate present as metal salts. The highest exposures were recorded in the lead-acid battery manufacturing industry (0.03-1.5 mg/m^3). Relatively high exposures were found in the electrolytic refining of metals (0.04-0.5 mg/m^3) whereas acid mist exposures in the other industries were low, e.g. in electroplating workplaces. Due to enclosure of the processes, also exposures in fertiliser production, wool carbonising, soap and margarine manufacture, tanning, catalytic alkylation of hydrocarbons, and H_2SO_4 manufacture were low (81).

In a recent investigation, the maximum H_2SO_4 concentration in phosphate fertiliser manufacture facilities in Florida measured as PM_{10} (particulate matter with an aerodynamic diameter up to 10 µm), including fine and coarse mode,

was 0.185 mg/m^3 obtained at the H_2SO_4 pump tank area. Geometric mean concentrations obtained at the H_2SO_4 pump tank area for PM_{23}, PM_{10} and $PM_{2.5}$ H_2SO_4 were 0.042, 0.038 and 0.022 mg/m^3, respectively, measured with a cascade impactor. By using the NIOSH method 7903, measurements were 1.5-229 times higher than those obtained by the cascade impactor. One possible explanation provided by the authors is interaction of SO_2 in the NIOSH method (113, 114).

For comparison, air levels from environmental pollution by inorganic acids are generally lower than occupational exposures. H_2SO_4 concentrations ranging from 0.02 to 0.03 mg/m^3, with peaks up to 0.1 mg/m^3, have been determined in outdoor air in Europe and the United States (67, 210). Elevated environmental H_2SO_4 concentrations of 0.027 mg/m^3 as a 12-hour average and > 0.1 mg/m^3 as a one-hour peak have been measured in the eastern United States and Canada. These concentrations were measured as H^+-concentrations and subsequently converted to H_2SO_4 (221). In Norway, the environmental concentrations of SO_2 in the centre of Oslo were in the range 4-6 µg/m^3 (as yearly averages) during 1997-2004. In comparison, the 24-hour environmental standard for SO_2 is 0.125 mg/m^3 (1). The concentration of H_2SO_4 is not regularly measured in this programme, but SO_2 can be converted to H_2SO_4 in the troposphere.

Hydrochloric acid

According to exposure data, picklers in a Dutch hot dip galvanising plant worked 27 % of their time in HCl concentrations above 7 mg/m^3. In earlier studies, the HCl levels were slightly lower than 7 mg/m^3 in German galvanising plants (191). In measurements performed during the 1950s to 1970s in Finland and the United States, air concentrations of HCl in pickling, cleaning, plating and electrochemical drilling ranged from 0.001 to 14.5 mg/m^3. In a German study, levels were 26.5-33.5 mg/m^3 in pickling industries (165).

Nitric acid

Few measurements are available of HNO_3 exposure. Individual air concentrations in acid treatment of metals (cleaning, etching, electrolytic refining, plating and anodising), mostly performed 1975-1983, were in the range 0.01-2.8 mg/m^3 (116).

Phosphoric acid

The few individual air measurements available on H_3PO_4 exposure from pickling, acid cleaning, and aluminium finishing operations performed in the 1970s and 1980s were below 0.67 mg/m^3. Air concentrations during phosphate fertiliser manufacture ranged from below 0.005 to 3.43 mg/m^3 (116).

Table 4. Reported occupational exposure levels of sulphuric acid.

Processing method/job	No. of samples	Sampling type	Sampling time	Exposure level, mg/m^3	Sampling method	Reference
Zink production/two cell houses (inspectors, strippers and cleaners)	59 70	Personal	Full-shift, 5.5-7.5 h	GM (range) 0.07 (0.01-0.48) 0.04 (0.01-0.15)	Millipore (37 mm)	(40)
	6 4 6 4	Stationary	4.5-8 h	GM (GSD) 0.11 (1.54) 0.11 (1.71) 0.09 (1.46) 0.09 (1.51)		
13 workplaces: Lead-acid battery plants Metal refining Fertiliser manufacture Electroplating Wool carbonising	94	Personal	Not given	GM (range) 0.03-1.45 0.04-0.47 0.09 (single sample) 0.03 (two samples, same level) 0.04-0.05	Measured and reported as total sulphate	(81)
3 anodising plants	"Several"	Personal	8 h	GM (range) 0.40 (0.24-0.87) 0.04 (0.03-0.05) 0.01 (0.005-0.03)	Millipore	(95)
3 titanium dioxide manufacturing plants	Plant A: 95 Plant B: 100 Plant C: 39	Personal	Mostly full-shift	<0.05 as means in all 3 plants except in the Moore filtration workshops (A: 0.38, B: 0.84 and C: 0.09).	Millipore (37 mm)	(108)

Table 4. Reported occupational exposure levels of sulphuric acid.

Processing method/job	No. of samples	Sampling type	Sampling time	Exposure level, mg/m^3	Sampling method	Reference
5 lead-acid battery plants	245	Personal	Full-shift, 6-7 h	AM (range) 0.18 (ND-1.7)	Millipore (37 mm)	(122)
Paper and paper board production and recycling	 10 5 6 10	Not described	> 1 h	AM (range) 4.1 (0.3-11.5) (pulping, refining) 0.89 (0.22-1.6) (paperboard machine) 0.11 (0-0.27) (paper/paperboard machine) ND (repulping)	Not described	(138)
8 phosphate fertiliser manufacturing plants	71	Stationary	12 h	GM 0.042 (PM_{23}) 0.038 (PM_{10}) 0.022 ($PM_{2.5}$) 0.185 (maximum)	Cascade impactor (Mark III) Dichotomous (SA241 CUM)	(113, 114)

AM: arithmetic mean, GM: geometric mean, GSD: geometric standard deviation, ND: not detectable, PM_x: particulate matter with aerodynamic diameter up to x µm.

Table 5. Exposure levels of the inorganic acids measured in various branches in Norway, registered in the EXPO database in the years 2000-2006 and 1984-1999, respectively (189).

Acid/ year	Branch	NACE-code [a]	No. of samples	Exposure level		
				Mean (mg/m^3)	Standard deviation	Maximum (mg/m^3)
Sulphuric acid						
2000-2006	Mining of non-ferrous metal ores, except uranium and thorium ores	13.200	36	0.14	0.68	4.1
	Operation of dairies and cheese making	15.510	2	0.0030	0.0007	0.0035
	Manufacture of dyes and pigments	24.120	12	0.075	0.030	0.13
	Manufacture of plastics in primary forms	24.160	3	0.034	0.043	0.083
	Manufacture of hollow glass	26.130	14	0.0037	0.0029	0.011
	Manufacture of basic iron, and steel and of ferro-alloys	27.100	3	3.50	5.80	10.2
	Production of first transformation of aluminium	27.422	31	0.076	0.076	0.3
	Forging, pressing, stamping and roll forming of metal, powder metallurgy	28.400	3	0.0088	0.0089	0.018
	Treatment and coating of metals	28.510	2	0.13	0.13	0.22
	General mechanical engineering	28.520	3	0.0012	0.0003	0.0015
	Manufacture of locks and hinges	28.630	5	0.089	0.13	0.3
	Manufacture of other fabricated metal products	28.750	3	0.026	0.029	0.06
	Manufacture of marine engines and parts	29.111	5	0.028	0.011	0.047
	Scheduled air transport	62.100	11	0.018	0.016	0.048
	Freight forwarding services	63.401	1	0.006		0.006
1984-1999	Manufacture of other organic basic chemicals	24.140	1	0.005		0.005
	Casting of steel	27.520	1	0.02		0.02
	Manufacture of other special purpose machinery	29.560	6	< DL [b]		< DL [b]
	Manufacture of computers and other information processing equipment	30.020	6	0.23	0.33	0.9
	Manufacture of accumulators, primary cells and primary batteries	31.400	32	1.23	1.24	4.77

Table 5. Exposure levels of the inorganic acids measured in various branches in Norway, registered in the EXPO database in the years 2000-2006 and 1984-1999, respectively (189).

Acid/ year	Branch	NACE-code [a]	No. of samples	Exposure level		
				Mean (mg/m^3)	Standard deviation	Maximum (mg/m^3)
Hydrochloric acid						
2000-2006	Manufacture of basic iron, and steel and of ferro-alloys	27.100	3	0.028	0.0099	0.036
	Forging, pressing, stamping and roll forming of metal, powder metallurgy	28.400	3	0.060	0.044	0.09
	Manufacture of locks and hinges	28.630	3	0.0033	0.0003	0.0035
	Manufacture of television and radio transmitters and apparatus for line telephone	32.200	1	0.22		0.22
	Scheduled air transport	62.100	11	0.1	0.18	0.6
	Research and experimental development in natural sciences and engineering	73.100	12	0.23	0.39	1.1
1984-1999	Treatment and coating of metals	28.510	4	0.90	0.18	1.1
	Manufacture of other special purpose machinery	29.560	6	0.25	0	0.25
	Manufacture of aircraft and spacecraft	35.300	4	0.31	0.14	0.5
Nitric acid						
2000-2006	Manufacture of basic iron, and steel and of ferro-alloys	27.100	3	0.036	0.012	0.044
	Forging, pressing, stamping and roll forming of metal, powder metallurgy	28.400	3	0.013	0.0008	0.013
	General mechanical engineering	28.520	11	0.019	0.037	0.13
	Manufacture of other machine tools	29.430	3	0.013	0.0005	0.014
	Research and experimental development in natural sciences and engineering	73.100	12	0.061	0.052	0.17
1984-1999	Manufacture of other electrical equipment	31.620	4	< DL [b]	0	< DL [b]
Phosphoric acid						
2000-2006	Production of first transformation of aluminium	27.422	2	0.0100	0.000	0.01
	Forging, pressing, stamping and roll forming of metal, powder metallurgy	28.400	3	0.0003	0.0001	0.0004
	General mechanical engineering	28.520	3	0.0012	0.0003	0.0015
	Scheduled motor bus transport	60.211	5	0.74	0.85	2
1984-1999	Production of first transformation of aluminium	27.422	4	0.050	0.0061	0.057

[a] An international coding system for industrial classification used by the European Union.
[b] Measurements below the detection limits.

7. Toxicokinetics

7.1 Deposition

The four inorganic acids may be present in the workplace air as aerosols or vapours depending on their volatility and the air temperature. Vapours containing volatile acids may be transformed to aerosols in the airways, due to the humidity and the hygroscopic nature of the compounds (50). Aerosols containing inorganic acids will be deposited in the airways as liquid particles (droplets). Adsorption of the acid to solid particles is also important for their pathogenesis (150).

The site of deposition of acid aerosols in the respiratory tract depends on e.g. the droplet size (aerodynamic diameter), the hygroscopicity of the particles and breathing pattern. Droplet size is usually the critical factor that determines the region of deposition within the respiratory tract. The diameters often reported are MMD and MMAD (see Chapter 5), of which the latter takes into account both the density of the particles and the aerodynamic drag (19). The particle size distribution of the aerosol is an important difference among various studies.

The airways are usually divided in three functional regions, the nasopharynx, the tracheobronchial region and the pulmonary region. Inert particles with an aerodynamic diameter in the range 5-30 μm generally deposit in the nasopharynx by impaction. Smaller particles with aerodynamic diameters of 1-5 μm deposit in the tracheobronchial regions by sedimentation, and particles with an aerodynamic diameter less than 1 μm are deposited in the alveoli by diffusion (245).

As compared to commonly used experimental animals, humans have larger airways and a more symmetrical upper bronchial airway branching pattern. In addition, humans do considerable oral breathing, thus bypassing the air cleaning capability of the nasal airways. These differences contribute to a greater amount of upper bronchial airway particle deposition in humans as well as a tendency to greater deposition near airway bifurcations (the point at which division into two branches occurs) (159).

All four acids are hygroscopic. Hygroscopic aerosols will take on water and grow in size within the respiratory tract. H_2SO_4 aerosols in ambient air typically have an MMAD of 0.3-0.6 μm, while industrial aerosols can have MMADs as large as 14 μm (160). In another study, the MMADs of acid mists in an industrial setting averaged about 5 μm (2.6-10 μm) (122). The size of submicrosized (< 1 μm) H_2SO_4 droplets has been predicted to increase by a factor of 2-3 (128). Because of their hydrophilic properties, H_2SO_4 aerosols are deposited mainly in the upper airways and the main target organ in man is the larynx. However, aerosol droplets of small diameters may reach the alveoli (67).

The growth of H_2SO_4 aerosols in the airways tends to increase respiratory retention compared to that of inert particles of the same size as the *original* acid droplets (since exhalation from small airways is hindered after expansion) as well as compared to inert particles of the same size as the *enlarged*, humified droplets (because of deeper penetration) (19).

HNO_3 vapour undergoes significant removal within the upper respiratory tract due to its high water solubility and reactivity, but when other particles act as vectors it can reach the lower respiratory tract (50).

After deposition in the respiratory tract, the high moisture content results in rapid dissociation and hydration of the acids. Inhaled inorganic acid aerosols are neutralised in the upper respiratory tract in a reaction with endogenous ammonia. A mathematical model developed to simulate the growth and endogenous ammonia neutralisation of sulphate containing aerosol particles in the human respiratory tract predicted substantial growth and neutralisation of smaller particles (below 0.1 µm) but negligible neutralisation of larger particles (above 1 µm) (196). The levels of oral ammonia in rabbits are 0.01-1.1 ppm (247), quite similar to the levels found in humans (146, 206).

7.2 Uptake

Sulphuric acid
Once absorbed, the sulphate ions formed become indistinguishable from sulphate derived from dietary sources. There are no data describing the extent of dermal absorption of the aerosol or liquid. Its polarity suggests little significant absorption by this route unless the acidity causes skin damage and thereby breaches the skin barrier (67, 210).

Hydrochloric, nitric and phosphoric acids
No information found.

7.3 Distribution

The four inorganic acids will be protolysed, yielding protons (H^+) dissolved in the mucosa. The anions will enter the body pool. Unless exposure is excessive, the proton and anion contributions to the body pool will be negligible, except for a high local proton-concentration that may lead to effects. Clearance from the respiratory tract will occur via the mucociliary escalator and other mechanisms such as macrophage phagocytosis and removal with the blood and lymph flow (157).

7.4 Biotransformation and excretion

Not applicable, see section 7.3.

8. Biological monitoring

Not applicable, see section 7.2.

9. Mechanisms of toxicity

Exposure to the four acids in the working atmosphere can lead to a number of effects, such as sensory irritation, dental erosion, skin corrosion, changes in mucociliary and alveolar clearance, decreased pulmonary function, and increased airway reactivity. Laryngeal cancer has been observed after exposure to strong inorganic mists containing H_2SO_4.

The toxic action of acid aerosols in the airways is determined by the site of deposition. The physical state and size of the droplets in the aerosol will therefore to a large extent determine the toxicological effects. The four acids are hygroscopic, and aerosol droplets of e.g. H_2SO_4 increase in size as they absorb water during transit in the airways and deposit mainly proximally in the airways (Chapter 7) (127, 239). The anions are essential and enter the body pool; at relevant exposure levels probably without causing toxicity since the contribution to systemic levels will be low. However, excessive exposure may cause toxic effects such as hyperphosphataemia, and hypocalcaemia.

The toxicity from inhalation of these inorganic acids seems to arise mainly from the free hydrogen ions. Respiratory symptoms such as cough and phlegm are related to the aerosol acidity (hydrogen ion content) (128, 239). It is also widely believed that a low pH is a major factor in dental erosion (230, 244).

H_2SO_4 causes skin corrosion due to generation of excessive heat and dehydration in the tissue. In small blood vessels, necrosis and thrombosis leading to eschars may occur. Contact is generally associated with considerable pain (79).

Chemosensory effects of chemicals including inorganic acids can either be irritating (trigeminal stimulation), odorous (olfactory stimulation) or both. For odorous irritants, a clear-cut distinction between odour and irritation is difficult to make (18). The challenge of identifying chemosensory thresholds for substances causing sensory irritation has been described in depth in several papers (18, 62, 130, 178, 216, 240).

Mucociliary clearance is a major respiratory tract defence mechanism. A large number of investigations suggest that mucociliary clearance is stimulated at short-term exposure to low/intermediate concentrations of gases or aerosols such as cigarette smoke, atmospheric pollutants, and oxygen. At higher exposure levels or long-term exposure, mucociliary clearance is impaired. Mucociliary impairment caused by H_2SO_4 exposure occurs in the smaller airways, the major deposition site of submicrosized aerosols (i.e. MMAD < 1 μm). Impaired mucociliary activity has also been observed to occur in the trachea (98, 199, 246). The mechanism by which mucociliary clearance is affected by exposure to acids is unknown but changes in pH, composition and viscosity of the mucus has been shown and may play a role (239). Increased alveolar clearance seen in experimental animals due to an inflammatory response takes place when there is an influx of macrophages in the lungs after exposure to acids (176). In some cases, pulmonary function decreases as a result of bronchoconstriction. Airway reactivity is increased because of airway inflammation.

Exposure to inorganic acid mists containing H_2SO_4 has been associated with laryngeal cancer in some epidemiological studies (7, 80, 217, 218, 225, 227, 243). Limited information on possible carcinogenic mechanisms of the four acids is available. Carcinoma may develop due to regenerative cell proliferation as a reaction to the cytotoxicity and irritation. Cytotoxic induced epithelial hyperplasia has been observed in monkeys (8) and rabbits (90, 204) and epithelial metaplasia in rats (127). Inhalation of inorganic acid aerosols lowers the pH in the airway mucosa and causes local irritation. Reduced pH influences chromosomal integrity. Reviews of *in vitro* studies describe that acid pH can induce e.g. chromosomal aberrations such as sister chromatid exchanges and micronuclei (106, 211, 229). The mechanisms by which chromosomal aberrations are induced by low pH are unknown (171, 229).

10. Effects in animals and *in vitro* studies

10.1 Irritation, corrosion and sensitisation

All four acids have corrosive and irritative properties and injure skin, eyes and the mucous membranes of the respiratory tract. Studies reporting on irritative effects on the respiratory tract are described below and are summarised in Tables 7-8 (Section 10.2).

Five *in vivo* studies of different acids including H_2SO_4 (concentration up to 96 %) and HCl (36 %) investigating skin burns in animals were reviewed by Flammiger and Maibach (79). The studies show the importance of early treatment to prevent skin destruction.

There are no data on sensitisation of animals after exposure to the four acids.

Sulphuric acid

Non-specific airway hyperresponsiveness to acetylcholine or histamine *in vitro* was investigated after exposure of male rabbits to 0.05-0.5 mg/m^3 (MMD 0.3 µm) for 3 hours *in vivo*. Bronchial hyperresponsiveness was seen in all groups exposed to 0.075 mg/m^3 and higher. No effect was seen in the 0.05 mg/m^3 group. Once a concentration threshold was reached (0.075 mg/m^3), no further increase in reactivity was seen. Reactivity in the trachea was increased only at the highest exposure level. According to the authors, the higher concentration needed to alter reactivity in the trachea compared to those needed for similar changes in the bronchi likely reflect dosimetry differences, i.e. there would be greater deposition of the acid within the bronchi (70).

Lung function changes at low levels were reported by Amdur *et al* who observed that a 1-hour exposure to 0.1-1.0 mg/m^3 H_2SO_4 produced significant and dose-related increases in pulmonary flow resistance in guinea pigs (sex not given). A decrease in pulmonary compliance was also produced at these low levels. In all exposures but one (0.1 mg/m^3, MMD 1 µm), values had not returned to normal 30 minutes post-exposure. Generally, 0.3-µm particles produced greater changes

than 1-µm particles. The smaller particles produced significant changes in both resistance and compliance during as well as after exposure to 0.1 mg/m^3, whereas the larger particles produced significantly increased resistance only during exposure. Tidal volume, respiratory frequency and minute volume were not affected. Each animal served as it own control (13).

Non-specific airway hyperresponsiveness *in vivo* was induced in male guinea pigs exposed for 1 hour to ultrafine H_2SO_4-particles at 0.2 mg/m^3 (mean diameter 0.06 µm) (48).

Male guinea pigs exposed for 1 hour to 0.3 mg/m^3 (MMD 0.08 µm) had a significantly decreased single breath diffusion capacity for carbon monoxide compared with animals exposed to 3 % argon in filtered air. Vital capacity was not altered in the acid exposed animals (46).

Ventilatory pattern (respiratory frequency, inspiratory volume and pressure changes) was monitored in male guinea pigs, exposed in whole-body plethysmographs to H_2SO_4 aerosols with co-exposure to 10 % CO_2 to stimulate ventilation. The guinea pigs were exposed nose-only to H_2SO_4 ranging from 1.8 to 55 mg/m^3 (1.8, 4.6, 9.2, 18, 46 and 55 mg/m^3, plus two additional intermediate concentrations not stated, aerodynamic diameter 0.6 µm) for 30 minutes. Below 10 mg/m^3, the response to H_2SO_4 was transient. An initial decline in inspiratory volume faded as the exposures continued, and was sometimes followed by an increase in volume (shown only for 9.2 mg/m^3). Also at higher concentrations, inspiratory volume decreased shortly after initiation of exposure. At 18 mg/m^3, inspiratory volume fluctuated somehow, but was still diminished at termination of exposure. At 46 mg/m^3, inspiratory volume continued to decrease until termination of exposure. Mean respiratory frequency was unaffected by H_2SO_4 up to 18 mg/m^3, but seemed to decrease at the highest exposure level (55 mg/m^3) (198). However, respiratory frequency was not reported for exposure levels between 18 and 55 mg/m^3, hampering interpretation of effects at these levels.

Five groups of 4 female guinea pigs were exposed to 10 % CO_2 concurrently with H_2SO_4 (24, 33, 40, 49, or 73 mg/m^3, MMD 0.92-1.06 µm) for 1 hour. Concentration-dependent reductions in CO_2-induced increases in tidal volume, respiratory frequency, and minute ventilation were seen. The CO_2-induced increase in tidal volume was significantly reduced after 30 minutes exposure in all groups, except in those exposed to 24 and 33 mg/m^3. Exposure to H_2SO_4 mist at and above 40 mg/m^3 reduced respiratory frequency. Following exposure to 73 mg/m^3, the animals showed definite signs of breathing difficulty, and significantly increased tidal volume. Recovery occurred in all animals during the 5 days after exposure (249).

Ventilation was measured in female guinea pigs in whole-body plethysmographs immediately following a 4-hour inhalation exposure to H_2SO_4 aerosol. Baseline respiratory pattern was monitored prior to exposure. Groups of 6 guinea pigs were exposed to 14, 20, or 43 mg/m^3 (MMD 0.90-0.96 µm). Dose-effect relationships were seen regarding ventilatory responses. The highest concentration caused an increase in tidal volume and a decrease in breathing

frequency immediately after exposure. At 24 hours post-exposure, frequency was increased, tidal volume decreased, and breathing was interspersed with short periods of apnoea. This rapid shallow breathing was associated with histological evidence of pulmonary oedema. By contrast, the lowest H_2SO_4 concentration caused increased breathing frequency with no effect on tidal volume, and 24 hours later ventilatory parameters were similar to baseline values. The middle exposure group seemed divided into two populations, with respiratory characteristics resembling that of either the high- or low-dose group (192).

In a study on rabbits performed according to OECD guidelines, 10 % H_2SO_4 in water was classified not irritating to eyes (120).

Hydrochloric acid

HCl is extremely irritating to the eyes, mucous membranes and exposed areas of skin. Evidence of corneal erosion and clouding has been reported (64, 142, 193).

Groups of 4 male mice were exposed to 56, 139, 343, 616 or 1 320 mg/m^3 (40, 99, 245, 440 or 943 ppm) HCl for 10 minutes to investigate the sensory irritation of the upper respiratory tract. Each animal was placed in a plethysmograph, allowing monitoring of inspiration and expiration. Sensory irritation was measured as the percentage decrease in the respiratory rate. The animals served as their own controls. The onset of the irritative response was rapid, with a plateau being reached within 5-7 minutes from the start of exposure. The decrease in respiratory rate was dose-related, i.e. at 56 mg/m^3 it decreased by approximately 10 % and at 1 320 mg/m^3 by 70 %. Return to control values was slow after exposure to concentrations of 343 mg/m^3 and above. The air concentration causing a 50 % decrease in the respiratory rate (RD_{50}) was estimated to be 432 mg/m^3 (309 ppm) (23).

Airway irritation was also investigated in male guinea pigs. Four or eight animals/group were exposed to 448, 952, 1 456 or 1 932 mg/m^3 (320, 680, 1 040, or 1 380 ppm) HCl for 30 minutes. Signs of sensory irritation appeared 6 minutes after initiation of exposure to 448 mg/m^3, but was evident in less than 1 minute at the higher exposure concentrations. Also pulmonary irritation was present, and the higher the concentration, the earlier the onset. Thus, pulmonary irritation was observed after 20 minutes at 448 mg/m^3, and after less than 4 minutes at 1 932 mg/m^3. Impairments of the respiratory function were also supported by evidence of morphological injury in both the airways and the alveolar region (42).

Baboons (12 males) were exposed head-only to 0, 500, 5 000 or 10 000 ppm HCl (700-14 000 mg/m^3) for 15 minutes in an inductive plethysmograph. The acute respiratory response consisted of a concentration-related increase in respiratory frequency and minute volume, with a marked decrease in arterial blood partial pressure of oxygen at the two highest concentrations. Pulmonary function was normal in all groups 3 days and 3 months after exposure (123).

The same research group compared the effects of HCl in mice, rats, and guinea pigs with those in baboons. Male mice were exposed to 500 ppm (700 mg/m^3) or 2 500 ppm (3 500 mg/m^3) HCl in plethysmographs for 15 minutes. Female rats

were exposed to 4 200 ppm (5 880 mg/m^3), and male guinea pigs to 500 and 4 200 ppm HCl under similar conditions. Respiratory function and arterial blood gases were monitored during exposure, and CO_2-challenge response tests were conducted prior to, 3 days and 3 months following exposure. In mice, exposure to 500 ppm caused reduced respiratory frequency (133 breaths/minute versus 178 in controls). During the 3-month follow-up period, 4/6 mice died. In guinea pigs, the respiratory frequency was also lowered after exposure to 500 ppm (97 versus 113 breaths/minute). Exposure to the highest levels of HCl showed species differences in respiratory response and sensitivity, the rat being the less sensitive. Results from the histopathological examination are described in Section 10.2. The combined results from the two studies showed that rodents were more sensitive than baboons regarding respiratory response, probably due to anatomical differences in the nose (124).

In a study on rabbits performed according to OECD guidelines, 10 % HCl in water was classified as a risk of serious damage to eyes (120).

Nitric acid

No bronchoconstriction (decreased post-exposure specific pulmonary flow resistance) was observed neither in normal nor in allergic sheep (sex not given) exposed head-only for 4 hours to 4.1 mg/m^3 (1.6 ppm) HNO_3 vapour. However, allergic sheep (animals that had a history of reacting with bronchospasm to inhalation challenge with *Ascaris suum* (large roundworm) antigen) showed increased airway hyperreactivity to aerosolised carbachol after exposure to HNO_3. This response is characteristic of hyperresponsive airways (2).

Phosphoric acid

No studies were found.

10.2 Effects of single exposure

Reported lethal concentrations for 50 % of the exposed animals at single inhalation exposures (LC_{50}s) of 30 minutes-8 hours are given in Table 6. The variation in exposure time makes a direct comparison of LC_{50} data difficult but it seems that HNO_3 and H_2SO_4 have a higher acute toxicity than HCl and probably also than H_3PO_4.

Other effects of single inhalation exposure to H_2SO_4 and HCl are summarised in Tables 7-8, respectively. The few single exposure studies on HNO_3 are summarised in Table 10 (Section 10.3).

Sulphuric acid

The guinea pig is the most sensitive animal species, with reported LC_{50}s in the range 18-50 mg/m^3 (Table 6). Reported pathological findings are distended lungs, probably from acute asphyxia due to laryngeal spasm.

A large number of animal studies of the effects from single exposure are published. The studies are listed in Table 7 and are also discussed in the text.

Table 6. Acute toxicity data (LC_{50}s) after inhalation of the inorganic acids (64, 142, 193).

Acid/ Species	Median diameter [a] (µm)	Exposure duration (h)	LC_{50} (mg/m^3)	LC_{50} ($mmol/m^3$) [b]
Sulphuric acid				
Guinea pig	NG	8	18	0.2
Guinea pig	0.8	8	40	0.4
Guinea pig	1	8	50	0.5
Mouse	NG	2	320	3.3
Rat	NG	2	510	5.2
Hydrochloric acid				
Aerosol				
Mouse	< 1	0.5	3 200	88
Mouse	< 1	0.5	12 000 [c]	329
Rat	< 1	0.5	7 900 [c]	217
Rat	< 1	0.5	8 300	228
Vapour (gas)				
Mouse		1	780	21
Mouse		1	1 600 [c]	44
Mouse		0.5	3 700 [c]	102
Mouse		0.5	3 900	107
Rat		1	2 200	60
Rat		1	4 400 [c]	121
Rat		0.5	6 600 [c]	181
Rat		0.5	7 004	192
Nitric acid (physical state not given)				
Rat	NG	4	130	2.1
Rat	NG	0.5	260	4.1
Phosphoric acid				
Rat	NG	1	> 850	> 8.7

[a] Either mass median diameter (MMD), mass median aerodynamic diameter (MMAD) or volume median diameter (VMD).
[b] Converted from the LC_{50} (mg/m^3).
[c] Converted from ppm-value given in reference.
LC_{50}: lethal concentration for 50 % of the exposed animals at single exposure. NG: not given.

The effects of H_2SO_4 on pulmonary defence mechanisms have been examined in a number of studies using insoluble particles or microbes. Respiratory tract clearance may occur by ciliary transport or by phagocytosis. Respiratory clearance has been monitored by measuring the retention of an insoluble aerosol labelled with a radioisotope, usually ^{99m}Tc Fe_2O_3- or ^{85}Sr latex-particles. Phagocytosis has usually been studied by determining the phagocytic index, which is the percentage of viable macrophages that have ingested at least one insoluble particle, or the phagocytic capacity, which is a measure of the number of ingested particles/ phagocytising cell (often quantified as the percentage of actively phagocytising macrophages that ingest at least 4 particles). Also the production and release of mediators participating in the pulmonary defence such as tumour necrosis factor alpha (TNFα) and superoxide anions have been investigated.

Male rabbits were exposed nose-only for 3 hours to H_2SO_4 at 0.05 or 0.125 mg/m^3 (MMD 0.3 µm). The animals were sacrificed immediately after termination of exposure, and lung lavage was performed. In the high but not the low dose group, intracellular pH in pulmonary macrophages was significantly lowered.

Intracellular pH regulation measured as the ability of pH recovery (after pH lowering with sodium propionate) was decreased in the low dose group. This was not investigated in the high dose group (49).

Depression of the release/activity of TNFα and reduction of superoxide anion production by the pulmonary macrophages were seen in lungs from male rabbits exposed nose-only for 2 hours to 0.075-0.5 mg/m^3. The effects were assumingly immunosuppressant. No effects were seen in the lowest dose group exposed to 0.05 mg/m^3 (250). In another study, male rabbits exposed for 3 hours to H_2SO_4 aerosol at 0, 0.05, 0.075, or 0.125 mg/m^3 (MMD 0.3 µm), after which broncho-pulmonary lavage was performed, exhibited similar effects, i.e. depressed phagocytic capacity of pulmonary macrophages, and depressed superoxide anion production and TNFα activity of stimulated macrophages at the two highest acid levels (205). In both studies, the reductions in TNFα activity were of borderline significance at 0.05 mg/m^3.

In male guinea pigs exposed nose-only for 3 hours to 0.3 mg/m^3 aqueous H_2SO_4 droplets (MMD 0.3 or 0.04 µm), bronchoalveolar lavage revealed an effect on the phagocytic function of macrophages. The 0.3-µm particles enhanced the phagocytic capacity 24 hours after exposure whereas the 0.04-µm particles depressed it. As the same concentration of H_2SO_4 (in mg/m^3) was used in both exposures, the number of droplets in the ultrafine aerosol greatly exceeded the number of droplets in the fine aerosol. Intracellular pH of macrophages was depressed immediately after exposure to both aerosols but the depression persisted after 24 hours only after ultrafine acid exposure. There was an increased release of TNFα from macrophages after fine acid exposure. Small and transient alterations in biochemical parameters of cellular function and viability, seen as increases in β-glucuronidase, lactate dehydrogenase and total protein, were observed after exposure to aerosols of both sizes (47).

Tracheal mucous clearance of radiolabelled macroaggregated albumin was measured in 8 beagle dogs (5 females and 3 males) after 1-hour exposures to H_2SO_4 mist with particle sizes of 0.3 and 0.9 µm (MMAD). Velocities were significantly depressed 30 minutes, 1 day and 1 week after exposure to 1 mg/m^3 of the aerosol with particle size 0.9 µm. At the lower level of 0.5 mg/m^3, there was a significant depression only after 1 week. Values had returned to normal 5 weeks after exposures. There were no significant changes after exposures to the 0.3-µm aerosols at the concentrations tested (1 or 5 mg/m^3) (246).

No inflammatory lesions in lung parenchyma or indications of cytotoxicity were registered in male rats exposed nose-only to 0.5 and 1.0 mg/m^3 H_2SO_4 (MMD 0.3 µm) for 4 hours (131).

In male rabbits exposed to 1 mg/m^3 (MMD 0.3 µm) for 1 hour, alveolar clearance of latex particles (MMAD 3.5 µm) was accelerated up to 3 days post-exposure. The numbers of polymorphonuclear neutrophils were elevated at 1 hour post-exposure in both acid exposed and control animals. In acid exposed animals, levels were still elevated after 24 hours. Also, *in vivo* phagocytosis was enhanced in the acid exposed animals during 3 hours post-exposure (176).

Tracheal mucociliary impairment was reported in male hamsters after exposure to H_2SO_4 mist at levels of 0.88 mg/m^3 for 2 hours (VMD 0.3 μm) and 1.1 mg/m^3 for 3 hours (mean size 0.12 μm) (98, 199).

In a comparative study in male rabbits and humans, a single inhalation exposure (1 mg/m^3 H_2SO_4 for 3 hours, MMAD 0.88 μm) reduced the activity/ability of recovered macrophages to attach to a solid substrate *in vitro*, as well as the serum-opsonised zymosan-stimulated superoxide anion production. The effects were observed in both rabbits and humans in response to H_2SO_4 exposure. In rabbits, the ability of bacterial uptake and intracellular killing by the pulmonary macrophages was reduced and the phagocytic capacity increased (252).

No impairment in tracheal mucous velocity was seen in sheep (sex not given) exposed to 14 mg/m^3 H_2SO_4 aerosol (VMD 0.1-0.2 μm) for 20 minutes and examined immediately after and up to 10 days later. Likewise, no impairment was seen in sheep exposed to 4 mg/m^3 H_2SO_4 aerosol for 4 hours and examined 0 and 2 hours post-exposure. Similar single H_2SO_4 aerosol exposures of anaesthetised dogs (1 or 8 mg/m^3 for 7.5 minutes or 4 mg/m^3 for 4 hours) did not produce any immediate or delayed adverse effect on cardiopulmonary function (195).

Four to six female guinea pigs in each group were exposed to 14, 20, or 43 mg/m^3 (MMD 0.90-0.96 μm) H_2SO_4 for 4 hours. Breathing frequency increased in animals exposed to the lowest concentration. Animals exposed to the highest concentration showed increased tidal volume and decreased breathing frequency immediately after exposure (Section 10.1). Analysis of fluid from bronchoalveolar lavage performed only in the 43 mg/m^3 exposure group showed an increased proportion of eosinophils and neutrophils, a decreased recovery of macrophages, and increased protein content. Histology showed hyaline membranes and acute inflammatory cells in the proximal acinar region. At 24 hours post-exposure, histology revealed evidence of diffuse pulmonary oedema in the highest exposed animals (192).

Chamber exposure of female guinea pigs (43 mg/m^3, MMD 0.93 μm) and female rats (94 mg/m^3, MMD 0.80 μm) to high levels of H_2SO_4 aerosol for 4 hours had an adverse effect on the biological properties of pulmonary surfactant in the guinea pig, but not in the rat. The number of macrophages was decreased and the number of neutrophils and eosinophils was increased in bronchoalveolar lavage fluid from guinea pigs (150).

In summary, single inhalation exposures of animals to H_2SO_4 (Section 10.1-10.2) give rise to airway irritation and impaired pulmonary function. At lower exposure levels, airway hyperresponsiveness and effects on the lung defences are reported. A lowest observed adverse effect level (LOAEL) of 0.075 mg/m^3 is indicated from studies in rabbits showing airway hyperresponsiveness as well as effects on the TNFα release and lowered superoxide anion production *in vitro* after exposure for 2-3 hours *in vivo*. In guinea pigs, an increased pulmonary flow resistance was observed after exposure to 0.1 mg/m^3 for 1 hour. At single exposure, 0.05 mg/m^3 can be regarded as an overall no observed adverse effect level (NOAEL).

Table 7. Effects in animals of single inhalation exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size MD [a], µm	Duration				
0.05	0.3	2 h, nose-only	Rabbit	5	No effects observed on pulmonary macrophages. However, reduced release/activity of TNFα of borderline significance (p=0.06).	(250)
0.05	0.03	3 h, nose-only	Rabbit	5	Intracellular pH in pulmonary macrophages not lowered by the exposure, but decreased ability to recover intracellular pH after addition of a pH-lowering agent in pulmonary macrophages.	(49)
0.05	0.3	3 h, nose-only	Rabbit	5	No effect on bronchial and tracheal reactivity after *in vitro* assessment of the airways (bronchial and tracheal rings).	(70)
0.05	0.3	3 h, nose-only	Rabbit	5	No significant effect on phagocytic capacity of pulmonary macrophages, superoxide anion production and TNFα activity by stimulated macrophages *in vitro*. The latter, however, was of borderline significance (p=0.06).	(205)
0.075	0.3	2 h, nose-only	Rabbit	5	Depression of the release of TNFα and lowered superoxide anion production by pulmonary macrophages *in vitro* after exposure *in vivo*. Also seen at higher exposure levels (0.125 and 0.5 mg/m^3) to a similar extent.	(250)
0.075	0.3	3 h, nose-only	Rabbit	5	Depressed phagocytic capacity of pulmonary macrophages, depressed superoxide anion production and TNFα activity by stimulated macrophages *in vitro*. Also seen at 0.125 mg/m^3 to a similar extent.	(205)
0.075	0.3	3 h, nose-only	Rabbit	5	Non-specific bronchial hyperresponsiveness *in vitro* after exposure *in vivo*. Also seen at higher exposure levels (0.125, 0.25 and 0.5 mg/m^3) to a similar extent.	(70)
0.1	0.3	1 h, head-only	Guinea pig	20-25	Ca 40 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. Decrease in compliance (-27 % at the end of exposure). No effect on tidal volume, respiratory frequency or minute volume.	(13)
0.1	1	1 h, head-only	Guinea pig	20	Ca 10-15 % increase in pulmonary flow resistance at the end of exposure. Values returned to normal within 0.5 h post-exposure. No effect on compliance, tidal volume, respiratory frequency or minute volume.	(13)

Table 7. Effects in animals of single inhalation exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size MD [a], µm	Duration				
0.125	0.03	3 h, nose-only	Rabbit	5	Lowered intracellular pH in pulmonary macrophages.	(49)
0.2	0.06 (mean)	1 h	Guinea pig	6-8	Non-specific airway hyperresponsiveness assessed 1.5 h post-exposure.	(48)
0.25	0.3	3 h, nose-only	Rabbit	5	No increase in tracheal reactivity after *in vitro* assessment of the airways (tracheal rings).	(70)
0.3	0.08	1 h	Guinea pig	7-10	Significantly decreased single breath diffusion capacity for carbon monoxide. No effect on vital capacity.	(46)
0.3	0.04	3 h, nose-only	Guinea pig	6	Small changes in biochemical parameters and depressed phagocytic capacity. Depression of intracellular pH of alveolar macrophages immediately and 24 hours after exposure.	(47)
0.3	0.3	3 h, nose-only	Guinea pig	6	Small changes in biochemical parameters and enhanced phagocytic capacity. Increased TNFα release from alveolar macrophages. Depression of intracellular pH of macrophages immediately after exposure.	(47)
0.4	1	1 h, head-only	Guinea pig	20	Ca 30 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. No effect on compliance, respiratory frequency, tidal or minute volumes.	(13)
0.5	0.3	1 h, head-only	Guinea pig	20	Ca 60 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. Decrease in compliance (-33 % at the end of exposure), still below control values 0.5 h post-exposure. No effect on tidal volume, respiratory frequency or minute volume.	(13)
0.5	0.3	3 h, nose-only	Rabbit	5	Increased tracheal reactivity after *in vitro* assessment of the airways (tracheal rings).	(70)
0.5	0.9	1 h, nose-only	Dog	8	Significant depression of tracheal mucociliary clearance 1 week after exposure. Velocities had returned to normal 5 weeks after exposure. No significant effects 30 min or 1 day after exposure.	(246)
0.7	1	1 h, head-only	Guinea pig	20	Ca 45 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. Decrease in compliance. No effect on tidal volume, respiratory frequency or minute volume.	(13)

Table 7. Effects in animals of single inhalation exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size MD [a], µm	Duration				
0.85	1	1 h, head-only	Guinea pig	20	Ca 60 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. Decrease in compliance. No effect on tidal volume, respiratory frequency or minute volume.	(13)
0.88	0.3	2 h	Hamster	10	Depressed ciliary beating in trachea.	(98)
1	0.3	4 h, nose-only	Rat	20	No inflammatory or cytotoxic effects seen at this exposure level, nor at 0.5 mg/m^3.	(131)
1	0.3	1 h, head-only	Guinea pig	20	Ca 78 % increase in pulmonary flow resistance at the end of exposure. Still above control values 0.5 h post-exposure. Decrease in compliance (-40 % at end of exposure), still below control values 0.5 h post-exposure. No effect on respiratory frequency, tidal volume or minute volume.	(13)
1	0.88	3 h	Rabbit	6	Reduced activity/ability of recovered macrophages to attach to a solid substrate *in vitro*, and serum-opsonised zymosan-stimulated superoxide anion production. Reduced ability of bacterial uptake and of intracellular killing by pulmonary macrophages. Increased phagocytic capacity.	(252)
1	0.3	1 h, nose-only	Dog	8	No significant depression of tracheal mucociliary clearance 30 min, 1 day or 1 week post-exposure.	(246)
1	0.9	1 h, nose-only	Dog	8	Significant depression of tracheal mucociliary clearance 30 min, 1 day and 1 week after exposure. Velocities had returned to normal 5 weeks after exposure.	(246)
1	0.3	1 h	Rabbit	30	Transiently increased alveolar clearance of tracer latex particles (MMAD 3.5 µm). Prolonged increase in PMN count. Enhanced *in vivo* phagocytosis during 3 h post-exposure.	(176)
1.1	0.12	3 h	Hamster	12	Depressed ciliary beating and damaged respiratory epithelium in the trachea.	(199)
4	0.1-0.2	4 h	Dog	5	No effect on cardiopulmonary function in anaesthetised animals.	(195)
4	0.1-0.2	4 h	Sheep	10	No mucociliary impairment in trachea up to 10 days after exposure.	(195)

Table 7. Effects in animals of single inhalation exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size MD [a], µm	Duration				
5	0.3	1 h, nose-only	Dog	8	No significant depression of tracheal mucociliary clearance 30 min, 1 day or 1 week after exposure.	(246)
8	0.1-0.2	7.5 min	Dog	5	No effect on cardiopulmonary function in anaesthetised animals at this or lower (1 mg/m^3) level.	(195)
9.2 [b]	0.6	30 min	Guinea pig	4	No effect on respiratory frequency. Transient initial decline in inspiratory volume faded as the exposures continued, which was followed by an increase in volume. Same results obtained at 1.8 and 4.6 mg/m^3 (i.e. the slope in the exposure-response curve approximated zero at concentrations between 1 and 10 mg/m^3).	(198)
14	0.1-0.2	20 min	Sheep	10	No mucociliary impairment in trachea up to 10 days after exposure.	(195)
14	0.90-0.96	4 h	Guinea pig	6	Increased breathing frequency. No effect on tidal volume.	(192)
18 [b]	0.6	30 min	Guinea pig	4	No effect on respiratory frequency. Inspiratory volume decline that remained at termination of exposure. At a higher exposure level (46 mg/m^3), the decline continued after exposure.	(198)
20	0.90-0.96	4 h	Guinea pig	6	Signs of dyspnoea.	(192)
33 [b]	1	1 h, head-only	Guinea pig	4	No significant effects on respiratory frequency, tidal volume or minute volume. Tendency to reduction of CO_2-induced increase in tidal volume.	(249)
40 [b]	1	1 h, head-only	Guinea pig	4	The CO_2-induced increase in tidal volume and respiratory frequency was reduced. Also seen in a dose-dependent manner in groups exposed to 49 or 73 mg/m^3.	(249)
43	0.93	4 h	Guinea pig	10	Pulmonary surfactant adversely altered. Decreased number of macrophages and increased number of neutrophils and eosinophils.	(150)
43	0.90-0.96	4 h	Guinea pig	6	Increase in tidal volume and decrease in breathing frequency immediately after exposure. Pulmonary oedema. Increased coughing and dyspnoea, changes in bronchoalveolar lavage (increased proportion of neutrophils and eosinophils, decreased recovery of macrophages) indicating lung injury.	(192)

Table 7. Effects in animals of single inhalation exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size MD [a], µm	Duration				
73 [b]	1	1 h, head-only	Guinea pig	4	Definite signs of breathing difficulty.	(249)
94	0.80	4 h	Rat	6	Pulmonary surfactant not adversely altered. No changes in the number of macrophages, neutrophils and eosinophils.	(150)

[a] Median diameter, either mass median diameter (MMD), mass median aerodynamic diameter (MMAD) or volume median diameter (VMD).
[b] In 10 % CO_2.
MD: median diameter, PMN: polymorphonuclear leukocytes, TNF: tumour necrosis factor.

Hydrochloric acid

Results from the LC_{50}-studies have shown that the respiratory tract is the primary target for HCl both as vapour and aerosol with effects such as emphysema and pulmonary oedema.

Mice seem to be more sensitive to HCl exposure than rats. In one study, the LC_{50} after 30 minutes of aerosol exposure was 8 300 mg/m^3 in rats and 3 200 mg/m^3 in mice, and the corresponding values for vapour were 6 600 mg/m^3 and 3 700 mg/m^3 (Table 6). The cause of death was the effects on the respiratory tract (64).

Male mice were exposed to 700 or 3 500 mg/m^3 HCl in plethysmographs for 15 minutes. Female rats were exposed to 5 880 mg/m^3, and male guinea pigs to 700 and 5 880 mg/m^3 HCl under similar conditions. Histopathological examination was carried out 3 months post-exposure. Exposure to 3 500 mg/m^3 in mice and 5 880 mg/m^3 in guinea pigs caused severe damage to the respiratory tract and was lethal to some animals, while rats exposed to 5 880 mg/m^3 experienced eye damage, but only minimal morphological changes to the respiratory tract 3 months post-exposure. Exposure to 700 mg/m^3 HCl did not cause any significant morphological changes in either the mouse or the guinea pig (124).

Exposure of male rats to 1 300 ppm HCl (1 820 mg/m^3) in plethysmographs via nasal breathing for 30 minutes caused marked toxicity after 24 hours in the nasal region, seen as epithelial and submucosal necrosis, accumulation of inflammatory cells, exudates and the extravasion of erythrocytes. Even higher toxicity (including an increased number of deaths) was seen after forced mouth breathing. In the airways, effects such as major tissue disruption in the trachea and accumulation of inflammatory cells and exudates were observed. Also more peripheral lung damage was demonstrated after forced mouth breathing than after nasal breathing. Breathing frequency was reduced by 4 %, minute ventilation by 6 %, and tidal volume by 7 % in exposed nose breathers compared to the controls. In the mouth breathing group, minute ventilation increased during exposure (223).

Acid instillation (0.1 ml HCl) into the left bronchus stimulated alveolar macrophages to produce TNFα in both lungs of male rats (145).

In summary, single exposure to HCl causes airway irritation seen as decreased respiratory rate, and at higher concentrations epithelial and submucousal necrosis and pulmonary congestion.

Details are given in Table 8.

Table 8. Effects in animals of single inhalation exposure to hydrogen chloride.

Exposure level mg/m^3	ppm	Exposure duration	Species	No. of animal/ group	Effect	Reference
56	39	10 min	Mouse	4	10 % respiratory depression.	(23)
432	309	10 min	Mouse	4	RD_{50}.	(23)
448	320	30 min, head-only	Guinea pig	4	Sensory irritation onset after 6 min exposure. Pulmonary irritation onset after > 20 min exposure. Reduced breathing frequency.	(42)
700	500	15 min, head-only	Mouse	6	Reduced respiratory frequency 3 days and 3 months after exposure, also seen in the high dose group (3 500 mg/m^3). No morphological changes in the respiratory tract. 4 exposure-related deaths.	(124)
700	500	15 min, head-only	Guinea pig	9	Reduced respiratory frequency 3 days and 3 months after exposure, also seen in the high dose group (5 880 mg/m^3). No morphological changes in the respiratory tract. One death, most likely due to suffocation (20 min).	(124)
700	500	15 min, head-only	Baboon	3	No differences from control group regarding respiratory frequency 3 days and 3 months after exposure. Tendency to an increased respiratory rate and minute volume during exposure, which was significant at 7 000 and 14 000 mg/m^3.	(123)
952	680	30 min, head-only	Guinea pig	4	Sensory irritation onset immediately. Pulmonary irritation after ca. 13 min exposure. Reduced breathing frequency.	(42)
1 456	1 040	30 min, head-only	Guinea pig	8	Sensory irritation onset immediately. Pulmonary irritation after ca. 9 min exposure. Persistent reduced breathing frequency. Alveolitis and congestion. Squamous metaplasia and loss of cilia in the larger conducting airways (only group examined lung morphologically). 2/8 died within the 16-day period. Corneal opacities in 4/6 survivors.	(42)
1 820	1 300	30 min, nose-only	Rat	5-8	Reduced breathing frequency, minute ventilation and tidal volume. Epithelial and submucousal necrosis, accumulation of inflammatory cells, exudates and extravasion of erythrocytes in the nasal region.	(223)

Table 8. Effects in animals of single inhalation exposure to hydrogen chloride.

Exposure level mg/m^3	ppm	Exposure duration	Species	No. of animal/ group	Effect	Reference
1 820	1 300	30 min, mouth-only	Rat	5-8	Increased minute ventilation. Deaths and major tissue disruption in the trachea and accumulation of inflammatory cells and exudates. Peripheral lung damage.	(223)
1 932	1 380	30 min, head-only	Guinea pig	8	Sensory irritation onset immediately. Pulmonary irritation in less than 4 min after onset of exposure. Persistent reduced breathing frequency. 3/8 died within the 16-day period. Corneal opacities in all survivors.	(42)
3 500	2 500	15 min, head-only	Mouse	6	Reduced respiratory frequency 3 days and 3 months after exposure. Morphological changes: moderate to severe lung congestion, necrosis of the tracheal mucosa, exudate in the paranasal sinuses. Lung oedema in 1 animal. 5 exposure-related deaths.	(124)
5 880	4 200	15 min, head-only	Guinea pig	9	Reduced respiratory frequency 3 days and 3 months after exposure. Decreased pH in arterial blood. Morphological changes: severe pulmonary congestion with minimal oedema, congestion of the nasal turbinates, severe tracheitis and desquamation of the epithelia of the bronchi and bronchioles. Cloudy corneas. 3 exposure-related deaths.	(124)
5 880	4 200	15 min, head-only	Rat	9	Reduced respiratory frequency 3 days and 3 months after exposure. Increase in $PaCO_2$-values in arterial blood. Eye damage, minimal histopathological changes to the respiratory tract. No exposure-related deaths.	(124)
7 000	5 000	15 min, head-only	Baboon	3	Increased respiratory frequency and minute volume and decreased blood PaO_2.	(123)
14 000	10 000	15 min, head-only	Baboon	3	Same changes as at 7 000 mg/m^3 but more pronounced.	(123)

$PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, RD_{50}: air concentration associated with a 50 % decrease in the respiratory rate; a measure of sensory irritation.

Nitric acid

In rats, the LC_{50} was 260 mg/m^3 after 30 minutes and 130 mg/m^3 after 4 hours (Table 6). Details of toxic effects other than death were not reported (193).

In an old study published 1907, rabbits and cats tolerated 15 ppm (38 mg/m^3) for 3 hours without visible damage (Diem[1], cited in (66)).

In male Fischer 344 rats, single exposure to 1 mg/m^3 HNO_3 vapour for 4 hours resulted in a modest but significant increase in elastase inhibitory capacity. Lavage fluid protein was unchanged. The same total dose was also given as repeated exposure (Table 10, Section 10.3) (175). The implications of the findings for human health are unclear.

Intratracheal instillation of 0.5 ml of 0.08 N HNO_3 in male hamsters caused secretory cell metaplasia in the bronchial airway epithelium and interstitial fibrosis, bronchiolectasis and bronchiolisation of alveoli (52). Similar results were obtained by Coalson *et al* (54). The relevance of these findings is unclear since the conversion of instilled doses to concentrations in inhaled air is difficult.

Phosphoric acid

The LC_{50} was above 850 mg/m^3 in rats exposed for 1 hour (Table 6). Details of other toxic effects other than death were not reported.

10.3 Effects of short-term exposure (up to 90 days)

Sulphuric acid

Details are given in Table 9.

Respiratory region clearance was studied in male rabbits exposed to clean air, H_2SO_4 at 0.05 mg/m^3 (MMAD 0.3 μm) for 1, 2, or 4 hours/day for 14 days or at 0.1 mg/m^3 for 0.5, 1, or 2 hours/day for 14 days. Exposure to 0.05 mg/m^3 for 4 hours/day or 0.1 mg/m^3 at 2 hours/day (same daily dose) resulted in accelerated clearance of radiolabelled latex particles (MMAD 3.5 μm) (201).

Exposure of male rats to 0.02, 0.1, or 0.15 mg/m^3 of H_2SO_4 aerosol (0.4-0.8 μm diameter) alone for up to 90 days did not affect body weight, lung lobe weight, or biochemical parameters and morphological measurements relating to pulmonary fibrogenesis (148).

No alterations in biochemical parameters except a transient increase in β-glucuronidase were seen in bronchoalveolar lavage from male guinea pigs exposed nose-only for 3 hours/day for 4 days to 0.3 mg/m^3 aqueous H_2SO_4 droplets (MMD 0.3 or 0.04 μm). This contrasts findings in the same study after single exposure at the same concentration (Section 10.2). In agreement with the results from single exposure, the TNFα releases from alveolar macrophages were increased by aerosols of both sizes. The smallest, ultrafine droplets depressed the phagocytic capacity (ingestion of 3-μm latex particles) of the alveolar macrophages, while the largest particles enhanced it, both after single and multiple exposures. This finding

[1] Diem L. *Untersuchungen über die Einatmung von Saltpetersäure-dämpfen* (thesis). Würzburg, 1907.

was regarded to be a result of the larger number of droplets being delivered to the macrophages from ultrafine acid aerosols. After repeated, but not single, exposure to both aerosols, the H_2O_2-production from macrophages was increased. Intracellular pH was depressed 24 hours after multiple exposures to ultrafine droplets (47).

The phagocytic activity of alveolar macrophages was studied in male rabbits exposed to 0.25, 0.5, 1 or 2 mg/m^3 H_2SO_4 (MMAD 0.3 µm) 1 hour/day for 5 days. The phagocytosis of latex spheres (3 µm diameter) *in vitro* was reduced by exposure at and above 0.5 mg/m^3 in a dose-dependent manner (202).

In male rabbits exposed to H_2SO_4 (MMD 0.3 µm) in concentrations of 0.25, 0.5 or 1 mg/m^3, 1 hour/day for 5 days, the levels of the eicosanoids (arachidonic acid metabolites) prostaglandins E2 and F2(a) and thromboxane B2 in lung lavage fluid decreased in a dose-related way. Thromboxane B2 values were significantly different from controls already at the lowest concentration of H_2SO_4. Tracheal explants exposed to acidic environments *in vitro* also showed reduced production of eicosanoids. The sulphate ion (Na_2SO_4) did not elicit such an effect. The hydrogen ion was therefore assumed to be the causative agent. Eicosanoids are potent mediators of smooth muscle tone and the inflammatory response. According to the authors, modulation of their metabolism may be a possible factor in the pathogenesis of lung disease (203).

Significant histological (squamous metaplasia) and cell proliferative changes were seen in larynges of female rats after exposure to 1.38 and 5.52 mg H_2SO_4/m^3 (MMAD 0.83 and 0.94 µm) for 6 hours/day for 5 days, or for 5 days/week over a 28-day period. Following exposure to the highest level, parakeratosis was seen in some animals. Partial recovery was observed after 4 weeks. No effects were observed at 0.3 mg/m^3 (MMAD 0.62 µm) after 5 days and only minimal squamous metaplasia in 6/10 animals compared to 0/10 among controls, and no increased cell proliferation after 28 days. The response at the lowest concentration was considered to be an adaptive response. Statistics were not reported. No compound-related histopathological changes in the lung or nasal cavity were seen after any exposure (127).

Significant reductions in uptake and intracellular killing of bacteria, in superoxide anion radical production, and in TNFα activity by male rabbit pulmonary macrophages were seen *in vitro* after nose-only inhalation for 2 hours/day for 4 days to 0.75 and 1 mg/m^3 H_2SO_4 aerosol (MMAD 0.3 µm). Exposure to 0.5 mg/m^3 stimulated the superoxide anion production. No clear dose-effect relationships were seen in the study. Once a critical exposure level was reached (0.75 mg/m^3), no further effects were observed (251).

Antigen-induced histamine release from isolated lung mast cells *in vitro* of male guinea pigs was significantly enhanced by *in vivo* continuous exposure to 1 and 3.2 mg/m^3 H_2SO_4 aerosol (MMD < 0.8 µm) for 2 weeks. Also non-specifically induced (A23187) histamine release was enhanced by exposure for 2 weeks at 1 mg/m^3. The effects were not seen in animals exposed continuously for 4 weeks. In contrast, A23187-induced histamine release was suppressed by exposure to 3.2

mg/m^3, but significantly only after 4 weeks. No changes in the number of lung mast cells were seen in any of the groups. Exposure to 0.3 mg/m^3 for 2 or 4 weeks elicited no changes in histamine release (84).

When groups of 10 male Sprague Dawley rats were exposed 4 hours/day for 2 days to 0.5 mg/m^3 of H_2SO_4 (two groups: MMD 0.3 µm or 0.06 µm), no morphological changes of the lungs, and no effects on cellular proliferation in the pulmonary parenchyma or in ventilatory parameters were seen compared with sham exposure except for a slight decrease in the minute volume on the second day in the group exposed to particles with MMD 0.06 µm. Co-exposure with ozone revealed that both acid aerosols increased ozone-induced morphologic effects (128).

Continuous exposure to 1 or 3.2 mg/m^3 H_2SO_4 aerosol (MMAD 0.54-0.56 µm) for 3, 7, 14, or 30 days in male guinea pigs had no effect on specific airway resistance. In the high dose group, the airway responsiveness to histamine treatment was transiently stimulated after 3 days of exposure and transiently inhibited after 14 days of exposure. It returned to normal levels after 7 and 30 days of exposure, respectively (133).

To conclude, repeated, short-term inhalation of H_2SO_4 affected the defences of the rabbit lung. An accelerated respiratory clearance was reported in animals exposed to 0.05 mg/m^3, 4 hours/day for 14 days (LOAEL) or to 0.1 mg/m^3, 2 hours/day for 14 days. Effects on inflammatory response mediators appeared at 0.25 mg/m^3 (1 hour/day for 5 days). At 0.3 mg/m^3, effects on TNFα release, H_2O_2-production, phagocytosis, and intracellular pH (3 hours/day for 4 days) as well as minimal squamous metaplasia in ciliated epithelium of rats (6 hours/day, 5 days/ week for 28 days) were demonstrated. The effects in the studies were observed at the lowest levels tested.

Hydrochloric acid

In male guinea pigs exposed 2 hours/day, 5 days/week for 7 weeks, a NOAEL of 15 mg/m^3 was established for effects on pulmonary function and histological changes in the lungs and airways (181).

Groups of 16-24 male mice were exposed to HCl vapour for 6 hours/day at the RD_{50} concentration of 309 ppm (432 mg/m^3). After 3 exposures, all animals were dead or moribund. Severe exfoliation, erosion, ulceration and necrosis, and mild inflammation of the respiratory epithelium were observed, as well as mild ulceration and necrosis of the olfactory epithelium, and serous exudate. No lesions were induced in the lower respiratory tract (41).

Nitric acid

Details are given in Table 10 (including single inhalation exposures).

Male rabbits (New Zealand white) exposed nose-only 4 hours/day, 3 days/week for 4 weeks to HNO_3 vapour (0.05, 0.15 and 0.45 mg/m^3) showed effects in the alveolar macrophages (lowered production of superoxide anions) already in the low dose group, and reduced *in vitro* bronchial responsivity in the groups exposed to ≥ 0.15 mg/m^3. Tracheal responsivity was not affected. There was an apparent

concentration-related trend toward a reduction in TNFα-activity, which at ≥ 0.15 mg/m^3 departed significantly from those of controls. This study indicates that HNO_3 impacts both the conducting and respiratory airways. The reason for reduced bronchial responsiveness is not clear, but the authors speculate that formation of airway smooth muscle relaxants such as NO-containing chemical species or *S*-nitrosothiols is possible (207).

In male Fischer 344 rats, short-term exposure (4 hours/day, 4 days) to 0.25 mg/m^3 HNO_3 vapour decreased respiratory burst activity (superoxide anion production) and increased elastase inhibitory capacity as measured in lung lavage fluid. Elastase inhibitory capacity was increased also when the same total dose was given as a single exposure (1 mg/m^3, 4 hours) (Section 10.2). Lavage fluid protein was unchanged by both exposures (175). The implications for humans of changes in elastase inhibitory capacity are unclear.

Seven dogs (sex not given) were exposed to nebulised 1 % HNO_3, 3 days/week for 4 weeks (185). The concentration in air is not given in the paper but may be estimated from the delivered volume (approximately 13 ml corresponding to 130 mg HNO_3), the exposure duration (approximately 2 hours), the body weight (15-19 kg), the tidal volume (15 ml/kg body weight corresponding to 0.23-0.29 l) and the breathing frequency (15-20 min^{-1}). The inhaled air volume is thus between 0.4 and 0.7 m^3 and the average air level during each 2-hour exposure 190-320 mg/m^3 (80-130 ppm). Lung function tests revealed both restrictive and obstructive impairment. Histopathology showed central as well as peripheral damage with inflammation, epithelial damage, peribronchiolar fibrosis and an increase in smooth muscle. Further, hyperresponsiveness to histamine developed 3-5 months after exposure. Similar findings were made in another study of 7 mongrel dogs exposed to the same concentration of HNO_3 on alternate days for 4 weeks (85).

Phosphoric acid

No peer-reviewed studies were found.

Table 9. Effects in animals of short-term exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size, MD [a], µm	Duration				
0.05	0.3	1, 2, or 4 h/day for 14 days	Rabbit	5	Accelerated respiratory clearance of latex particles (MMAD 3.5 µm) after the 4-hour/day exposure.	(201)
0.1	0.3	0.5, 1, or 2 h/ day for 14 days	Rabbit	5	Accelerated respiratory clearance of latex particles (MMAD 3.5) after the 2-hour/day exposure.	(201)
0.15	0.4-0.8	23.5 h/day for up to 90 days	Rat	6	No effect on body weight, lung lobe weight or biochemical parameters and morphological measurements relating to pulmonary fibrogenesis. Same results at 0.02 and 0.1 mg/m^3.	(148)
0.25	0.3	1 h/day, 5 days	Rabbit	3	No effect on alveolar phagocytosis of latex spheres (diameter 3 µm) *in vitro*.	(202)
0.25	0.3	1 h/day for 5 days, nose-only	Rabbit	5	Decreased level of the eicosanoid [b] TxB_2 in bronchopulmonary lavage fluid. Also seen at 0.5 mg/m^3 for the eicosanoids TxB_2 and PGE_2 and at 1 mg/m^3 for TxB_2, PGE_2 and $PGF_{2\alpha}$.	(203)
0.3	0.04	3 h/day for 4 days, nose-only	Guinea pig	6	Increased TNFα release and H_2O_2-production from alveolar macrophages. Depressed *in vitro* phagocytic capacity. No changes in biochemical parameters. Depressed intracellular pH 24 hours after exposure.	(47)
0.3	0.3	3 h/day for 4 days, nose-only	Guinea pig	6	Increased TNFα release and H_2O_2-production from alveolar macrophages. Enhanced *in vitro* phagocytic activity. No changes in biochemical parameters.	(47)
0.3	0.62	6 h/day for 5 or 28 days	Rat	10	No histopathological changes in the lung or nasal cavity. No increase in cell proliferation in the larynx. At 28 days, minimal squamous metaplasia in ciliated epithelium in the larynx (6/10 compared to 0/10 in controls). Also seen at 1.38 and 5.52 mg/m^3 to a greater extent.	(127)
0.3	0.65	Continuously for 2 or 4 weeks	Guinea pig	3-4	No changes in antigen- or non-specifically (A23187) induced histamine release in lung mast cells or in the number of lung mast cells.	(84)
0.5	0.06 or 0.3	4 h/day for 2 days, nose-only	Rat	10	No effect on morphology, cellular proliferation in the pulmonary parenchyma or ventilatory parameters except for a slight decrease in the minute volume on the 2nd day in the group exposed to particles with MMD 0.06 µm.	(128)

Table 9. Effects in animals of short-term exposure to sulphuric acid.

Exposure			Species	No. of animal/ group	Effect	Reference
Level, mg/m^3	Droplet size, MD [a], µm	Duration				
0.5	0.3	1 h/day for 5 days	Rabbit	3	Reduced alveolar phagocytosis (phagocytic capacity) of latex spheres (3 µm diameter) *in vitro*. The effect increased in a dose-dependent manner at 1 and 2 mg/m^3.	(202)
0.5	0.3	2 h/day for 4 days, nose-only	Rabbit	5	No immunosuppressive effects *in vitro* after exposure *in vivo*. Stimulated superoxide anion production by pulmonary macrophages.	(251)
0.75	0.3	2 h/day for 4 days, nose-only	Rabbit	5	Immunosuppressive effects *in vitro* after exposure *in vivo* (reduction in uptake and intra-cellular killing of bacteria, in superoxide anion production and in TNFα activity). The same effects of similar magnitude were also seen at the highest exposure level (1 mg/m^3).	(251)
1	0.5	Continuously, 3, 7, 14 or 30 days	Guinea pig	72	No effect on specific airway resistance and airway hyperresponsiveness to histamine.	(133)
1	0.55	Continuously, 2 or 4 weeks	Guinea pig	3-4	Enhanced antigen as well as non-specifically (A23187) induced histamine release in the lung mast cells *in vitro* after 2 weeks exposure *in vivo* but not after 4 weeks. No changes in the number of lung mast cells.	(84)
1.38	0.83	6 h/day for 5 days	Rat	10	Squamous metaplasia in ciliated epithelium of the larynx. Increased cell proliferation in larynx. No histopathological changes in the lung or nasal cavity. Effects were dose-dependent and seen also in rats exposed to 5.52 mg/m^3 (parakeratosis in some animals).	(127)
3.2	0.5	Continuously, 3, 7, 14 or 30 days	Guinea pig	72	Airway responsiveness to histamine treatment transiently stimulated and later inhibited during exposure. No effect on specific airway resistance.	(133)
3.2	0.73	Continuously, 2 or 4 weeks	Guinea pig	3-4	Enhanced antigen-induced histamine release from isolated lung mast cells *in vitro* after exposure *in vivo* after 2 weeks but not after 4 weeks. Reduced non-specifically induced (A23187) histamine release, significant after 4 weeks but not after 2 weeks. No changes in the number of lung mast cells.	(84)

[a] Median diameter, either mass median diameter (MMD), mass median aerodynamic diameter (MMAD) or volume median diameter (VMD).
[b] Eicosanoids are potent mediators of smooth muscle tone and the inflammatory response.
MD: median diameter, PG: prostaglandin, TNF: tumour necrosis factor, Tx: thromboxan.

Table 10. Effects in animals of single and short-term inhalation exposure of nitric acid vapour.

Exposure level mg/m^3	ppm	Exposure duration	Species	No. of animals /group	Effect	Reference
0.05	0.02	4 h/day, 3 days/ week , 4 weeks, nose-only	Rabbit	6	Reduced production of superoxide anions in the alveolar macrophages, seen also at 0.15 and 0.45 mg/m^3. No effect on viability or numbers of cells.	(207)
0.15	0.06	4 h/day, 3 days/ week, 4 weeks, nose-only	Rabbit	6	Reduced bronchial reactivity to smooth muscle constrictor challenge (acetylcholine and histamine) and a reduction in TNFα activity in alveolar macrophages. The same effects were seen in the higher exposed group (0.45 mg/m^3) but there were no clear dose-effect relationships.	(207)
0.25	0.1	4 h/day for 4 days, nose-only	Rat	10	Decreased spontaneous and stimulated respiratory burst activity (superoxide anion production) in isolated pulmonary macrophages. Increase in elastase inhibitory capacity of lung lavage fluid. No change in lavage fluid protein.	(175)
1	0.4	4 h, nose-only	Rat	10	Increase in elastase inhibitory capacity of lung lavage fluid. No change in lavage fluid protein content.	(175)
4.1	1.6	4 h, head-only	Sheep, normal and allergic	7	No bronchoconstriction (decreased specific pulmonary flow resistance post-exposure). Allergic sheep showed increased airway hyperreactivity to aerosolised carbachol.	(2)
190-320 [a]	80-130 [a]	3 days/week for 4 weeks	Dog	7	Bronchial injury was induced, with airway obstruction and chronic inflammation of the small airways.	(85)
190-320 [a]	80-130 [a]	Alternate days for 4 weeks	Dog	7	Bronchial injury was induced, with airway obstruction and chronic inflammation of the small airways.	(185)

[a] Administered as spray, exposure level estimated by the Nordic Expert Group, for details see the text.
TNF: tumour necrosis factor.

10.4 Mutagenicity and genotoxicity

No data were available on the genetic and related effects of exposure to H_2SO_4 mists *in vitro*. However the effects of pH-reduction have been investigated.

Low pH did not affect the frequency of point mutations in various bacteria strains, yeast and fungi but induced gene conversion in *Saccharomyces cerevisiae* (116).

Low pH led to sister chromatid exchanges and chromosomal aberrations in Chinese hamster cells treated *in vitro* in media over the pH range 5.4-7.2 during 24 hours continuous or 3 hours pulse treatments (172). Similar clastogenic effects of low pH have been reported in other studies of cultured mammalian cells, including human lymphocytes and epithelioid carcinoma (HeLa) cells (39, 169-171).

Sublethal pH decrease also caused developmental and mitotic abnormalities to embryos and sperm from eukaryotic sea urchins but failed to induce any changes in reversion rates in *Salmonella typhimurium* (53).

HCl, HNO_3 or H_3PO_4 did not transform Syrian hamster embryo cells in a SA7/SHE-system *in vitro*. The concentrations ranged from 31 to 500 µg/ml for HCl and from 62 to 1 000 µg/ml for the two other acids (reviewed by Heidelberger *et al*, 1983 (107).

At relevant inhalation exposure levels, the local pH in the respiratory tract may be lowered by the acids although it can be assumed that systemic pH is not affected.

10.5 Effects of long-term exposure and carcinogenicity

Many of the published studies are based on combined exposure simulating environmental atmospheric pollution of H_2SO_4 aerosol, ozone and NO_2. Here, mainly studies with isolated exposure to the acids are reported (Tables 11-12).

No animal inhalation studies according to modern standards on the carcinogenicity of strong inorganic acid aerosols were located. The few available studies have various weaknesses in study design such as inadequate exposure duration or an insufficient number of animals to address the carcinogenic potential of inorganic acid aerosols (Table 12). In a review by Swenberg and Beauchamp (1997), in which they assessed available animal studies on chronic toxicity and carcinogenicity from inorganic acid mists, it was concluded that the evidence from experimental animals neither strongly supports nor refutes the induction of cancer by inorganic acid mists (229).

Sulphuric acid

The studies are compiled in Table 11. In a series of reports, Schlesinger and co-workers evaluated effects from H_2SO_4 exposure on the lung defence in donkeys and rabbits. A sustained impairment of bronchial mucociliary clearance of radiolabelled Fe_2O_3 (MMAD 5 µm) was observed in 2/4 donkeys exposed to approximately 0.1 mg/m^3 H_2SO_4 (MMAD 0.5 µm), 1 hour/day, 5 days/week for

6 months (200). All 4 animals (1 female and 3 males) showed an increased variability in clearance rates.

In male rabbits exposed to 0.125 mg/m^3 H_2SO_4, 2 hours/day, 5 days/week for up to 12 months, an accelerated tracheobronchial clearance of Fe_2O_3 (MMAD 4.5 µm) was observed after 4 and 8 months of exposure. A slowing trend was seen towards the end of the 12-month exposure. Clearance did not return to normal within the 6-month follow-up period but actually became slower. The animals developed increased secretory cell number in the small airways, an effect that was reversible (204). In contrast, male rabbits exposed to 0.25 mg/m^3 H_2SO_4 (nose-only, MMD 0.3 µm), 1 hour/day, 5 days/week for 4, 8 or 12 months (the same daily dose as in the previous study) showed a retarded tracheobronchial clearance of radiolabelled Fe_2O_3 (MMAD 4.5 µm) 18-20 hours after the preceding day's exposure. The lowering in clearance progressed with continued exposure. After cessation of exposure, clearance became extremely slow and did not return to normal during a 3-month follow-up period. Histological analysis revealed that acid-exposed animals had a narrowing of the bronchial airways and an increased lung epithelial secretory cell number. Significantly enhanced sensitivity to acetyl-choline, a response characteristic of hyperresponsive airways, was seen in rabbits exposed for 4, 8, or 12 months. In addition, animals exposed for 8 or 12 months exhibited an increased airway reactivity, which had started to appear also in the 4-month exposure group (88-90). The authors concluded that both clearance and the morphometric endpoint were more dependent on inhaled acid concentration than on total dose.

Monkeys and guinea pigs were exposed to various combinations of SO_2, H_2SO_4 and fly ash. Guinea pigs (males and females) exposed to 0.08 (MMD 0.54 or 2.23 µm) or 0.90 mg/m^3 (MMD 0.49 µm) H_2SO_4 for up to 52 weeks showed no signs of exposure-related toxicity. In contrast, monkeys (of both sexes) exposed to 0.88-0.99 mg/m^3 H_2SO_4 for 78 weeks developed lesions in their lungs. These consisted of focal epithelial and goblet cell hypertrophy and hyperplasia, erosion, thinning and squamous metaplasia of the bronchiolar epithelium. H_2SO_4 was considered responsible for the effects. No effects were demonstrable in 9 monkeys exposed to 0.09-0.11 mg/m^3 H_2SO_4 (9).

Eight female dogs were exposed to 0.9 mg/m^3 H_2SO_4 for 21 hours/day for 620 days. Pulmonary function was seriously impaired and heart weights reduced, but no exposure-related histopathologic changes were demonstrated (154).

In guinea pigs (males and females) exposed to 0.08 or 0.1 mg/m^3 H_2SO_4 (MMD 2.8 or 0.8 µm) for 23 hours/day for 52 weeks, no exposure-related effects occurred. In monkeys of both sexes, chronic exposure to 2.4 and 4.8 mg/m^3 of H_2SO_4 mists (MMD 3.6 or 0.73 µm) for 23 hours/day for 78 weeks was associated with impaired lung function and histopathological changes. The lesions consisted of epithelial hypertrophy and hyperplasia, thickening of alveolar septa and bronchioles, and enlargement of air spaces. These effects were less pronounced or absent in the groups of monkeys exposed to lower concentrations (0.38 or 0.48 mg/m^3). However, submicrometer particles (MMD 0.54 µm) produced no alterations of

pulmonary structures at 0.48 mg/m^3 whereas particles with MMD 2.15 μm at 0.38 mg/m^3 produced some histological changes (slight bronchiolar epithelial hyperplasia and slight thickening of walls of respiratory bronchioles) and an increased respiratory frequency. The results indicate that particle size was the important factor (8).

A lifetime study of the carcinogenic effect of H_2SO_4 in rats and mice of both sexes is published, but the administration routes were not relevant to occupational exposure (intratracheal instillation and gastric intubation). The animals were exposed to maximum tolerated doses once a week for life. The concentrations were 0.3-0.5 ml 0.6 % H_2SO_4 in distilled water administered both perorally and intratracheally to rats and 0.2 ml 0.2 % H_2SO_4 for mice dosed perorally only. Tumours were seen in the second year of dosing in the organs where the acid acted directly. H_2SO_4 was considered a weak, locally acting chemical carcinogen by the authors. The findings of tumours in the forestomach in mice were not significantly different from the controls (235).

There is only one study designed to evaluate pulmonary carcinogenicity in animals exposed chronically to aerosols. In male hamsters, no tumours were observed in the respiratory tract after inhalation exposure to 100 mg/m^3 H_2SO_4, 6 hours/day, 5 days/week for life but laryngeal and tracheal epithelial hyperplasia was increased. No general toxic effects were noted (147) at this high level, which may indicate that the hamster is not a suitable animal model for assessing carcinogenicity.

In conclusion, the LOAEL after long-term exposure is 0.1 mg/m^3 at which impaired mucociliary clearance in donkeys was reported. In rabbits, accelerated mucociliary clearance and secretory cells hyperplasia in small airways were observed at 0.125 mg/m^3 and narrowing of the airways, airway hyperresponsiveness and decreased mucociliary clearance when the same daily dose was administered at a slightly higher level (0.25 mg/m^3). In monkeys exposed to larger particles (MMD 2.15 μm) at 0.38 mg/m^3, an increased respiratory rate and slight findings of hyperplasia of bronchiolar epithelium and thickening of the walls of respiratory bronchioles were reported. At higher levels, pulmonary function is impaired (LOAEL 0.9 mg/m^3 in dogs).

Hydrochloric acid

In a 90-day inhalation study, male and female mice and rats were exposed to 0, 10, 20, or 50 ppm HCl (0, 15, 30, or 75 mg/m^3), 6 hours/day, 5 days/week for 90 days. A slight but significant decrease in body weight gain was reported in male and female mice and in male rats in the highest dose group. No effects were observed in haematology, clinical chemistry and urinalysis parameters. Local irritative effects on the nose were observed in both rats and mice. In rats, concentration- and time-dependent minimal to slight rhinitis in the anterior nasal cavity were observed after 5 and 90 days. In mice, dose-dependently increasing lesions on skin and mucosa, particularly around the mouth and nose, were observed after 90 days at or above 30 mg/m^3. In mice, histology revealed ulcerative dermatitis, necrotic

cells in the subcutis and increased phagocytised blood pigments in macrophages and intracytoplasmatically in sub-epithelial cells. The systemic NOAEL was found to be 30 mg/m^3, and the LOAEL for irritation 15 mg/m^3 (industry report[1] cited in reference (68)).

No nasal cancer was observed after inhalation of 14 mg/m^3 HCl, 6 hours/day, 5 days/week for life in male Sprague Dawley rats. The exposure had no effect on body weight or mortality rate (10). In a study, with similar exposure regimen, no nasal cancer was observed, but the incidences of hyperplasia in larynx and trachea were increased (22 % and 26 % versus 2 % and 6 % among controls) (212). These studies were carried out as part of an investigation of the combined effect of formaldehyde and HCl. IARC pointed out (115) that as the studies were not designed to test the carcinogenicity of HCl, higher doses might have been tolerated. In neither study did HCl appreciably influence the tumourigenic effects of formaldehyde. No other experimental studies according to modern standards on the carcinogenicity of HCl were identified (Table 12).

Nitric acid

In male rats, chronic exposure to low levels of HNO_3 vapour (0.05 mg/m^3, nose-only for 4 hours/day, 3 days/week for 40 weeks) did not affect body weight or lung polyamine contents (essential for cell growth, multiplication, differentiation, and free radicals scavenging). Lung clearance of tracer microspheres was not statistically different from the control group. The level of stress inducible heat-shock protein 70 was markedly elevated in lungs from the exposed animals (164, 215, 248). The relevance of this finding is uncertain. The results of the studies originate from the same animal experiment.

No experimental inhalation studies according to modern standards on the carcinogenicity of HNO_3 were located (Table 12).

Phosphoric acid

No published studies on long-term exposure or carcinogenicity were identified.

[1] Chemical Industry Institute of Toxicology (1984). *90-Day inhalation study of hydrogen chloride gas in B6C3F1 mice, Sprague-Dawley rats, and Fischer-344 rats.* ToxiGenics, Inc for CIIT Research Triangle Park, NC, USA, CIIT Docket No. 20915.

Table 11. Effects in animals of long-term exposure to sulphuric acid.

Exposure			Species	No. of animals	Effect	Reference
Level, mg/m^3	Droplet size, MD [a], µm	Duration				
0.08 or 0.1	2.8 and 0.8	23 h/d for 52 weeks	Guinea pig	50/group	No treatment-related histopathologic effects in sections of the lungs or trachea.	(8)
0.09-0.11 and fly ash or SO_2	< 1 or 1-4	23 h/d for 78 weeks	Cynomolgus monkey	9/group	No changes in bronchial mucosa, pulmonary function or biochemical and haematological parameters.	(9)
0.1	0.5	1 h/d, 5 d/week for 6 months	Donkey	4 totally	Increased variability in bronchial mucociliary clearance rates in all animals. A sustained impairment of mucociliary clearance in 2 animals (measured on tagged Fe_2O_3 with MMAD 5 µm).	(200)
0.125	0.3	2 h/d, 5 d/week for up to 12 months	Rabbit	20 totally	6 months post-exposure, animals exposed for up to 8 months showed acceleration of tracheobronchial mucociliary clearance. Histological examination of animals sacrificed directly after 12 months of exposure revealed an increased secretory cell number in small airways and possibly mild focal epithelial hyperplasia.	(204)
0.25	0.3	1 h/d, 5 d/week for 4, 8, or 12 months, nose-only	Rabbit	4-5/group	Development of airway hyperresponsiveness shown by: a) enhanced sensitivity to acetylcholine in all groups to a similar extent b) an increase in airway reactivity in animals exposed for 4 months ($p < 0.075$) and in animals exposed for 8 and 12 months ($p < 0.05$). Dynamic compliance was not affected in any group. Decreased tracheobronchial mucociliary clearance of Fe_2O_3 particles (MMAD 4.5 µm) in all groups. Lowering of clearance progressed with continued exposure and were not normalised 6 months post-exposure. Decreased airway diameter, and secretory cell hyperplasia in the bronchial tree in all groups.	(88-90)

Table 11. Effects in animals of long-term exposure to sulphuric acid.

Exposure			Species	No. of animals	Effect	Reference
Level, mg/m^3	Droplet size, MD [a], µm	Duration				
0.38	2.15	23 h/d for 78 weeks	Cynomolgus monkey	9/group	Slight findings of hyperplasia of bronchiolar epithelium and thickening of walls of respiratory bronchioles. Increased respiratory rate. No change in distribution of ventilation (nitrogen washout) or oxygen tension.	(8)
0.48	0.54	23 h/d for 78 weeks	Cynomolgus monkey	9/group	No exposure-related histological alterations in the lungs. No change in respiratory rate. Slight deterioration of the distribution of ventilation (nitrogen washout) at specific time intervals.	(8)
0.88-0.99 and fly ash or SO_2	< 1 or 1-4	23 h/d for 78 weeks	Cynomolgus monkey	9/group	Changes in the bronchial mucosa (focal epithelial and goblet cell hypertrophy and hyperplasia, erosion, thinning and squamous metaplasia of epithelium). No changes in pulmonary function or biochemical and haematological parameters.	(9)
0.9	< 0.5	21 h/d for 620 d	Dog	8 totally	Impaired pulmonary function (reduced carbon monoxide diffusion capacity, residual volume, total lung volume, increased total expiratory resistance). No exposure-related histopathological changes. Reduced heart weight.	(154)
0.9	0.49	23 h/d for 52 weeks	Guinea pig	50/group	No exposure-related microscopic alterations in lungs. No effects on pulmonary function or biochemical parameters. Same results obtained also at exposure to 0.08 mg/m^3 (MMD 0.54 or 2.23 µm) combined with fly ash.	(9)
2.4	3.6	23 h/d for 78 weeks	Cynomolgus monkey	9/group	Hyperplasia of bronchiolar epithelium and thickening of alveolar septa and bronchioles. Decreased pulmonary function (increased respiratory rate, decreased oxygen tension, deterio-ration of the distribution of ventilation). Same effects but more pronounced at 4.8 mg/m^3 (smaller particles, MMD 0.73).	(8)

[a] Median diameter, either mass median diameter (MMD), mass median aerodynamic diameter (MMAD) or volume median diameter (VMD).

Table 12. Carcinogenicity studies in animals exposed to the inorganic acids.

Exposure				Species	No. of animals	Effect/Comment	Reference
Level	Route	Particle size	Duration				
Sulphuric acid							
4-156 mg/m^3	Inhalation	NG	6 h/d on alternate weekdays for 2 wk, 6 exposures	Rat	50/group	No significant increases in neoplasia. Animals were observed for lifetime. Inadequate reporting of study design, results, and short duration of exposure.	[a, b] cited in (229)
100 mg/m^3	Inhalation	2.6 µm	6 h/d, 5 d/wk, for life	Hamster	60/group	Laryngeal and tracheal epithelial hyperplasia, no tumours of the respiratory tract.	(147)
0.2 ml 0.2 %, in distilled water	Oral (gastric intubation)		Once a week for life	Mouse	50-60/ group	Tumours in the forestomach, but not statistically significant from controls.	(235)
0.3-0.5 ml 0.6 %, in distilled water (maximum tolerated doses)	Oral (gastric intubation) or intratracheal (instillation)		Once a week for life Twice a month for 12 months	Rat Rat	60/group 60/group	In the second year, various tumours in organs where H_2SO_4 acted directly (both benign and malign in the forestomach after intubation and in the trachea and lungs after instillation).	(235)
Hydrochloric acid							
10 ppm vapour (14 mg/m^3)	Inhalation		6 h/d, 5 d/wk for life	Rat	100/group	No nasal carcinomas or neoplasms of other sites.	(10)
10 ppm vapour (14 mg/m^3)	Inhalation		6 h/d, 5 d/wk for life	Rat	100/group	Increased incidence of hyperplasia in larynx and trachea (22 % and 26 % versus 2 % and 6 % among controls). No nasal cancer. No other observations reported.	(212)

Table 12. Carcinogenicity studies in animals exposed to the inorganic acids.

Exposure				Species	No. of animals	Effect/Comment	Reference
Level	Route	Particle size	Duration				
5-22 mg/m^3 aerosols	Inhalation	NG	6 h/d on alternate weekdays for 2 wk, 6 exposures	Rat	50/group	No significant increases in neoplasia. Animals were observed for lifetime. Inadequate reporting of study design, results, and short duration of exposure.	[a, b] cited in (229)
0.25 ml 0.5 %	Subcutaneous injections		6 times/wk for 10.5-16 months	Mouse	2 totally	Subcutaneous sarcomas at the site of injection.	[c] cited in (229)
Nitric acid							
13-49 mg/m^3 aerosols	Inhalation	NG	6 h/d on alternate weekdays for 2 wk, 6 exposures	Rat	50/group	No significant increases in neoplasia. Animals were observed for lifetime. Inadequate reporting of study design, results, and short duration of exposure.	[a, b] cited in (229)
Phosphoric acid							
No studies found.							

NG: Not given.

[a] Ballou JE, Gies RA, Dagle GE, Burton FG, Moss OR. Late effects of acid inhalation. In: *Pacific Northwest Laboratory Annual Report.* Richland, WA: Pacific Northwest Laboratory, 1978: 6.1-6.2.

[b] Ballou JE, Gies RA, Dagle GE, Burton FG, Moss OR. Late effects of acid inhalation. In: *Pacific Northwest Laboratory Annual Report.* Richland, WA: Pacific Northwest Laboratory, 1981: 223-225.

[c] Suntzeff V, Babcock RS, Loeb L. The development of sarcoma in mice following long continued injections of a buffered solution of hydrochloric acid. *Am J Cancer* 1940;39:56-60.

10.6 Reproductive and developmental effects

Pregnant CF-1 mice and New Zealand white rabbits were exposed to H_2SO_4 aerosol (0, 5 or 20 mg/m^3) in exposure chambers 7 hours/day, during organogenesis (day 6-15 in mice, 6-18 in rabbits). There were 35 mice and 20 rabbits in each dose group. No embryotoxic, foetotoxic or teratogenic effects from the exposures were observed. Slight maternal toxicity was seen in both species at 20 mg/m^3 (174).

No published studies on reproductive and developmental toxicity of HCl, HNO_3, or H_3PO_4 were found.

Reproductive and developmental effects of the four acids are unlikely at relevant exposure levels since the contributions of protons and anions to the systemic levels will be low. However, effects secondary to lung damage cannot be excluded.

11. Observations in man

11.1 Irritation, corrosion and sensitisation

All four acids are classified as corrosive in the European legislation on classification and labelling of chemicals, with HNO_3 as the strongest and classified as corrosive in solutions containing more than 5 % (the most dilute solution classified). H_2SO_4 is classified as corrosive in concentrations from 15 %, and HCl and H_3PO_4 from 25 %; more dilute solutions are irritating to eyes, skin, and respiratory system. Thus, H_2SO_4 is classified as irritating in the range 5-15 %, and HCl and H_3PO_4 in the range 10-25 % (76).

Selected case-reports are described in Section 11.2. At lower air concentrations, the inorganic acid vapours or mists are respiratory tract and mucous membrane irritants (Section 11.3). Discolouration and erosion of the teeth have been reported after occupational exposure to the inorganic acids (Section 11.4) (110).

Repeated skin contact with the inorganic acids may lead to dermatitis (110). No sensitising effects have been reported after exposure to any of the four acids.

Sulphuric acid

H_2SO_4 is corrosive and highly irritating to skin. On direct contact, H_2SO_4 causes violent dehydration, which can carbonise (char) the skin. In the reaction with water, heat is released in sufficient quantities to produce burns similar to thermal burns (110). H_2SO_4 is rapidly injurious to the eyes and the mucous membranes of the respiratory tract and can etch teeth (6).

Hydrochloric acid

Exposure to a high concentration of HCl gas or to a concentrated solution of HCl will cause burns of the skin and mucous membranes; repeated or prolonged

exposures of the skin to dilute solutions may cause dermatitis. Contact with the eyes may produce reduced vision or blindness (5, 110).

Nitric acid
HNO_3 can cause severe burns in eyes and skin. Permanent corneal opacification leading to blindness has been reported. Dermal contact with concentrated solutions of HNO_3 may cause deep ulcers and yellowish staining of the skin. Dilute solutions of HNO_3 is irritating to the skin, eyes and mucous membranes. Acute occupational exposure to HNO_3 fumes (reported in cases with concurrent inhalation of NO_2 and NO) can elicit prompt irritation of the upper respiratory tract, leading to coughing, dyspnoea, cyanosis and acute pulmonary oedema. Inhalation of high (but unknown) concentrations of HNO_3 fumes has been responsible for numerous fatalities; death can be delayed several days (3).

Phosphoric acid
H_3PO_4 mist is a mild irritant of the eyes, upper respiratory tract and the skin; the dust is especially irritating to skin in the presence of moisture (4).

11.2 Case reports

Human case reports (exemplified below) describe severe reactions to the four acids when in contact with the skin, eyes and mucous membranes. These include corrosion and destruction of body tissue from chemical burns leading to ulcers, blindness and death. In a prospective study of 16 patients with acid ingestion including H_2SO_4, HCl or HNO_3, all had oesophageal and gastric injuries. Two died of gastric perforation and one of bronchopneumonia. In surviving patients with severe injuries, late complications developed, e.g. oesophageal stricture (69). Life-threatening acute (or adult) respiratory distress syndrome (ARDS) as well as persistent reactive airways dysfunction syndrome (RADS) have been reported after single exposure to high acid levels.

Sulphuric acid
The death of a man 5 days after he was splashed with concentrated H_2SO_4 was attributed to extensive burns and chemical damage to the respiratory tract (208). In a survey of burns caused by chemicals including H_2SO_4, 3 deaths were identified in patients whose injuries exceeded 50 % of the total body surface (36). A case of accidental inhalation of fumes of strong H_2SO_4 during application to blocked drainpipes with fatal outcome is reported. Autopsy revealed congestion of the respiratory passages and severe pulmonary oedema (26). A 40-year old man accidentally exposed to liquid fuming H_2SO_4 and for 8 minutes to acid mist and fumes from the action of water (safety shower) on the liquid developed a disabling pulmonary fibrosis, residual bronchiectasis, and pulmonary emphysema that persisted 18 months (93). A 45-minute exposure to a cleaning compound containing 66 % H_2SO_4 in an unventilated washroom caused cough, chest tightness, dyspnoea and mild rhinoconjunctivitis in a 45-year-old woman immediately after exposure

(33). A plumber developed ARDS, after accidental exposure in a manhole to unknown levels of a 95 % H_2SO_4 mixture from a pipe (132).

Hydrochloric acid

A case developing tracheobronchial stenosis from HCl ingestion and aspiration presenting as asthma has been reported (194). A man with a history of mild asthma that inhaled high concentrations of a product containing HCl for 1 hour developed rapidly progressive and severe bronchospasm. One year later, marked asthma symptoms remained (33). A 30-year-old woman presented with RADS after a single accidental inhalation of HCl (78). Among 9 pharmaceutical workers exposed to HCl fumes, 5 had severe symptoms, reduced peak expiratory flow rate or hypoxaemia. One patient developed long-term airway hyperreactivity, superimposed on a background of chronic obstructive airways disease (35).

Following an accident with a container truck leaking HCl, burning and tearing eyes, burning throats, headache, chest pain, shortness of breath and flu-like symptoms were observed among the exposed residents. A follow-up on 45 exposed adults and 56 age-matched controls was performed 20 months later. The exposed differed significantly from controls in neurobehavioural tests for balance, reaction time, digit-symbol and perceptual motor speed. Respiratory, neurobehavioural, general and vegetative function symptoms were also more frequent among exposed than among controls. Furthermore, balance scores, reaction times and forced expiratory flow at 25-75 % (FEF_{25-75}) of forced vital capacity (FVC) were poorer in subjects living closest to the accident site (126).

Nitric acid

Headache together with nausea and/or vomiting, phono- and photophobia and lachrymation induced 5 minutes after inhalation of HNO_3 vapour from a metal polish, has been observed in a goldsmith. The headache was resistant to non-steroidal anti-inflammatory drug therapy but responded to triptans. The patient suffered from migraine with a monthly frequency when not exposed to HNO_3 but every day when exposed to HNO_3 vapour. The effects were assigned to the formation of nitrous gases and not to HNO_3 itself. No further details were given, e.g. on the level and duration of the exposure (94).

Symptoms and findings after accidental inhalation of HNO_3 fumes (and nitrous gases), including cases of deaths, were described in a paper by Hall and Cooper (1905). Few details were given on exposure levels. Symptoms listed were dyspnoea, cough, pain in the chest, stomach, lungs, throat, loins and head, dizziness, and nausea and vomiting. Pulmonary congestion (cough with bloody or voluminous expectoration) typically arose with a delay of 6-7 hours after the exposure to HNO_3 and developed into bronchitis (102).

Three cases of fatal pulmonary oedema caused by 10-15 minutes of accidental exposure to HNO_3 fumes from an exploding tank containing 68 % HNO_3 at a pulp mill have been reported (101).

A man who was accidentally exposed to NO_2 fume from a reaction between HNO_3 and the metal of a bucket for about 30 minutes, died 14 days after the exposure from extreme cyanosis with extensive pneumonia (63).

Phosphoric acid

A man exposed to high but unknown levels of H_3PO_4 by accident for 3 × 20 minutes on a tank ship during a storm developed RADS (34).

A 64-year-old man ingested H_3PO_4 in a suicide attempt and developed hyperphosphataemia, hypocalcaemia and systemic metabolic acidosis. Local caustic effects were mild (43).

The death of one individual 19 days after ingestion of an unknown amount of H_3PO_4 was reported by Hawkins *et al*. Death was a result of recurrent internal abdominal haemorrhage (105).

11.3 Effects of single and short-term exposure

Sulphuric acid

In several volunteer studies, subjects were exposed to clean air and different concentrations of H_2SO_4, and mixtures of H_2SO_4 with ozone, NO_x or particulate matter, usually one week apart. As the effect of each chemical compound in a mixture is challenging to isolate and interpret, only the results of exposure to H_2SO_4 alone is reported (Table 13). The studies vary with regard to exposure system, test concentrations, particle size, relative humidity, exposure duration, physical activity and choice of test persons; they include healthy as well as asthmatic volunteers, and include exposures in chambers, via mouthpieces or nasal masks. The latter has been used by one team to minimise *in situ* neutralisation of the acid by ammonia. Others have e.g. let the subjects gargle citrus juice before exposure or rinse with mouthwash to suppress airway ammonia. The droplet sizes vary considerably among the studies, the MMADs being in the range of 0.1-10 µm. The pulmonary function has been measured before (baseline) and after exposure, each subject being its own control. Sex differences have, in general, not been addressed in the studies.

The few studies on occupationally exposed workers are presented below and are listed in Table 15.

Sulphuric acid: Pulmonary function and symptoms

A self-administered questionnaire on respiratory and eye symptoms and their severity was completed by 75 controls and 82 workers exposed to H_2SO_4 in 13 workplaces representing several industries. The exposed were divided in a low-exposure group (below 0.15 mg/m^3) and a high-exposure group (0.15-0.50 mg/m^3). The respondents had been exposed for at least 6 months. Highly significant relationships were found between symptom reporting and exposure level. Those with low exposure (< 0.15 mg/m^3), typically reported 1 symptom, whereas those with exposure of about 0.5 mg/m^3 reported an average of 5 symptoms. The most

commonly reported symptoms were sneezing, irritated nose and cough. Runny nose increased most markedly with exposure. Younger workers (below 40 years) consistently reported more symptoms than the older workers. The results indicate that workers suffer symptoms of respiratory and eye irritation at exposures in the range 0.1-0.5 mg/m^3 (presented as conference proceedings) (81).

In a cross-sectional study, 225 workers (98 % white males) in 5 plants manufacturing lead acid storage batteries were administered a questionnaire on work-related symptoms, underwent spirometry, and had personal samples for H_2SO_4 taken over the shift. Most personal samples were below 1 mg/m^3. MMADs were 2.6-10 µm estimated from area samples. Workers with the higher exposure to acid (greater than 0.3 mg/m^3, n=41) did not have an increased rate of acute work-related symptoms of e.g. skin, eyes or respiratory airways as compared to the low-exposure group (less than 0.07 mg/m^3, n=116). Changes in pulmonary function over the shift were not related to levels of airborne acid (86).

In healthy volunteers, one study demonstrated no significant decreases in specific airway conductance, forced expiratory volume in one second (FEV_1), or maximum flow rates at 40 or 60 % of total lung capacity, but enhanced airway reactivity to inhaled carbachol after exposure to 1 mg/m^3 (237). Otherwise, single exposures of healthy volunteers at 0.1-0.47 and 1-2 mg/m^3 have not produced changes in pulmonary function (details below and in Table 13) (14, 20-22, 83, 149, 151, 152, 156, 195, 219, 220, 232).

In 14 adolescent asthmatic volunteers (9 males, 5 females, 13-18 years), however, a small but significant (6 %) fall in FEV_1 was seen after exposure for 45 minutes to concentrations as low as 0.035 mg/m^3. A tendency to decreased FEV_1 ($p = 0.08$) was seen also after exposure for 45 minutes to 0.07 mg/m^3. After a 90-minute exposure at both levels no such effect was seen. The changes after acid exposure were compared to the changes after air exposure (136).

Another study conducted in the same laboratory demonstrated small but significant changes in FEV_1 and FVC in 22 adolescent asthmatics (15 males, 7 females, 12-19 years) after exposure to 0.05-0.18 mg/m^3 (MMAD 0.72) for 40 or 45 minutes during intermittent moderate exercise. The changes were no longer significant 20 minutes after exposure (103). The study has weaknesses in reporting and design.

Small but significant reductions in FEV_1, total respiratory resistance and maximal flow calculated at 50 % of FVC (FEF_{50}) were seen in 10 adolescent asthmatics (4 males, 6 females, 12-17 years) exposed to 0.1 mg/m^3 (MMAD 0.6 µm) for 40 minutes (30 minutes at rest followed by 10 minutes of moderate exercise) compared with changes obtained after a saline aerosol exposure. The effects appeared after exercise and were reversible. Symptom scores (nasal, respiratory and non-respiratory effects) were not affected by the acid exposure (134). In the three studies on adolescent asthmatics, the relative humidity was 65-75 % (103, 134, 136).

Pulmonary function and symptom scores were not affected in healthy or asthmatic adult men exposed for 2 hours with intermittent exercise to 0.1 mg/m^3 H_2SO_4 aerosol (MMAD 0.5 µm) at a relative humidity of 40 % (20), nor in healthy

and asthmatic volunteers of both sexes exposed at similar conditions for 3 hours (MMAD 0.64 µm) (83).

Exposure of 45 adult volunteers (15 non-atopic or atopic, 30 asthmatic) to 0.1 mg/m^3 (MMAD 0.5 µm) H_2SO_4 caused no significant changes in lung function, symptom scores, or bronchial reactivity relative to clean air (156).

Utell *et al* reported no effects in neither healthy nor adult asthmatics (sex not given) after 16 minutes exposure at rest to 0.1 mg/m^3 (MMAD 0.6-1 µm), but enhanced bronchoconstriction as well as increased reactivity to carbachol in asthmatics after similar exposures to 0.45 and 1 mg/m^3. An increased reactivity to carbachol was demonstrated in healthy after exposure to 1 mg/m^3. A saline aerosol served as control. Relative humidities were 25 % or less (236, 237).

Fifteen asthmatics (sex not given) inhaled 0.35 mg/m^3 (MMAD 0.8 µm) of an H_2SO_4 aerosol for 20 minutes at rest followed by 10 minutes of exercise at high and low oral ammonia levels. A saline aerosol at a low ammonia level served as control exposure. The relative humidity was 20-25 %. A significant reduction in FEV_1 following exercise was observed at acid inhalation combined with low oral ammonia levels as compared to the other exposures. Also maximum expiratory flow at 60 % of total lung capacity was reduced (238).

No increase in symptom scores, bronchial reactivity to methacholine or effects on lung function were observed in 15 healthy and 15 asthmatics volunteers of both sexes exposed to 0.1 mg/m^3 (MMAD 1.0 µm) for 1 hour including exercise at a relative humidity of 50 % (14).

Framton *et al* exposed 12 healthy volunteers (10 men and 2 women) for 2 hours to 0 or 1 mg/m^3 H_2SO_4 aerosols (MMAD 0.9 µm, relative humidity 40 %) with intermittent exercise and performed bronchoalveolar lavage 18 hours post-exposure. Acid exposure did not result in alveolar inflammation, influx of plasma proteins into the alveolar space, or alterations in selected antiviral functions of alveolar macrophages (82).

No differences in symptom scores (ordinate scale), ventilation, lung function (FEV_1, FEF_{50}, FVC), antioxidant levels in nasal lavage or exhaled nitric oxide were observed in 12 healthy and 12 asthmatic volunteers (sex not given) exposed 1 hour to 0, 0.2 and 2 mg/m^3 aerosol (MMD 0.3 µm) (232).

Sackner *et al* (1978) reported no effects on ventilation, lung function or cardio-pulmonary function in 5 healthy and 5 asthmatic volunteers of both sexes exposed up to 1 mg/m^3 for 10 minutes (MMAD 0.1 µm, relative humidity 20-30 %) (195).

After exposure of 22 adults of both sexes to larger H_2SO_4-particles (VMD 10 µm) at 0, 0.5, 1 and 2 mg/m^3 for 1 hour including exercise at 10 ˚C and 100 % relative humidity, a significant dose-dependent increase in upper and lower respiratory symptom scores was observed over the whole exposure range among healthy volunteers and at 1 and 2 mg/m^3 in asthmatics. The healthy subjects showed only a small symptom increase at the lowest exposure level. A trend towards small decrements in pulmonary function (seen as a decrease in peak expiratory flow rate) was reported among asthmatics at the higher levels. The exposures lasted 1 hour and included 3×10 minutes of heavy exercise (22).

In a similarly designed study with 0.9 µm H_2SO_4 particles, healthy and asthmatic volunteers of both sexes were exposed to 0, 0.38, 1 and 1.5 mg/m^3. At the two highest concentrations, asthmatics showed significant increases in lower respiratory symptoms as well as non-respiratory symptoms (headache, fatigue, eye irritation) and decrements in pulmonary function (FVC and FEV_1) but no changes in airway reactivity. There were no significant effects among the healthy participants apart from increased cough with increasing acid concentration, which was scored "minimal" at the highest concentration (21). Taken together, these two studies suggest that symptoms were less pronounced with the 0.9-µm aerosol although the physiologic response of asthmatics seemed greater. According to the authors, the rationale for this could be that symptoms are caused primarily by larger acid droplets deposited in the upper airway or proximal bronchi, whereas disturbances of pulmonary mechanics in asthmatics are caused primarily by smaller acid droplets deposited in more distal airways (99).

In 10 asthmatics exposed to 0, 0.1, 0.3 and 1 mg/m^3 (MMAD 0.5 µm) for 1 hour, decrements in respiratory function was produced (specific airway conductance, FEV_1/FVC, FEF_{25}, and FEF_{50}). The study also demonstrated effects on respiratory clearance and is described in more detail below (219).

In a series of exposures assessing the influence of particle size, osmolarity, relative humidity, liquid water content and physical exercise, 7 male and 4 female asthmatics were exposed to H_2SO_4 aerosols at 3 mg/m^3 via mouthpiece for 16 minutes at rest and exercise. Ten of the subjects were also exposed to 1 and 1.4 mg/m^3 for 1 hour at intermittent exercise (100 W) in a chamber. No effects on specific airway resistance, lower respiratory or non-respiratory symptom ratings were observed. Throat irritation was significantly greater after exposure to acid aerosol with < 10 % relative humidity than after exposure to acid aerosol of 100 % relative humidity or to saline at a low relative humidity (15).

Sulphuric acid: Respiratory clearance

A number of studies have examined the effect of H_2SO_4 inhalation on the clearance of insoluble particles from the respiratory tract. In some studies, in which exposure lasted for 1 or 2 hours, bronchial mucociliary clearance was affected at exposure levels from 0.1 mg/m^3 H_2SO_4 (MMAD 0.5 µm) (151, 152, 220). In the study by Leikauf *et al* in 10 healthy volunteers whereof 3 females, aerosol exposure via nasal mask to 0.1 mg/m^3 (MMAD 0.5 µm) resulted in an accelerated bronchial mucociliary clearance of Fe_2O_3 (MMAD 7.5) compared to sham exposure, whereas exposures to 0.3 mg/m^3 gave rise to a variable bronchial clearance, and 1 mg/m^3 caused a transient slowing of clearance. Tracheal mucociliary transport rates following the acid exposures did not differ from those obtained after sham exposures. The 7.5-µm particles used for assessment of clearance were calculated to be primarily deposited in the larger bronchial airways, where submicrometer H_2SO_4 has little deposition (151). Another study was therefore designed to determine the effect of submicrometer H_2SO_4 on clearance from the distal ciliated airways (152) (both studies also reported by

Lippmann *et al* 1981) (158). Clearance of 4.2-µm Fe_2O_3-particles inhaled before the aerosol exposure was measured in 8 healthy volunteers (4 of each sex) exposed via nasal mask to 0, 0.1, 0.3, or 1 mg/m^3 (MMAD 0.5 µm) H_2SO_4. In contrast to results obtained with larger radiolabelled particles, bronchial mucociliary clearance of the smaller particles was slower after all H_2SO_4 inhalations than after sham exposure. Respiratory mechanics and tracheal mucociliary transport rates were not affected by any aerosol exposure. The authors' explanation to the differences between results obtained with larger and smaller tagged particles, respectively, is the deposition patterns of the Fe_2O_3 and acid aerosols. Submicrometer H_2SO_4 is primarily deposited in the distal small airways in a pattern more like that of the 4.2-µm than the 7.5-µm particles. In the larger bronchial airways, the 0.1 mg/m^3 acid dose acted as a small stimulatory dose to mucociliary transport, whereas in the distal ciliated airways, the acid dose was sufficient to depress mucociliary transport (152). The ability of an irritant to stimulate mucociliary clearance at a low dose while slowing it at higher doses has also been shown by others; reviewed by Wanner (241).

In a parallel study, 10 asthmatics (6 males and 4 females) were exposed according to essentially the same protocol (inhalation of 3.9-µm tagged Fe_2O_3-particles preceding H_2SO_4-exposure at 0, 0.1, 0.3 and 1 mg/m^3 for 1 hour). For the 6 asymptomatic mild asthmatics, bronchial mucociliary clearance was delayed in a dose-dependent manner and significantly so at the highest exposure level. In addition, exposure to 1 mg/m^3 produced decrements in respiratory function. The remaining 4 asthmatics on daily medication exhibited variable and inconsistent clearance patterns. Mean tracheal mucociliary transport rates were not altered for either group following any of the acid exposures, although their variability was increased compared with sham exposure. Sham exposure clearance rates were slower among both the medicated and non-medicated asthmatics in this study (219) than among the healthy volunteers in the study by Leikauf *et al* (152).

In another study, tracheobronchial mucociliary clearance of 5.2-µm Fe_2O_3-particles was reduced following exposure of 10 healthy male volunteers to 0.1 mg/m^3 of H_2SO_4 aerosol (MMAD 0.5) for 1 or 2 hours compared with exposure to a distilled water aerosol. Respiratory mechanics were not affected (220).

Exposure to larger droplets of H_2SO_4 at 0.47 mg/m^3 (MMAD 10.3 µm) for 40 minutes at rest followed by 20 minutes during exercise accelerated *tracheal* clearance and small airway mucociliary clearance of a radioaerosol (MMAD 3.4 µm) in 7 healthy male subjects compared with saline fog. No effects were observed on symptom ratings (headache, irritation of eyes, upper or lower airways) ventilatory function or airway reactivity (149).

Exposure of 10 healthy volunteers (9 males, 1 female) to 1 mg/m^3 (MMAD 0.5 µm) for 2.5 hours increased bronchial mucociliary clearance of a radiolabelled aerosol (MMD 3 µm) compared with exposure to a distilled water mist. Tracheal clearance was not studied (177).

In a comparative study in rabbits and humans (10 males and 2 females) of a single exposure by inhalation, similarities in effects on pulmonary immuno-

competence were observed in response to H_2SO_4 exposure (1 mg/m^3 H_2SO_4 for 3 hours, MMAD 0.9 μm) (Section 10.2). The ability of recovered human pulmonary macrophages to attach to a solid substrate *in vitro* and the capacity to produce superoxide anion was reduced. Cell viability and phagocytosis of latex particles were not significantly affected (252).

Sulphuric acid: Conclusion

A reduced bronchial mucociliary clearance has been reported in healthy volunteers after exposure to 0.1 mg/m^3 for 1 or 2 hours. An accelerated tracheal clearance was observed in healthy volunteers exposed for 1 hour to larger droplets at 0.47 mg/m^3. A 1-hour exposure to larger droplets at 0.5 mg/m^3 was associated with a small increase in upper and lower respiratory symptom ratings. One occupational study indicates that symptoms of respiratory irritation occur at exposures in the range 0.1-0.5 mg/m^3 (presented as conference proceedings). Pulmonary function changes (bronchial hyperreactivity) were demonstrated in healthy volunteers exposed 16 minutes to 1 mg/m^3.

In adolescent asthmatics, one research team reported small pulmonary function changes at 0.1 mg/m^3 or even lower. In adult asthmatics, the LOAEL for pulmonary function effects is 0.35 (low oral ammonia levels) or 0.45 mg/m^3. However, there are other studies showing no effects at or even above 1 mg/m^3.

Hydrochloric acid

Human inhalation exposure studies with HCl are few. In a relatively recent study, 5 male and 5 female adult asthmatics were exposed via half-face mask to air containing 0, 1.12, and 2.52 mg/m^3 HCl for 45 minutes. The 45-minute exposure was divided into three equal periods: exercise, rest, exercise. Pulmonary function was measured and self-reported symptoms registered. The test subjects did not show any adverse respiratory health effects and did not report any symptoms (upper and lower respiratory, and non-respiratory symptoms) from the HCl exposure (228). The authors also listed earlier human studies and case reports of HCl exposure. It was estimated that the odour threshold was in the range 1.5-7.5 mg/m^3, that work can be carried out undisturbed at 15 mg/m^3, is difficult at 15-75 mg/m^3, intolerable at 75-150 mg/m^3, and that 1 950-3 000 mg/m^3 is a lethal concentration (228). Other sources assign odour thresholds between 1 and 50 mg/m^3 (0.7-35 ppm) (Table 2).

In a report compiling HCl air levels and subjective irritant effects among workers (number not given) in steel pickling facilities, it was concluded that no irritation of the mucous membranes was observed at 3-4.5 mg/m^3, initial mild irritation of the airway mucosa, which regressed rapidly, occurred at 5.2 mg/m^3, slight irritation at 7-11 mg/m^3, and breathing difficulties at 26-34 mg/m^3 (165). The study is based on many years of observations but does not comply with current standards (Table 15).

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
0.035	0.6	45 or 90 min during intermittent moderate exercise	Mouthpiece	14 asthmatic adolescents	*45 min exposure:* 6 % fall in FEV_1 immediately after exposure compared to the before level. The changes were no longer significant 20 minutes after the exposure. *90 min exposure:* No significant change in FEV_1. No change in FVC or total respiratory resistance after any exposure.	(136)
0.068	0.6	40 min (30 min rest and 10 min intermittent moderate exercise)	Mouthpiece prestudy	9 asthmatic adolescents	3 % fall in FEV_1 after exposure compared to the before level (non-significant).	(135)
0.07	0.6	45 or 90 min during intermittent moderate exercise	Mouthpiece	14 asthmatic adolescents	*45 min exposure:* Decreasing trend in FEV_1 (-3 %), but not statistically significant. No other lung function changes. *90 min exposure:* No significant change in FEV_1, FVC or total respiratory resistance.	(136)
0.07+0.13	0.72	40 or 45 min during intermittent moderate exercise	Mouthpiece	22 asthmatics adolescents	Small changes in FEV_1 and FVC. The changes were no longer significant 20 minutes after exposure.	(103)
0.1	0.5	2 h during intermittent exercise	Chamber	6 healthy, 6 asthmatics	No effects on symptoms (upper and lower respiratory symptoms and non-respiratory symptoms) or lung function.	(20)
0.1	0.6-1	16 min during exercise	Mouthpiece	17 asthmatics	No effects on SGaw or FEV_1.	(236)
0.1	0.6-1	16 min	Chamber	14 healthy, 17 asthmatics	No effects on SGaw or FEV_1.	(237)
0.1	1.0	1 h with alternate 10 min periods of heavy exercise and rest	Chamber	15 healthy, 15 asthmatics	No effect on the incidence of symptoms of irritancy, bronchial reactivity to methacholine, or lung function.	(14)

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
0.1	0.64	3 h	Chamber	30 healthy, 30 asthmatics	No effects on symptoms or pulmonary function in healthy or asthmatic subjects.	(83)
0.1	0.5	6.5 h with 50 min exercise periods and 10 min rest	Chamber	15 healthy, 30 asthmatics	No changes in symptoms of irritancy, bronchial reactivity, or lung function.	(156)
0.1	0.5	1 h	Nasal mask	6 asthmatics	No significant effect on bronchial mucociliary clearance of 3.9-µm Fe_2O_3-particles (clearance reduced in a dose-dependent manner, non-significantly at 0.1 and 0.3 mg/m^3 and significantly at 1.0 mg/m^3). No effect on mean tracheal mucociliary transport rates or lung function.	(219)
0.1	0.6	30 min rest and 10 min moderate exercise	Mouthpiece	10 asthmatic adolescents	Small but significant reductions in FEV_1, total respiratory resistance and FEF_{50}, all reversible. No changes in symptom scores (nasal, respiratory and non-respiratory effects).	(134)
0.1	0.5	1 h	Nasal mask	8 healthy	Reduced bronchial mucociliary clearance of Fe_2O_3-particles (MMAD 4.2 µm). Average half-time increased from 80 to 110 min. Same effect seen at 0.3 and 1 mg/m^3. No effect on muco-ciliary tracheal transport, FEV_1, FVC, FEF_{50}.	(152)
0.1	0.5	1 h and 2 h on separate occasions	Nasal mask	10 healthy	Reduced bronchial mucociliary clearance of Fe_2O_3-particles (MMAD 5.2 µm), persistent 2 h after exposure. Average clearance half-time increased from 42 to 84 and 110 min respectively (for volunteers exposed 1 and 2 h). No effects on FEV_1, FVC, FEF_{50}, PEPR, or airway resistance.	(220)
0.1	0.5	1 h	Nasal mask	10 healthy	Markedly increased bronchial clearance of 7.5-µm Fe_2O_3-particles in 6/10 exposed volunteers. No change in tracheal mucociliary transport rate or in pulmonary mechanics.	(151)

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
0.2	0.3	1 h	Head-only, cast acrylic head dome	12 healthy, 12 asthmatics	No changes in symptom scores, ventilation, lung function (FEV_1, FEF_{50}, FVC), antioxidant levels in nasal lavage or exhaled nitric oxide.	(232)
0.3	0.5	1 h	Nasal mask	10 healthy	Variable bronchial clearance of 7.5-µm Fe_2O_3-particles (both faster and slower than the controls). No change in tracheal mucociliary transport rate or in pulmonary mechanics.	(151)
0.3	0.5	1 h	Nasal mask	8 healthy	Reduced bronchial mucociliary clearance of 4.2-µm Fe_2O_3-particles. Tracheal transport was not significantly affected. Same results after exposure to 1 mg/m^3.	(152)
0.3	0.5	1 h	Nasal mask	6 asthmatics	No significant effect on bronchial mucociliary clearance (3.9-µm Fe_2O_3). Clearance was reduced (dose-dependently), non-significantly at 0.1 and 0 and significantly at 1.0 mg/m^3). No effect on mean tracheal mucociliary transport rates or lung function.	(219)
0.35	0.8	20 min at rest and 10 min of exercise	Mouthpiece	15 asthmatics	Following exercise, low oral NH_3 caused significantly greater reductions in FEV_1 and maximum expiratory flow at 60 % of total lung capacity compared to saline or acid + high oral NH_3 levels.	(238)
0.38	0.9	1 h including three 10 min periods of heavy exercise	Chamber	21 healthy, 21 asthmatics	No change in pulmonary function, airway reactivity or reporting of upper, lower respiratory or non-respiratory symptoms.	(21)
0.45	0.6-1	16 min	Chamber	17 asthmatics	Bronchial hyperreactivity after provocation with carbachol.	(237)
0.45	0.6-1	16 min during exercise	Mouthpiece	17 asthmatics	Bronchoconstriction (reduced SG_{aw}).	(236)
0.47	10.3	40 min at rest and 20 min of exercise	Chamber	7 healthy	Accelerated tracheal and small airways mucociliary clearance of a sulphur colloid (MMAD 3.4 µm). No effects on symptom ratings (headache, irritation of eyes, upper or lower airways) ventilatory function or airway reactivity.	(149)

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
0.5	10 (VMD)	1 h including three 10 min periods of heavy exercise	Chamber	22 healthy, 22 asthmatics	Small increase in upper and lower respiratory symptoms among healthy. Scores were successively increased at 1 and 2 mg/m^3. No increase beyond that from sham exposure among asthmatics.	(22)
1	10 (VMD)	1 h including three 10 min periods of heavy exercise	Chamber	22 healthy, 22 asthmatics	Dose-dependent increase in upper and lower respiratory symptoms in healthy and asthmatics. Also seen at 2 mg/m^3. No pulmonary function effects apart from a trend to dose-dependent decrease in PEFR in asthmatics at this and higher level (2 mg/m^3).	(22)
1	0.9	1 h including three 10 min periods of heavy exercise	Chamber	21 healthy, 21 asthmatics	In healthy, no change in pulmonary function, airway reactivity or reporting of upper or lower respiratory or non-respiratory symptoms. In asthmatics, increases in lower respiratory and non-respiratory symptoms and decrements in pulmonary function (FVC and FEV_1) but no changes in airway reactivity.	(21)
1	0.9	3 hours, with intermittent exercise	Chamber	12 healthy	Reduced ability of recovered pulmonary macrophages to attach to a solid substrate *in vitro* and production of superoxide anion by stimulated pulmonary macrophages. Viability or phagocytosis of latex particles was not significantly affected.	(252)
1	0.1	10 min	Mouthpiece	11 healthy, 11 asthmatics	No effects on ventilation, lung function, or cardiopulmonary function. Same results obtained at 0.01 and 0.1 mg/m^3.	(195)
1	0.6-1	16 min during exercise	Mouthpiece	17 asthmatics	Bronchoconstriction (reduced SG_{aw} and FEV_1).	(236)
1	0.6-1	16 min	Chamber	14 healthy, 17 asthmatics	In healthy, no effect on SG_{aw}, FEV_1 or maximum flow rates at 40 or 60 % of total lung capacity. Bronchial hyperreactivity after provocation with carbachol in asthmatics and healthy subjects.	(237)

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
1	0.5	2.5 h, intermittent exercise during the 1st hour	Chamber	10 healthy	Increased bronchial mucociliary clearance of tagged albumen saline aerosol (MMAD 3.5 µm).	(177)
1	0.5	1 h	Nasal mask	Healthy 8 (small tracers) 10 (large tracers)	Reduced bronchial mucociliary clearance of both small (MMAD 4 µm) and large (MMAD 7.5 µm) Fe_2O_3-particles. No effect on tracheal transport.	(151, 152)
1	0.5	1 h	Nasal mask	6 asthmatics	Transient slowing of tracheobronchial mucociliary clearance of Fe_2O_3-particles (MMAD 3.9 µm) and decrements in respiratory function (SGaw, FEV_1, FEV_1/FVC, FEF_{25}, FEF_{50}). No effect on mean tracheal mucociliary transport rates.	(219)
1	0.5	1 h	Nasal mask	10 healthy	Decreased bronchial clearance of Fe_2O_3-particles (MMAD 7.5 µm). No effect on tracheal transport.	(151)
1	0.9	2 h with intermittent exercise	Chamber	12 healthy	No effects in total protein, cell recovery, cell differential counts or influx of inflammatory cells into the alveolar space, nor in alveolar macrophage function (superoxide anion release or ability to inactivate influenza virus).	(82)
1	0.9	2 h	Chamber	12 healthy	No change in airway mucin glycoproteins.	(61)
1.5	0.9	1 h including three 10 min periods of heavy exercise	Chamber	21 healthy, 21 asthmatics	In healthy, no change in pulmonary function and airway reactivity, and no upper or lower respiratory and non-respiratory symptoms. In asthmatics, increases in lower respiratory and non-respiratory symptoms and decrements in pulmonary function (FVC and FEV_1) but no changes in airway reactivity.	(21)
2.0	0.3	1 h	Head-only, cast acrylic head dome	12 healthy, 12 asthmatics	No differences in symptom scores, ventilation, lung function (FEV_1, FEF_{50}, FVC), antioxidant levels in nasal lavage or exhaled nitric oxide.	(232)

Table 13. Volunteer studies with exposure to sulphuric acid aerosol.

Exposure				No. of volunteers [a]	Effect	Reference
Level, mg/m^3	Droplet size, MMAD, µm	Duration (at rest if not otherwise stated)	System			
3.0	0.4 and 6 (VMD)	16 min rest and exercise, respectively, with mouthpiece, later 1 h intermittent moderate exercise in chamber	Mouthpiece, chamber	18 asthmatics	No effect on specific airway resistance, cough, upper and lower respiratory, or non-respiratory symptom scores, apart from increased throat irritation at low relative humidity.	(15)

[a] Adult unless otherwise stated.
FEF_x: forced expiratory flow at x % of FVC, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, MMAD: mass median aerodynamic diameter, PEFR: peak expiratory flow rate, SG_{aw}: specific airway conductance, VMD: volume median diameter.

Nitric acid

Ten healthy volunteers (6 males, 4 females) exercised for 2 hours in an atmosphere containing 0.4 mg/m^3 HNO_3 fog (VMD 6 µm, relative humidity 100 %). No significant differences in pulmonary function (FEV_1, FVC, specific airway resistance, respiratory rate, tidal volume) or symptom scores (lower and upper respiratory symptoms or non-respiratory symptoms) were reported as compared to exposures to water fog or clean-filtered air (16).

Ten healthy volunteers (8 males, 2 females) exposed to 0 and 0.5 mg/m^3 of HNO_3 vapour for 4 hours during moderate exercise did not report any exposure-related symptoms. Further, no proximal airway or distal lung injury could be detected with lung function tests (FEV_1, FVC or specific airway resistance), proximal airway lavage, bronchoalveolar lavage or bronchial biopsies (17).

Exposure of 1 female and 8 male healthy subjects to 0 and 0.2 mg/m^3 of HNO_3 vapour for 2 hours, of which 100 minutes during moderate intermittent exercise, did not affect pulmonary function (spirometry and airway resistance) and subjective symptoms. Nor were there any significant increases in indicators of airway injury or inflammation assessed by bronchoalveolar lavage 18 hours post-exposure. However, there was an effect from HNO_3 on alveolar macrophage function (significant increases in the phagocytic activity and the resistance to infection with respiratory syncytial virus, and decreased superoxide anion production) (25).

Adolescent asthmatics (19 males, 9 females, 12-19 years old), inhaled a combination of 0.05 ppm (0.125 mg/m^3) HNO_3, 0.12 ppm O_3 and 0.30 ppm NO_2 for 90 minutes via a mouthpiece. Pulmonary function parameters were not affected when compared with changes after clean air exposure. The study protocol also included exposure to oxidants alone and oxidants combined with H_2SO_4. Six subjects left the study before completion because of unpleasant symptoms (137).

In an old study published 1907, the author and a colleague were exposed to concentrations of 11-12 ppm (27-30 mg/m^3). Symptoms described included sneezing, pressure in the chest, pains in the trachea and larynx, coughing, secretion from the nose and salivary glands, moderate burning in the eyes, and lachrymation, burning and itching of the facial skin. The author considered exposure at those levels for more than 1 hour intolerable and dangerous to human health. Exposure to 84 ppm (210 mg/m^3) was tolerated by the author for only 2-3 minutes (Diem[1], cited in (66)).

Other reports on observations in man are from accidental exposure to HNO_3 (Section 11.1).

Phosphoric acid

No studies were found. A few case reports are included in Section 11.1.

[1] Diem L. *Untersuchungen über die Einatmung von Saltpetersäure-dämpfen* (thesis). Würzburg, 1907.

11.4 Effects of long-term exposure

Only a few studies have demonstrated effects of long-term exposure to the acids in humans, most of them concerning dental effects (Table 15). Exposure to inorganic acids in the working environment can lead to dental etching and erosion. Systems for grading dental etching and erosion are exemplified by the one presented by Ten Bruggen Cate in 1968 (230) (Table 14). In a recent review of occupational risk factors for dental erosion (including the studies presented below), it was concluded that battery, galvanising and associated workers exposed to H_2SO_4 or HCl and to a lesser degree to H_3PO_4, HNO_3 and hydrofluoric acid were at higher risk of dental erosion based on prevalence studies including a control group. However, prevalence data in both acid-exposed workers and controls exhibited a great variation, amounting to 26-100 % for battery and galvanising workers and to 0-80 % for controls (244).

The prevalence of dental erosion varies greatly with age, time period, and dietary factors. Relatively little is known about the prevalence of erosion in the general population. In a Swiss study, a prevalence of grade 2 erosion was found to be 62 % in the age group 46-50 years (161). In a review, prevalences were reported to range from 4 % to 82 % in adults aged 18-88 years (121).

Sulphuric acid

There was no association between exposure to H_2SO_4 (average 0.15 mg/m^3) and respiratory symptoms (cough, phlegm, dyspnoea and wheezing) among 248 workers (243 males, 5 females) in 5 battery plants in a cross-sectional study. Differences were analysed between workers having a cumulative exposure above 15 mg/m^3 × months (average exposure level 0.21 mg/m^3) and workers with cumulative exposure below 7 mg/m^3 × months (average exposure level 0.10 mg/m^3). FVC was impaired in the highly exposed workers compared to the less exposed workers. Tooth etching and erosion was strongly associated with H_2SO_4 exposure and was observed in 15-33 % of the workers in 4 of the 5 plants investigated (and in no workers in the remaining plant). Dental etching was observed in 38 % of the highly exposed workers, and in 8 % in the low exposure group workers ($p < 0.0005$ adjusted for age and smoking). The earliest cases of etching and erosion, respectively, occurred after 4 and 30 months of exposure to an estimated average exposure of 0.23 mg/m^3 (see Table 15 for details) (87). The exposure concentrations were estimated for the various workplaces after personal sampling on presumably one occasion, and can therefore only be taken as

Table 14. Grades of etching and erosion according to Ten Bruggen Cate (230).

Grade	Description
Etching	Dull, ground-glass appearance of the enamel surface without loss of contour.
Grade 1 erosion (G1)	Loss of enamel only.
Grade 2 erosion (G2)	Loss of enamel with involvement of dentine.
Grade 3 erosion (G3)	Loss of enamel and dentine with exposure of secondary dentine.
Grade 4 erosion (G4)	Loss of enamel and dentine resulting in pulpal exposure.

approximate. The authors also reviewed previous studies[1] of H_2SO_4-exposed workers. Most of these studies reported on the prevalence of respiratory diseases such as bronchitis but showed no effect on the respiratory system clearly attributable to low levels of H_2SO_4 in battery plants and H_2SO_4 plants. However, the potential effect on pulmonary function was not examined in these studies. Tooth etching and erosion was common.

The effects of H_2SO_4 exposure on the teeth have been documented in other studies. Usually, only current and no historical exposure levels were given. In a cross-sectional study, Petersen and Gormsen (1991) reported dental erosion and attrition in relation to exposure to H_2SO_4 (0.4-4.1 mg/m^3 at the time of the investigation) in a modern battery factory in 61 male dentate workers, in the processes known as forming and charging. Dental erosion and attrition was seen in 42 % of the workers exposed for less than 10 years and in 56 % of the workers exposed for more than 10 years (186).

In a Finnish study on acid exposed workers from battery and galvanising factories exposed predominantly to H_2SO_4, blind dental examinations were used. Referents were from acid-free departments of the same companies. Of the acid exposed workers, 18 % had one or more teeth with erosion compared to 9 % of the referents (p=0.075). The number of teeth with erosion (all three grades according to Eccles' classification, which is similar to that of Ten Bruggen Cate) was significantly higher among the acid exposed workers than among the referents. Concentrations of H_2SO_4 fumes varied from 0.06 to 2.0 mg/m^3 (233). In another study, the prevalence of tooth surface loss was 63 % among acid exposed workers in Tanzania, compared to 38 % among controls. Reported H_2SO_4 levels ranged from below 1 to above 5 mg/m^3. The occurrence of tooth surface loss was significantly higher among workers than among controls already after 1-5 years of employment (234).

Among workers at an electro-winning facility in South Africa, the odds ratio (OR) for dental erosion was 5.5 for workers exposed to 0.3-1 mg/m^3 compared to those exposed to 0.1-0.3 mg/m^3 (referents). There was also a significant difference in the severity of tooth surface loss between the two groups. The authors expressed some uncertainty regarding the reliability of the stated concentrations as representtative of the exposure (51).

In battery workers (males), prevalences of erosion and etching were 87 % (exposure 3-17 mg/m^3), and 47 % (exposure < 0.8-2.5 mg/m^3). The average exposure of those showing etching was 5 years (163).

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[1] Anfield BD, Warner CG. A study of industrial mists containing sulphuric acid. *Ann Occup Hyg* 1968;11:185-194.

El-Sadik YM, Osman HA, El-Gazzar RM. Exposure to sulphuric acid manufacture of storage batteries. *J Occup Med* 1972;14:224-226.

Morando A. Experimental and clinical contribution to human pathology due to sulphuric acid fumes. *Med Lav* 1956;47:55-61.

Pelnar T. The influence of work in sulfuric acid production in employee health. *Prac Lek* 1951;3:287-294.

Williams MK. Sickness absence and ventilatory capacity of workers exposed to sulphuric mist. *Br J Ind Med* 1970;27:61-66.

El-Sadik *et al* (1972) reported the prevalence of tooth erosion to be 39 % in plants with very high exposure (> 12.6 mg/m^3) (71). Ten Bruggen Cate (1968) also found a high prevalence and incidence of tooth etching and erosion among workers in battery plants, but no air concentrations were reported (230).

Nasal symptoms and alterations of the nasal mucosa were studied in 52 workers exposed to H_2SO_4 mists in 5 anodising plants. The workers included were not exposed to other vapours or metals. Work-related nasal symptoms (e.g. itching, bleeding and discharge) were reported by 21 workers (40 %). The major clinical findings in the exposed were hyperaemia (30 %), pale mucosal patches (29 %) and ulcerations (12 %). Stationary measurements during a 5-day working week revealed average geometric mean air levels between 0.035 and 2.1 mg/m^3 in the 5 plants. Pale mucosal patches or ulcerations were only observed in workers (15/37) from the three plants with the highest exposure levels (above 0.2 mg/m^3) and in none of 15 workers exposed at lower levels. Histopathological evaluation (nasal biopsy) showed that squamous metaplasia, squamous atypia and mild dysplasia were more frequent among the exposed (20 selected workers) than among unexposed (n=11). According to the authors, the risk of squamous atypia or dysplasia increased with increasing exposure to H_2SO_4 but did not correlate with exposure duration (mean 6 years, range: 4 months to 16 years) (95). The study has weaknesses in design and reporting, e.g. regarding control groups, data handling and statistics.

Hydrochloric acid

In a report compiling HCl air levels and subjective irritant effects among workers in steel pickling facilities, chronic bronchitis was reported after years of exposure at approximately 30 mg/m^3. It was also stated (no further details given) that no damage to the teeth occurred at average concentrations of 4.5-7.7 mg/m^3 (165). The study is based on many years of observations but does not comply with current standards.

In a hot dip zinc galvanising plant, 90 % of 38 workers had some dental erosion (grade 1 or 2) of the incisor teeth. Exposure levels (geometric means) ranged from 1.8 to 12.4 mg/m^3 HCl at different sites. The dental effect could not be causally linked to the HCl exposure from the pickling process (where a 15 % HCl solution was used to remove corrosion) as the number of workers was small and there was no control group (191).

A high prevalence of dental erosion was observed among industrial workers exposed to HCl but no air concentrations were reported (230).

Nitric acid

Dental erosion from occupational exposure to HNO_3 fumes was suggested by some authors but no corresponding levels of exposure were presented (3, 230).

Phosphoric acid

No studies were found.

Mix of acids

Dental erosion, especially among battery formation workers (exposed to H_2SO_4), and black staining of the teeth among iron picklers (who were exposed to various acids including H_2SO_4, HCl, HNO_3) were reported to be due to acid exposure in the working environment. Etching or erosion (grade 1-3) was observed in more than 30 % of the workers. No grade 4 cases were observed. HCl and H_2SO_4 accounted for far more erosion cases than HNO_3 or chromic acids, but it is not possible to conclude whether this was due to differences in erosive potential of the acids or in exposure levels. Dental etching increased to a peak in workers exposed for 2-5 years and then diminished, while dental erosion grade 1 cases started to appear in workers exposed from 4-6 months and increased steadily. Dental erosion grade 2 cases first appeared after 2-5 years and increased while the dental erosion grade 3 cases were seen after 6-10 years. The exposure levels were not given, and other effects were not described (230). Exposure to H_2SO_4 at the time when the study was published (pre 1970s) has been characterised as high for workers in metal pickling (> 1 mg/m^3 8-hour time weighted average) and low for workers in lead battery production (< 0.1 mg/m^3) (197).

Long-term (up to 5 years) exposure to low levels of SO_2, HCl and SO_4^{2-} (7-hour TWA maximum 0.30, 2.1 and 0.5 mg/m^3, respectively) was not associated with any increase in the airway hyperresponsiveness to histamine among male workers in synthetic fibre plants. The source of SO_4^{2-} was H_2SO_4 (141). In previous reports on the same study population, the authors found an association between exposure to SO_2, HCl and SO_4^{2-} and a higher prevalence of work-related cough and nasal symptoms compared with the reference group (139, 140).

Conclusion

Only a few studies have demonstrated effects of long-term exposure to the acids in humans (none on H_3PO_4). Dental etching or erosion is a concern after exposure to acids and has been reported after exposure to approximately 0.2 mg/m^3 of H_2SO_4. Histopathological changes of the nasal mucosa were reported at about the same levels of H_2SO_4 exposure. Respiratory symptoms and effects on pulmonary function have been investigated or reported to a small degree. In one study, FVC was impaired in workers with cumulative H_2SO_4 exposure above 15 mg/m^3 × months (average 0.21 mg/m^3) compared to less exposed workers (below 7 mg/m^3 × months (average 0.10 mg/m^3). Chronic bronchitis is reported after exposure to approximately 30 mg/m^3 of HCl.

11.5 Genotoxic effects

The number of chromosomal aberrations, micronuclei and sister chromatid exchanges were increased in lymphocytes from workers of a phosphate fertiliser factory. The workers had been exposed to phosphoric acid, but also to other chemicals and radioactivity (91). No studies on the other acids were found.

In vitro studies of human cells are presented in Section 10.4.

Table 15. Effects of occupational exposure to the inorganic acids.

Exposure level, mg/m^3	Droplet size, MD, µm	Exposure duration	Industry	Study size	Study design/con-founders adjusted for	Effect	Reference
Sulphuric acid							
Effects of short-term exposure							
< 0.15 (low) 0.15-0.50 (high)	NG	≥ 6 months	13 workplaces representing several industries	82 workers 75 controls	Cross-sectional/ smoking	Highly significant trends between individual symptom reporting and exposure level. The most commonly reported symptoms were sneezing, irritated nose and cough. Runny nose increased most markedly with exposure.	(81)
< 0.07 mg/m^3 (low) > 0.3 mg/m^3 (high)	3-10	10 years (average for all plants as given by Gamble *et al* (87).	5 battery plants	225 mostly male workers [a] 116 (low) 41 (high)	Cross-sectional/ age, smoking	Workers with the higher exposure (n=41) did not have an increased rate of acute work-related symptoms as compared to the low-exposure group (n=116). Changes in pulmonary function over the shift were not related to levels of airborne acid.	(86)
Effects of long-term exposure							
0.06-2.0	NG	1-39 years	2 battery and 2 galvanising factories	76 male workers, 81 controls	Cross-sectional/ age, smoking, food and drink intake	Number of teeth with erosion significantly higher among acid exposed than among controls.	(233)
0.15 (average) 0.10 (average, low [b]) 0.21 (average, high [c])	3-10	10 years (average for all plants)	5 battery plants	243 male/5 female workers no referents 99 (low) 100 (high)	Cross-sectional/ age, smoking	No increase in respiratory symptoms. FVC reduced in the high-exposure group (4.83 litres) compared to the low-exposure group (5.11 litres). Tooth etching and erosion associated with exposure.	(87)

Table 15. Effects of occupational exposure to the inorganic acids.

Exposure level, mg/m^3	Droplet size, MD, µm	Exposure duration	Industry	Study size	Study design/con-founders adjusted for	Effect	Reference
0.035-2.1	NG	6 years	5 anodising plants	52 workers (histopathology on 20) 11 controls	Cross-sectional/ age, smoking	Nasal symptoms reported by 21 workers. Pale mucosal patches and ulcerations only in workers exposed to > 0.2 mg/m^3. Squamous metaplasia, squamous atypia and mild dysplasia of the nasal mucosa more frequent among a subset of exposed than among unexposed. The risk of squamous atypia or dysplasia increased with increasing concentration of H_2SO_4 but did not correlate with exposure duration.	(95)
0.1-0.3 (referents) 0.3-1	NG	1 month-24 years, average 4.2 years	Electro-winning facility	103 workers 102 referents	Cross-sectional/ age, length of service	Significantly increased risk for dental erosion (OR 5.5). Significantly increased severity of tooth surface loss. No relation-ship between exposure time and erosion.	(51)
0.4-4.1 (range) (average NG)	NG	< 10 years > 10 years	Battery factory	61 workers no referents	Cross-sectional/NG	Dental erosion and attrition in 42 % of the workers exposed for < 10 years and in 56 % of the workers exposed for > 10 years.	(186)
< 0.8-2.5 (charging) 3-17 (forming)	NG	Years	Battery plant	60 workers 117 controls	Cross-sectional/ socio-economical status, age	Significantly higher incidence of erosion in men in forming than in charging or controls.	(163)
< 1 - > 5	NG	1-19 years	Fertiliser factory	68 workers 61 controls	Cross-sectional/ health, dietary habits	Significantly increased prevalence of tooth surface loss (63 % vs. 38 %). Prevalence increased among workers already after 1-5 years of exposure.	(234)
12-35	NG	NG	Battery factories	33 workers 20 controls	Cross-sectional/age	Prevalence of erosion 39 % versus 0 % among controls.	(71)

Table 15. Effects of occupational exposure to the inorganic acids.

Exposure level, mg/m^3	Droplet size, MD, µm	Exposure duration	Industry	Study size	Study design/con-founders adjusted for	Effect	Reference
Hydrochloric acid							
1.8-12.4 (average)	NG	NG	Hot dip zinc galvanising plant	38 workers no controls	Cross-sectional	90 % had dental erosion (grade 1 or 2) of the incisor teeth.	(191)
3-4.5 5.2 4.5-7.7 7-11 26-34 ~30	Vapour	Years	Steel pickling	NG	Cross-sectional	No irritation of the mucous membranes. Initial mild irritation. No dental damage. Slight irritation. Breathing difficulties. Chronic bronchitis.	(165)
Mix of irritants							
2.1 HCl 0.5 H_2SO_4 0.30 SO_2	NG	< 5 years	Synthetic fibre plants	119 workers 180 referents	Cross-sectional/ smoking, age, allergy	Higher prevalence of work-related cough and nasal symptoms. No increase in chronic respiratory symptoms or airway hyper-responsiveness.	(139-141)
H_2SO_4, HCl, HNO_3 and others. Levels not given.	NG	< 10 years	Battery factory and iron pickling facility	555 workers 293 referents	Prospective/age	Dental etching and erosion (grade 1-3), especially from exposure to HCl and H_2SO_4.	(230)

[a] Basically the same population as in Gamble *et al* (87).
[b] Cumulative exposure < 7 mg/m^3×months.
[c] Cumulative exposure > 15 mg/m^3×months.
FVC: forced vital capacity, MD: median diameter, NG: not given, OR: odds ratio.

11.6 Carcinogenic effects

An overview of epidemiological studies is given in Table 16.

Sulphuric acid
The exposure is poorly characterised in most studies, but for the older studies it is assumed that the pre 1970s exposure levels presented for various types of industries in Chapter 6 can be applied.

Occupational exposure to strong inorganic acid mists containing H_2SO_4 was classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC) in 1992 (116). Several studies were evaluated and the classification was primarily based on the human studies by Ahlborg *et al* (7), Beaumont *et al* (24), Siemiatycki (214), Steenland and Beaumont (226), Steenland *et al* (225), Soskolne *et al* (217, 218) and Weil *et al* (243). In all studies, H_2SO_4 mists were regarded to be the commonest exposure. Additional support was provided by Forastiere *et al* (80) and Hagmar *et al* (100). In several of these studies, exposure to acid mists was associated with laryngeal cancer. In the years following the publication of the IARC monograph, a follow-up of the Steenland *et al* study (225) has been published, showing a positive association between exposure to acid mist and laryngeal cancer (227). In this study, the incidence of laryngeal cancer was investigated in a cohort of male steel workers exposed primarily to H_2SO_4 mists 1940-65. Exposure data from 1975-79 from the two plants indicated that personal exposure levels of H_2SO_4 had averaged 0.19 mg/m^3 and area samples 0.29 mg/m^3, and that the exposure duration was on average 9.2 years. The average first year of exposure was 1949. The rate ratio for laryngeal cancer among the 1 031 workers was 2.2 (95 % confidence interval (CI) 1.2-3.7) as compared to national rates (the expected number of laryngeal cancers in the general population) after adjustment for tobacco and alcohol consumption (227).

In a cohort of 1 409 workers employed in H_2SO_4 production, with or without previous exposure in mines, no excess mortality in laryngeal (4 cases versus 3.1 expected) or lung cancer (27/32.8) was observed. An increased mortality from myeloid leukaemia could not be attributed to any of the exposures (184).

In a recent nested case-control study in a cohort of nickel refinery workers exposed to low levels of H_2SO_4 (generally less than 0.5 mg/m^3) with 213 cases and 525 age-matched controls, no excess risk of lung cancer from H_2SO_4 mist was found. The resulting OR (CI) for the different exposure groups (mg/m^3 × years) were: low: 1.0 (0.4-2.3), medium: 1.0 (0.4-2.4), high 0.8 (0.3-2.0) (97).

In a recent case-control study, no association was found between exposure to environmental pollution of H_2SO_4 (historic levels exceeding 0.5 mg/m^3) and lung cancer in Lithuanian men. After control for smoking and age, the OR for lung cancer was 1.03 (95 % CI 0.76-1.39) (187) (NEG noted that historic levels, if correct, were extremely high).

To test the hypothesis of a role of occupational risk factors in the aethiology of gastric cancer, Cocco *et al* conducted a case-control study based on death certificates concerning stomach cancer in the United States. The data base

included 41 957 deaths from gastric cancer. No excess risk was associated with H_2SO_4 exposure at the workplace (OR 0.99, 95 % CI 0.95-1.03) after adjustment for other exposures, ethnic origin, marital and socio-economic status, and residence (56). The same team evaluated the risk of gastric cardia cancer by occupation and industry in a case-control study (n=1 056) based on death certificates. Exposure intensity was classified in three categories without quantitative dose measures. Among white males, a significantly increased risk with increasing exposure was observed (55).

One case of laryngeal cancer and three cases of naso-pharyngeal carcinoma were reported. H_2SO_4 was suggested to be the causative agent (111, 112).

Histopathological effects of the nasal mucosa were reported in a study by Grasel *et al* (95) detailed in Section 11.3.

There is one population-based case-control study suggesting an excess risk of oesophageal cancer with exposure to H_2SO_4 (214) (also published by Parent *et al* (183)). The exposure was coded by chemists and hygienists based on the confidence that the exposure had occurred, the frequency of exposure during a normal working week and the relative concentration of H_2SO_4 and other agents. Exposure was classified as none, non-substantial or substantial.

In conclusion, one follow-up study published after the IARC monograph supports the conclusion about laryngeal cancer whereas the evidence for an association with lung cancer is weak. These conclusions are in accordance with other recent evaluations (27, 106, 197).

Hydrochloric acid

There is inadequate evidence for the carcinogenicity in humans of HCl according to IARC (115). No association was found between exposure to HCl and risk of lung cancer (129 exposed cases) in a nested case-control study among chemical factory workers. The exposure was up to 3 mg/m^3 for several years. A latency period of 15 years was applied in the analysis (31, 32). An excess of lung cancer was observed in a study of steel-pickling workers in a subset of 189 workers who had been exposed to mists of acids other than H_2SO_4, primarily HCl (24).

In the population-based case-control study by Siemiatycki (described above), an increased risk of non-Hodgkin's lymphoma (n=18), rectum cancer (n=18) and lung oat-cell carcinoma (n=19) was suggested in workers exposed to HCl ($p < 0.10$). No risk was observed for other histological types of lung cancer (214).

Nitric acid

No association was found between exposure to nitrogen products (HNO_3 and urea) and mortality from bladder cancer in exposed chemical plant workers (166). The study is however, inconclusive with regard to risk for bladder cancer and exposure to HNO_3 due to a small number of cases (n=4) and the relatively good prognosis of bladder cancer making mortality an inappropriate outcome to study.

In a study by Hilt *et al*, the possibility of co-exposure to asbestos limits the interpretability with respect to HNO_3 exposure and lung cancer (109).

In the population-based case-control study described above, an excess risk for pancreas (n=5), prostate (n=9) and kidney (n=4) cancer was suggested in workers exposed to HNO_3 ($p < 0.10$) (214).

Phosphoric acid

The population-based case-control study by Siemiatycki indicated an excess risk of kidney (n=6) and lung (n=14) cancer among H_3PO_4 exposed ($p < 0.10$) (214).

Mixed acids

In a cohort study among former and present battery and steel work employees exposed to acid mists, the standard mortality ratio for upper aerodigestive tract tumours was 0.92 (95 % CI 0.85-0.98). A case-control study in the same cohort showed that the risk was moderately but non-significantly increased among workers exposed for at least five years to H_2SO_4 or HCl (H_2SO_4 was substituted with HCl) in excess of 1 mg/m^3 (OR 2.0, 95 % CI 0.4-10). This included cases of lip cancer. The authors distinguished between three levels of exposure to acids: zero, low (< 1 mg/m^3 H_2SO_4 or HCl) and high ($\geq$ 1 mg/m^3), taking into account the time periods during which jobs had been held (57). Hathaway later commented on the data analysis, e.g. that exclusion of the lip cancer cases would presumably result in an OR near unity, and that the study produced no evidence that acid aerosols may cause upper aerodigestive cancer (104)

In cohort mortality studies from the phosphate industry, the workers were exposed to H_3PO_4, as well as to H_2SO_4. The standard mortality ratios for lung cancer (SMR 1.22 and 1.24) was slightly increased among white as well as non-white workers in a study (44), which was later analysed anew and described as non-causal in relation to occupational exposure (45).

In another study, a pronounced increase of lung cancer among African American workers was reported (SMR 4.11). The levels of H_2SO_4 and H_3PO_4 were 0.013-0.22 mg/m^3 and 0.03-0.52 mg/m^3, respectively. Exposure to other substances known as carcinogens during vessel cleaning had occurred (224). There were no adjustments for smoking in the above-mentioned studies.

A multicentre case-control study was conducted to evaluate the role of occupational exposures in risk of laryngeal/hypopharyngeal cancer. No overall excess risk was found linked to inorganic acid mists, but a significantly higher risk for hypopharyngeal cancer (4 exposed cases) among those exposed for at least 15 years. No association, however, was observed with cumulative exposure. Exposure was mainly to HCl but included also HNO_3, H_3PO_4, H_2SO_4, hydrofluoric, and chromic acid (213).

11.7 Reproductive and developmental effects

No studies were located regarding reproductive or developmental effects in humans for any of the four acids but effects at relevant exposure levels are unlikely (see Section 10.7).

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
Sulphuric acid						
NG	Cohort, morbidity	Isopropanol manufacture, USA	182 (71 exposed > 5 years)	No	Sinonasal cancer: 4 cases represented an apparent, large excess compared with the national rate.	(243)
NG	Cohort, mortality	Steel workers - sheet and tin mills (incl. pickling), USA	2 763	No	Lung cancer: SMR 1.10 (0.73-1.60), 27.	(167)
NG (diethyl sulphate)	Cohort, mortality, morbidity	Alcohol manu-facturing plant, USA	335	No	Laryngeal cancer: SIR 5.04 (1.36-12.90), 4. (Assumed to be due to diethyl sulphate).	(162)
NG	Cohort, mortality	Isopropyl alcohol plant, United Kingdom	262	No	Non-significant excess of deaths from neoplasms. 1 man died from nasal cancer (0.02 expected), and 2 each from kidney cancer (p = 0.039) and brain cancer (p = 0.007).	(11)
NG (125 also exposed to epichlorohydrin)	Cohort, mortality	Isopropanol production, USA	433	No	Lung cancer: RR 2.48 (0.67-6.36), 4; for workers co-exposed to epichlorohydrin, RR 0.69 (0.14-2.02), 3; for workers not exposed to epichlorohydrin.	(73)
"Moderate and high exposure"	Nested case-control, morbidity	Refinery and chemical plant, USA	50 cases of upper respiratory cancer, each matched to at least 3 controls, 30 cases of laryngeal cancer	Smoking, alcohol, history of ear, nose or throat disease	Dose-response for laryngeal cancer risk: OR 4.6 (0.83-25.4) and OR 13.4 (2.08-86.0), for moderate and high exposure, respectively. Number of cases in each group not given.	(217)
NG (lead)	Cohort, mortality	Lead battery plant, USA	4 519 (comparison with national rates)	No	Laryngeal cancer: RR 1.28 (0.47-2.80), 6. Lung cancer RR: 1.24 (1.02-1.50), 109.	(60)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
0.64-1.12 mg/m^3 (nickel)	Cohort, mortality and morbidity	Soap production, Italy	361	No	Lung cancer: SMR 1.69 (0.55-3.86), 5. Laryngeal cancer: SMR 2.3 (0.09-11.4), 1. Laryngeal cancer: SIR 6.94 (2.25-16.2) or 3.47 (1.13-8.10), 5; depending on reference population.	(80, 116)
NG (SO_2, fluorides, silica dust, radiation from radon decay products)	Cohort, mortality	Phosphate company, USA	2 607 Caucasians 840 African Americans	No	Lung cancer: SMR 1.62 (1.14-2.23), 37. Laryngeal cancer: SMR 1.91 (0.23-6.9), 2. No excess risk among African Americans.	(28)
0.1-3.1 mg/m^3	Cohort, mortality and morbidity	Sulphuric acid plant, Sweden	400	No	Respiratory tract cancer: SIR 2.0, p=0.11. Urinary bladder cancer: SIR 3.77, p=0.01.	(72)
NG	Case-control, morbidity	Population-based, USA	183 cases 250 controls	Smoking, alcohol	Laryngeal cancer: RR 0.76 (0.42-1.35), 22.	(38)
NG	Case-control, morbidity	Population-based, Canada	*Lung cancer:* 857 cases 1 360 controls *Oesophageal cancer:* 99 cases 2 546 controls	No	Lung cancer: OR 1.2 (0.8-1.9) [b], 60. Lung (oat-cell) cancer: OR 1.7 (1.0-2.9) [b], 16. Lung (squamous-cell) cancer: OR 1.5 (1.0-2.4) [b], 38. Oesophageal cancer: OR 2.2 (1.3-3.6) [b], 15 (also published by Parent *et al* (183)).	(214)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
NG	Case-control, morbidity	Population-based, Canada	183 cases 183 controls	Smoking, alcohol	Laryngeal cancer: OR 1.97 (0.63-6.13), 10; ≤ 10 yrs low exposure. OR 3.57 (1.19-10.73), 10; ≤ 10 yrs high exposure. OR 4.30 (1.69-10.91), 50; >10 yrs low exposure. OR 5.57 (2.00-15.50), 63; >10 yrs high exposure.	(218)
NG	Cohort, mortality	Two chemical plants: ethanol and isopropanol production, USA	1 031	No	*Strong acid process:* Deaths from laryngeal cancer from both plants combined: 2 observed, 1 expected. *Weak acid process* (currently used method)*:* No evidence for carcinogenicity related to the exposure.	(231)
NG	Case-control, morbidity	Population-based, Canada	183 cases 183 controls	Smoking, alcohol	Laryngeal cancer: OR 1.97 (0.63-6.13), 10; ≤ 10 yrs low exposure. OR 3.57 (1.19-10.73), 10; ≤ 10 yrs high exposure. OR 4.30 (1.69-10.91), 50; >10 yrs low exposure. OR 5.57 (2.00-15.50), 63; >10 yrs high exposure.	(218)
Estimated from detailed job histories	Case-control, morbidity	Population based, Canada	99 cases of which 63 squamous cell carcinomas 533 population controls + 533 patient controls	Respondent status birthplace, education, alcohol, smoking, carotene intake	Oesophageal cancer (OC): OR 2.2 (1.2-4.3), 15; any exposure. OR 2.0 (1.0-4.0), 12; non-substantial exposure. OR 4.1 (1.0-17.2), 3; substantial exposure. OC/Squamous cell carcinoma: OR 2.8 (1.2-6.1), 10; any exposure. OR 2.2 (1.2-6.3), 9; non-substantial exposure. OR 3.1 (0.3-28.1), 1; substantial exposure. (Data originally published by Siemiatycki 1991 (214))	(183)
> 0.5 mg/m^3	Case-control, mortality	Population-based, Lithuania	277 cases 1 108 controls	Smoking	Lung cancer: OR 1.03 (0.76-1.39), 96.	(187) [c]

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
< 0.5 mg/m^3	Nested case-control, morbidity	Nickel refinery workers, Norway	213 cases 525 controls	Smoking	No excess risk of lung cancer relating to H_2SO_4 exposure ORs 0.8-1 (0.3-2.0), 9-14 depending on exposure level.	(97) [c]
Hydrochloric acid						
NG (Cl_2, SO_2, CCl_4)	Case-control, mortality	Chemical plant, USA	28 cases. Two matched control groups from same company.	No	Brain tumours: OR 1.40 (0.70-2.80), 13. OR 1.02 (0.81-1.29), 13 (ORs calculated for comparisons with both control groups).	(29)
NG	Case-control, mortality	Chemical plant, USA	26 cases. Two matched control groups from same company (n = 92 +98).	No	Renal cancer: OR 0.90 (0.44-1.83), 12 [b] OR 0.86 (0.40-1.86), 12 [b] (ORs calculated for comparisons with both control groups).	(30)
Up to ≥ 2.8 mg/m^3 , (also e.g. Cl_2, SO_2, CCl_4, rarely e.g. butadiene)	Nested case-control, mortality	Same as (29), USA	308 cases 2×308 controls	No	Lung cancer: OR 1.02 (0.77-1.35), 129; pooled controls.	(31)
NG (acrylamide)	Cohort, mortality	Four chemical plants, USA and the Netherlands	161 lung cancer deaths	Smoking	Excess of lung cancer (SMR 1.32) (no further details given). The excess was confined to 2 groups in one facility, including the muriatic acid department (11 deaths).	(58)
< 2.8 mg/m^3 ≥ 2.8 mg/m^3	Nested case-control, mortality (follow up with focus on HCl)	Same as (29), USA	See (31) 308 cases 2×308 controls	Race, smoking	Exposure for several years gave no excess lung cancer risk when either duration, cumulative or highest average exposure was used as indices of HCl exposure. Highest average exposure: < 2.8 mg/m^3: RR 0.8 (0.5-1.2), 41. ≥ 2.8 mg/m^3: RR 1.2 (0.8-1.6), 88.	(32)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
NG	Case-control, morbidity	Population-based, Canada	*Rectum cancer:* 257 cases 1 299 controls *Lung (oat cell) cancer:* 159 cases 1 360 controls *Non-Hodgkin's lymphoma:* 215 cases 2 357 controls		Rectum cancer: OR 1.9 (1.1-3.4) [b], 18. Lung (oat-cell) cancer: OR 1.6 (1.0-2.6) [b], 19. Non-Hodgkin's lymphoma: OR 1.6 (1.0-2.5) [b], 18.	(214)
Nitric acid						
NG (asbestos)	Cohort, incidence	HNO_3 production plant, Norway	287	Smoking	Lung cancer: RR 1.6-5 in different groups, but only statistically significant for maintenance workers.	(109)
NG	Case-control, morbidity	Population-based, Canada	*Pancreas cancer:* 116 cases 2 454 controls *Prostate cancer:* 449 cases 1 550 controls *Kidney cancer:* 177 cases 2 481 controls	No	Pancreas cancer: OR 4.6 (1.9-11-1) [b], 5. Prostate cancer: OR 3.9 (1.3-11.7) [b], 9. Kidney cancer: OR 3.1 (1.2-7.8) [b], 4.	(214)
Nitrogen products, esp. HNO_3 and urea. Exposure measured by duration in years.	Cohort, mortality Nested case-control, mortality	Chemical plant, Lima Ohio, USA	995	Smoking	Bladder cancer: SMR 3.31 (0.90-8.47), 4.	(166)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
Phosphoric acid						
NG	Case-control, morbidity	Population-based, Canada	*Lung cancer:* 857 cases 1 360 controls *Kidney cancer:* 177 cases 2 481 controls	No	Lung cancer: OR 1.9 (1.0-3.8) [b], 14. Kidney cancer: OR 3.7 (1.7-8.1) [b], 6.	(214)
Mixed acids						
H_2SO_4, HNO_3 (1950s), oxalic acid, ammonium bifluoride and soap (1960s-70s)	Cohort, morbidity	Steel pickling, Sweden	110	No	Laryngeal cancer: 3 observed cases, 0.06 expected (>10 years' induction-latency time).	(7)
H_2SO_4 H_3PO_4 (ionising radiation)	Cohort, mortality	Phosphate industry, USA	17 601 white and 4 722 non-white male workers	No	Lung cancer: SMR 1.22 ($p<0.05$), 117; compared to national rates. SMR 1.03; compared to local rates (Florida).	(44)
H_2SO_4 H_3PO_4 ionising radiation	Cohort, mortality	Phosphate industry, USA	Sub-cohorts from previous study (44)	No	RR 0.87 for length of employment > 10 years and work area with exposure to H_2SO_4 and H_3PO_4.	(45)
H_2SO_4: 0.013-0.22 mg/m^3 H_3PO_4: 0.03-0.52 mg/m^3	Cohort, mortality	Phosphate fertiliser production facility, USA	3 199	No	Tracheal, bronchial and lung cancer: SMR 1.13 (0.61-1.92), 10 (entire cohort). SMR 4.11 ($p<0.05$) (African American workers with > 10 years employment and follow-up).	(224)
H_2SO_4, HNO_3, HCl and others (self-reported)	Case-control, morbidity	Population based, UK	698 cases of which 477 self respondent, 1 683 controls	Sex, race	Multiple myeloma: OR 1.0 (0.6-1.9), 20 (all cases). OR 1.5 (0.8-2.8), 19 (self-respondent cases).	(173)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
H_2SO_4 (and other acids mainly HCl, 0.2 mg/m^3). MMAD probably ~ 5 μm	Cohort, mortality	Steel industry, pickling process, USA	1 165	Smoking	Lung, tracheal and bronchial cancer: SMR 1.64 (1.14-2.28), 35; any acid. Laryngeal cancer: SMR 1.93 (0.23-6.99), 2; any acid. Lung cancer: SMR 1.92 (1.10-3.13), 14; ≥ 20 years latency, daily exposure to H_2SO_4 only. SMR 2.24 (1.02-4.25), 9; subset of 189 workers exposed to acids other than H_2SO_4, primarily HCl.	(24)
H_2SO_4: 0.2 mg/m^3 and other acid mists	Cohort, incidence	Steel industry, pickling, USA	879	Smoking, alcohol	Laryngeal cancer: SIR 2.30 (1.1-4.4), 9.	(225)
H_2SO_4 mist: 0.2 mg/m^3 and other acid mists	Cohort, mortality,	Steel industry, pickling operations, USA	1 165 follow-up of (24)	Smoking	Lung cancer: SMR 1.36 (0.97-1.84), 41. SMR 1.50 (1.05-2.07), NG; > 20 yr since 1st exposure.	(226)
	Cohort, mortality	Phosphate fertiliser manufacture, Sweden	1 148	No	Respiratory cancer: SMR 1.51 (1.03-2.2), 29. Laryngeal cancer: SMR 1.60 (0.44-4.10), 4.	(100)
Inorganic acids	Case-control, morbidity	Population-based, Canada	*Lung cancer:* 857 cases 1 360 controls *Kidney cancer:* 177 cases 2 481 controls	No	Lung cancer: OR 1.2 (1.0-1.6) [b], 129; mixed acids. Kidney cancer: OR 1.7 (1.2-2.4) [b], 32; mixed acids.	(214)

Table 16. Carcinogenicity studies in workers (predominantly males) exposed to the inorganic acids (in chronological order).

Acid exposure level (co-exposure)	Design	Industry/product, Country	Study size	Adjustment in addition to age [a]	Outcome and risk estimate (95 % CI), no. of cases (cohort) no. of exposed cases (case-control)	Reference
H_2SO_4 (later substituted with HCl) >1 mg/m^3	Cohort, mortality, and case-control	Battery manu-facturers and steel workers, United Kingdom	4 401 total cohort, 15 cases 73 controls	No	Laryngeal cancer (cohort): SMR 0.48 (0.01-2.70), 1. Lung cancer (cohort): 0.98 (0.78-1.22), 83. Upper aerodigestive cancer (case-control): OR 2.0 (0.4-10), 12.	(57)
H_2SO_4 mist (0.19+0.29 mg/m^3) and other acids	Cohort, mortality, morbidity	Steel industry, pickling operations, USA, follow-up of (225).	1 031	Smoking, alcohol	Laryngeal cancer: RR 2.2 (1.2-3.7), 14 RR 2.5 (1.7-4.7), NG; daily contact with H_2SO_4 mist.	(227) [c]
Mainly HCl. Also HF, HNO_3, H_3PO_4, H_2SO_4 and chromic acid	Multi-centre, case-control	Population-based	316 laryngeal cancer + 34 hypopharyngeal cases, 728 controls	Country, smoking, alcohol	Laryngeal cancer: OR 0.94 (0.60-1.49), 37. Hypopharyngeal cancer: OR 3.72 (1.08-12.81), 5; exposure for >15 years.	(213)

[a] Smoking and alcohol are the strongest known confounders for laryngeal cancer .
[b] 90 % CI.
[c] Published following the IARC monograph (116).
CI: confidence interval, NG: not given, SMR: standardised mortality rate, SIR: standardised incidence ratio, RR: relative risk (risk ratio), OR: odds ratio.

12. Dose-effect and dose-response relationships

Comprehensive compilations of toxicity data have been presented in Chapters 10-11 (Tables 6-16). The LC_{50}s suggest that H_2SO_4 and HNO_3 have a higher acute toxicity than HCl and probably also than H_3PO_4.

12.1 Sulphuric acid

Toxicity data from low-level exposures to H_2SO_4 are summarised in Table 18.

12.1.1 Single/short-term exposure

Animal studies

Details have been presented in Chapter 10 (Tables 6, 7 and 9).

Single and repeated, short-term inhalation of low concentrations of H_2SO_4 has resulted in non-specific bronchial hyperresponsiveness *in vitro* and effects on the defences of the rabbit lung (accelerated respiratory clearance, depressed phagocytic capacity, reduced TNFα release and superoxide anion production in macrophages). Effects have appeared at 0.05-0.075 mg/m^3 (70, 201, 205, 250). A lowered intracellular pH in pulmonary macrophages was demonstrated after exposure of rabbits at 0.125 mg/m^3 (49).

A dose-related increase in pulmonary flow resistance in guinea pigs was reported during exposure to 0.1-1 mg/m^3 for 1 hour (MMD 0.3 and 1 µm). The smaller droplets also reduced pulmonary compliance in a dose-related manner during and after exposure (13).

Non-specific airway hyperresponsiveness *in vivo* was induced in male guinea pigs exposed for 1 hour to ultrafine H_2SO_4-particles at 0.2 mg/m^3 (mean diameter 0.06 µm) (48).

Rabbits were exposed to H_2SO_4 at 0.25, 0.5 or 1 mg/m^3 (MMD 0.3 µm), 1 hour/day for 5 days. A dose-dependent decrease in eicosanoid concentration in the lung lavage fluid was reported (203) suggesting modulation of the inflammatory response.

At 0.3 mg/m^3, the phagocytic capacity of macrophages was depressed by ultra-fine acid particles (MMD 0.04 µm) and enhanced by larger, sub-micrometer acid particles (MMD 0.3 µm) in guinea pigs after both single and repeated exposure. Further, an increased release of TNFα by macrophages was reported after some exposures (47, 48). A 1-hour exposure at the same level (MMD 0.08 µm) decreased single breath diffusion capacity for carbon monoxide (46).

Minimal squamous metaplasia in ciliated epithelium in the larynx in rats was observed after a 28-day inhalation exposure to 0.3 mg/m^3 (6 hours/day, 5 days/week). At higher concentrations (1.38 and 5.52 mg/m^3), changes were more severe (some cases with parakeratosis) and were accompanied by cell proliferation in the larynx. No effects were observed in the nose or lungs (127). The changes observed at 0.3 mg/m^3 can be regarded as an adaptive response, but suggest a risk of respiratory tract epithelial changes following exposures of longer duration.

Increased *in vitro* tracheal reactivity in rabbit was reported after single exposure for 3 hours to 0.5 mg/m^3 (MMD 0.3 µm). At the same level, depressed tracheal mucociliary clearance in dogs was reported after 1-hour exposures to aerosols with larger particles (MMAD 0.9 µm), whereas no such effect was reported after exposures to aerosols with MMAD 0.3 µm even at 5 mg/m^3 (70, 246). Depressed ciliary beating in trachea was observed in hamster at single exposures to 0.9 (98) and 1.1 mg/m^3 (98, 199). At the higher level, also the respiratory epithelium of the trachea was damaged (98, 199).

Clear dose-effect relationships regarding airway irritation and changes in pulmonary function were reported in three whole-body plethysmograph guinea pig studies with exposures in the range 10-55 mg/m^3 (198), 14-43 mg/m^3 (192), and 24-73 mg/m^3 (249).

Human studies

Acute effects of H_2SO_4 aerosols have been studied in a number of controlled exposure experiments with healthy and asthmatic volunteers (Table 13), with exposure duration ranging from 10 minutes to 6.5 hours, droplet sizes ranging from 0.1-10 µm (MMAD), relative humidities varying between below 10 to 100 % and exposures carried out at rest, during exercise or combinations thereof.

In three studies on healthy volunteers, bronchial mucociliary clearance was affected after exposures for 1 hour to 0.1 mg/m^3 (MMAD 0.5 µm) (151, 152, 220). In those and other studies, tracheal transport rates were not affected after exposures to 0.1-1 mg/m^3. However, an effect on tracheal mucociliary clearance was observed in a study with exposure to larger, fog droplets (MMAD 10.3 µm) at 0.47 mg/m^3 (149).

Respiratory symptoms increased among healthy volunteers exposed to large particles (VMD 10 µm) at 0.5 and 1 mg/m^3 for 1 hour with intermittent heavy exercise. Exposure to submicrometer particles (MMAD 0.9 µm) at 1 mg/m^3 did not increase symptom ratings compared with air exposure (21, 22). One study (presented as conference proceedings) indicated that workers suffered symptoms of respiratory irritation at exposures in the range 0.1-0.5 mg/m^3 (81).

Bronchial hyperreactivity (after provocation with carbachol) was demonstrated in healthy subjects after a 16-minute exposure to 1 mg/m^3 (237). Generally, no effects on lung function are reported among healthy volunteers at exposures up to 1 mg/m^3 (14, 20-22, 83, 149, 151, 152, 156, 195, 219, 220, 232, 237). However, a few studies indicate that asthmatics respond to lower concentrations. One research team exposed adolescent asthmatics to acid and air or saline in a slightly humid atmosphere (65-75 %). FEV_1 was reduced in subjects exposed to H_2SO_4 for 45 minutes to as little as 0.035 and 0.07 mg/m^3 (MMAD 0.6 µm), significantly so at the lower exposure level. The effect did not remain after 90 minutes of exposure. Exposure to 0.1 mg/m^3 (MMAD 0.6 µm) produced reversible significant changes in lung function in 10 adolescent asthmatics following exposure during exercise (134, 136).

In adult asthmatics, enhanced bronchoconstriction as well as increased reactivity to carbachol was demonstrated after exposure for 16 minutes to 0.45 mg/m^3 (236, 237). The same research team also reported that prevention of oral ammonia-induced neutralisation of inhaled acid resulted in decrements in pulmonary function following exercise in asthmatics exposed 30 minutes to 0.35 mg/m^3 (238). Other studies showed unaffected pulmonary function in adult asthmatics exposed to up to 1 mg/m^3 or more (195, 232).

Exposure of workers to high but unknown concentrations has been associated with severe effects such as burns, ARDS, pulmonary oedema and fibrosis, bronchioectasis, emphysema and even death (26, 93, 132, 208).

12.1.2 Long-term exposure

Animal studies

Details have been presented in Chapter 10 (Tables 11-12).

The LOAELs after long-term exposure are 0.1 mg/m^3 (1 hour/day, 5 days/week for 6 months) at which impaired mucociliary clearance in donkeys was reported (200) and 0.125 mg/m^3 (2 hours/day, 5 days/week for up to 12 months) at which an accelerated tracheobronchial mucociliary clearance and bronchial epithelial secretory cell hyperplasia were observed in rabbits (204). At 0.25 mg/m^3 (4-12 months, same daily dose as in the previous study) tracheobronchial mucociliary clearance was retarded and a narrowing of the airways, airway hyperresponsiveness, and secretory cell hyperplasia were observed in rabbits (88-90).

In monkeys exposed to larger particles (MMD 2.15 μm) at 0.38 mg/m^3 for 78 weeks, an increased respiratory rate, slight hyperplasia of bronchiolar epithelium and thickening of the walls of the respiratory bronchioles were observed. No such changes were reported after exposure to submicrometer particles (MMD 0.54 μm) at 0.48 mg/m^3 using an otherwise similar protocol (8).

Dogs exposed to 0.9 mg/m^3 for 620 days exhibited impaired lung function and reduced heart weights (154).

Monkeys exposed to 0.88-0.99 mg/m^3 combined with sulphur dioxide and/or fly ash for 78 weeks developed a variety of lung lesions such as hypertrophy, hyperplasia and metaplasia of the bronchiolar epithelium. The effects were attributed to H_2SO_4. These effects were not seen in monkeys exposed to 0.1 mg/m^3 (9).

The few cancer studies in animals have weaknesses in design and reporting. Thus, no conclusion can be drawn regarding the carcinogenic potential of H_2SO_4 in animals.

Human studies

A number of studies on workers exposed to H_2SO_4 for several years show tooth etching and erosion (Table 15). This has been reported after estimated average exposure levels of 0.2 mg/m^3 (87) and above (186, 230) and after exposure in the range 0.06-2 mg/m^3 (233). In the study by Gamble *et al,* the earliest cases of etching and erosion, respectively, occurred after 4 and 30 months of exposure (87).

In the same study, reduced FVC was observed in the high (average 0.21 mg/m^3, cumulative exposure > 15 mg/m^3 × months) but not in the low (average 0.10 mg/m^3, cumulative exposure < 7 mg/m^3 × months) exposure group (87).

In another field study, exposure averaged 0.035-2.1 mg/m^3. Pale mucosal patches and ulcerations were found only in the workers exposed to more than 0.2 mg/m^3. Squamous metaplasia, squamous atypia and mild dysplasia of the nasal mucosa were more frequent among exposed than among unexposed workers. The risk of squamous atypia or dysplasia increased with increasing concentration of H_2SO_4, but did not correlate with exposure duration. Work-related nasal symptoms were also reported (95).

Human carcinogenicity studies have previously been presented in Table 16, Chapter 11. The IARC classification of strong inorganic acid mist containing H_2SO_4 as carcinogenic to humans (Group 1) was based on several studies (7, 24, 214, 217, 218, 225, 226, 243) with additional support provided by yet another few (80, 100). The risk for laryngeal cancer after exposure to H_2SO_4 was increased in several cohort and case-control studies, but the exposure levels were poorly characterised. Later, one follow-up (227) supporting an association with laryngeal cancer has been published. The evidence for an association with lung cancer is weak (Table 17).

The only study of oesophageal cancer suggests an excess risk with exposure to H_2SO_4 (183, 214).

It should be stated that the validity regarding measurements of the acids in both older and in some more recent field studies is uncertain.

Table 17. Cohort and case-control studies of laryngeal and lung cancer with significantly elevated risk estimates related to exposure to strong inorganic acid mist containing sulphuric acid.

Cancer type/ Industry	Risk estimate	95 % CI	Reference
Laryngeal cancer			
Soap production	SIR 6.94 or SIR 3.47 [a]	2.25-16.2 or 1.13-8.10	(80)
Steel-pickling	SIR 2.30	1.1-4.4	(225)
Steel-pickling	RR 2.2	1.2-3.7	(227) [b]
Steel-pickling	3 cases vs. 0.06 expected		(7)
Refinery and chemical plant	OR 4.6 OR 13.4	0.83-25.4 (moderate exposure) 2.08-86.0 (high exposure)	(217)
Population-based	OR 1.97 OR 3.57 OR 4.30 OR 5.57	0.63-6.13 (≤ 10 yrs low exposure) 1.19-10.73 (≤ 10 yrs high exposure) 1.69-10.91 (> 10 yrs low exposure) 2.00-15.50 (> 10 yrs high exposure)	(218)
Lung cancer			
Steel-pickling	SMR 1.92	1.10-3.13 (≥ 20 yrs latency, daily exposure to H_2SO_4)	(24)
	SMR 1.64 (incl trachea/ bronchus)	1.14-2.28 (any acid)	
Steel-pickling	SMR 1.36 SMR 1.50	0.97-1.84 1.05-2.07 (> 20 yrs since 1st exposure)	(226)
Phosphate fertiliser manufacture	SIR 1.51	1.03-2.20 (respiratory tract)	(100)
Population-based	OR 1.2 OR 1.7 (oat-cell) OR 1.5 (squamous-cell)	1.0-1.6 [c] (mixed acids) 1.0-2.9 [c] (H_2SO_4) 1.0-2.4 [c] (H_2SO_4)	(214)

[a] Depending on reference population.
[b] 10-year extension of the 1988-study (225).
[c] 90 % CI.
CI: confidence interval, OR: odds ratio, RR: relative risk (risk ratio), SIR: standardised incidence ratio, SMR: standard mortality ratio.

Table 18. No observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for low-level inhalation exposures to sulphuric acid.

NOAEL (mg/m^3)	LOAEL (mg/m^3)	Species/ subjects [a]	Exposure duration	Effects	Reference
Animal studies					
-	0.05	Rabbit	4 h/d, 14 d	Accelerated respiratory clearance.	(201)
0.05	0.075	Rabbit	2-3 h	Depressed phagocytic capacity, superoxide anion production and TNFα activity by pulmonary macrophages. Increased bronchial hyperresponsiveness (*in vitro*).	(70, 205, 250)
-	0.1	Guinea pig	1 h	Increased pulmonary resistance and decreased compliance.	(13)
-	0.1	Donkey	1 h/d, 5 d/wk, 6 mo	Impaired bronchial mucociliary clearance.	(200)
-	0.125	Rabbit	2 h/d, 5 d/wk, up to 1 yr	Accelerated tracheobronchial mucociliary clearance. Increased secretory cell density in the small airways and possible focal epithelial hyperplasia.	(204)
-	0.2	Guinea pig	1 h	Non-specific airway hyperresponsiveness *in vivo*.	(48)
-	0.25	Rabbit	1h/d, 5d	Decreased concentration of the eicosanoid TxB_2 in broncho-pulmonary lavage fluid.	(203)
-	0.25	Rabbit	1 h/d, 5 d/wk, up to 1 yr	Airway hyperresponsiveness. Decreased tracheobronchial mucociliary clearance, increased airway secretory cell density, and narrowing of the bronchial airways.	(88-90)
-	0.3	Guinea pig	1 h	Decreased single breath diffusion capacity for carbon monoxide.	(46)
-	0.3	Guinea pig	3 h and 3 h/d, 4 d	Increased release of TNFα from pulmonary macrophages. Phagocytic capacity depressed by 0.04-µm particles and enhanced by 0.3-µm particles.	(47)

Table 18. No observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for low-level inhalation exposures to sulphuric acid.

NOAEL (mg/m^3)	LOAEL (mg/m^3)	Species/ subjects [a]	Exposure duration	Effects	Reference
0.3 (5 days)	0.3 (28 days)	Rat	5 d and 28 d	Minimal squamous metaplasia in ciliated epithelium of the larynx, not accompanied by cell proliferation. The severity increased in a dose-dependent manner at 1.4 and 5.5 mg/m^3 and was accompanied by cell proliferation.	(127)
0.48 (MMD 0.54 µm)	0.38 (MMD 2.15 µm)	Monkey	23 h/d, 78 weeks	Slight hyperplasia of bronchiolar epithelium and thickening of walls of respiratory bronchioles. Increased respiratory rate. More severe effects at 2.4 mg/m^3 and 4.8 mg/m^3.	(8)
0.25	0.5	Rabbit	3 h	Increased tracheal reactivity.	(70)
-	0.9	Hamster	2 h	Tracheal mucociliary impairment (depressed ciliary beating).	(98)
-	0.9	Dog	21 h/d, 620 d	Impaired pulmonary function and reduced heart weights.	(154)
0.09-0.11 (with SO_2 and/or fly ash)	0.88-0.99	Monkey	23 h/d, 78 weeks	Lung lesions: Focal epithelial and goblet cell hypertrophy and hyperplasia, erosion, thinning and squamous metaplasia of bronchiolar epithelium.	(9)
0.48 (MMD 0.54 µm)	2.4 (MMD 3.6 µm)	Monkey	23 h/d, 78 weeks	Impaired lung function (increased respiratory rate, decreased oxygen tension, deterioration of the distribution of ventilation) and histopathological pulmonary changes.	(8)
Human studies					
-	0.035 and 0.07	Adolescent asthmatics	45, 90 min	Marginal fall in FEV_1 immediately after exposure for 45 but not for 90 min. Values had returned to normal 20 min post-exposure.	(136)
-	0.1	Adolescent asthmatics	40 min incl exercise	Impaired pulmonary function (reversible reductions in FEF_{50}, FEV_1 and total respiratory resistance).	(134, 136)
-	0.1	Healthy	1-2 h	Increased bronchial mucociliary clearance of large tracers (MMAD 7.5 µm). Reduced bronchial mucociliary clearance of smaller tracers (MMAD 4-5 µm).	(151, 152, 220)

Table 18. No observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for low-level inhalation exposures to sulphuric acid.

NOAEL (mg/m^3)	LOAEL (mg/m^3)	Species/ subjects [a]	Exposure duration	Effects	Reference
-	~ 0.1	Workers	> 6 months	Symptoms of eye and respiratory irritation.	(81)
-	~ 0.2	Workers	10 yr average	Tooth etching and erosion.	(87)
0.1	~ 0.2	Workers	10 yr average	Reduced FVC.	(87)
-	> 0.2	Workers		Cellular changes of the nasal mucosa.	(95)
0.35 (high oral NH_3)	0.35 (low oral NH_3)	Asthmatics	20 min rest + 10 min exercise	Impaired pulmonary function (reduced FEV_1 and maximum expiratory flow rates at 60 % total lung capacity).	(238)
0.1	0.45	Asthmatics	16 min	Enhanced bronchoconstriction.	(236, 237)
-	0.47	Healthy	1 h incl exercise	Accelerated tracheal clearance and accelerated small airway mucociliary clearance.	(149)
0.47 (MMAD 10 µm)	0.5 (VMD 10 µm)	Healthy	1 h incl exercise	Small increase in upper and lower respiratory symptoms.	(22, 149)
0.38 (MMAD 0.9 µm)	1 (MMAD 0.9 µm)	Asthmatics	1 h incl exercise	Lower respiratory and non-respiratory symptoms increase.	(21)
0.5 (VMD 10 µm)	1 (VMD 10 µm)	Asthmatics	1 h incl exercise	Upper and lower respiratory symptoms increase.	(22)
0.3	1.0	Asthmatics	1 h	Reduced bronchial mucociliary clearance.	(219)
0.5 (VMD 10 µm)	1 (MMAD 0.6-1)	Healthy	16 min	Enhanced bronchoconstriction.	(22, 237)

[a] Adult; unless stated otherwise.

FEV_1: forced expiratory volume in one second, FEF_{50}: forced expiratory flow at 50 % of forced vital capacity, FVC: forced vital capacity, MMAD: mass median aerodynamic diameter, MMD: mass median diameter, TNF: tumour necrosis factor, Tx: thromboxan, VMD: volume median diameter.

12.2 Hydrochloric acid

Toxicological effects after low-level exposures are compiled in Table 19.

12.2.1 Single/short-term exposure

Animal studies

Details are presented in Chapter 10 (Tables 6 and 8). In male guinea pigs exposed 2 hours/day, 5 days/week for 7 weeks, a NOAEL of 15 mg/m^3 was identified for histological changes in the lungs and airways and for effects on pulmonary function (181).

In mice, the respiratory rate decreased by approximately 10 % at 56 mg/m^3 and RD_{50} was calculated to be 432 mg/m^3 (23). Male mice exposed for 6 hours/day to the same level were all dead or moribund after 3 exposures. Severe exfoliation, erosion, ulceration and necrosis, and mild inflammation of the respiratory epithelium were observed, as well as mild ulceration and necrosis of the olfactory epithelium, and serous exudate. No lesions were induced in the lower respiratory tract (41). At approximately the same level (448 mg/m^3), sensory and pulmonary irritation in guinea pigs is reported (42).

In mice and guinea pigs, 700 mg/m^3 (lowest dose tested) reduced the respiratory frequency. The exposure resulted in the death of 4/6 mice and of 1/9 guinea pigs (124). In baboons, there was no significant effect in pulmonary function at the same level of exposure (123). In both studies, the exposure duration was 15 minutes (head-only). Mice, guinea pigs, and rats exposed to higher levels (3 500, 5 880 and 5 880 mg/m^3, respectively) experienced damaged respiratory tract epithelium and lung injuries. In baboons, higher level (7 000-14 000 mg/m^3) of exposure increased respiratory frequency and minute volume registered by plethysmography.

Exposure of rats to 1 820 mg/m^3 HCl in plethysmographs for 30 minutes caused marked toxicity in the nasal region in nose breathers. Even higher toxicity was seen after forced mouth breathing, such as major tissue disruption in the trachea, accumulation of inflammatory cells and exudates in the airways and more peripheral lung damage. Breathing frequency, pulmonary ventilation, and tidal volume was reduced by 4-7 % in animals breathing through the nose compared to the controls. In the mouth breathing group, pulmonary ventilation increased during exposure (223).

Human studies

The toxicological database for humans is very limited.

No pulmonary function impairment and no lower or upper respiratory symptoms were observed in asthmatic adults exposed to 1.12 and 2.52 mg/m^3 HCl for 45 minutes (228). The authors also listed earlier human studies and case reports of HCl exposure in which it was estimated that the odour threshold was in the range 1.5-7.5 mg/m^3, that work can be carried out undisturbed at 15 mg/m^3, is difficult at 15-75 mg/m^3, intolerable at 75-150 mg/m^3, and that 1 950-3 000 mg/m^3 is a lethal concentration (228).

Table 19. No observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for low-level inhalation exposures to hydrochloric acid.

NOAEL (mg/m^3)	LOAEL (mg/m^3)	Species/ subjects	Exposure duration	Effects	Reference
Animal studies					
2.8 [a]	14	Rat	6 h/d, 5 d/wk, for life	Increased incidences of hyperplasia in larynx and trachea.	(212)
-	15	Rat	6 h/d, 5 d/wk, 90 d	Nasal irritation.	[b] cited in (68)
-	56	Mouse	10 min	Respiratory rate reduced by 10 % (RD_{50} = 432 mg/m^3).	(23)
15	-	Guinea pig	2 h/d, 5 d/wk, 7 wk	No histological changes in the lungs and airways or effects on pulmonary function.	(181)
Human studies					
4.5-7.7 [c]	1.8-12.4	Workers	Occupational	Tooth erosion indicated (lack of control group).	(165, 191)
2.5	-	Asthmatics	45 min	No irritation of the respiratory tract and no pulmonary function impairment.	(228)
3-4.5 [c]	5.2 [c]	Workers	Occupational	Initial mild irritation of the airway mucosa, which regressed rapidly.	(165)
-	26-34 [c]	Workers	Occupational	Breathing difficulties, chronic bronchitis (after years of exposure).	(165)

[a] Calculated from the LOAEL by the German MAK-committee by linear interpolation between the incidences at 0 and 14 mg/m^3.
[b] Chemical Industry Institute of Toxicology. *90-day inhalation study of hydrogen chloride gas in B6C3F1 mice, Sprague-Dawley rats, and Fischer-344 rats.* ToxiGenics, Inc for CIIT Research Triangle Park, NC, USA, CIIT Docket No. 20915.
[c] No further details given (see below).

No irritation of the mucous membranes was observed among workers in steel pickling facilities exposed to 3-4.5 mg/m^3 whereas initial mild irritation of the airway mucosa, which regressed rapidly was observed at 5.2 mg/m^3, slight irritation at 7-11 mg/m^3 and breathing difficulties at 26-34 mg/m^3 (165). The study is based on many years of observations but is not conducted and reported according to current standards.

Accidental exposure to high air levels of HCl has produced severe symptoms, and respiratory impairments (35, 126). Exposure of the skin to a high concentration of HCl gas or to a concentrated solution of HCl will cause burns; repeated or prolonged exposures to dilute solutions may cause dermatitis (5).

12.2.2 Long-term exposure

Animal studies

In male and female mice and rats exposed to 0, 10, 20, or 50 ppm (0, 15, 30, or 75 mg/m^3) for 6 hours/day, 5 days/week for 90 days, local irritative effects on the

nose were observed in both species. The systemic NOAEL was found to be 30 mg/m^3, and the LOAEL for irritation 15 mg/m^3 (industry report[1] cited in (68)).

Animal carcinogenicity studies are listed in Table 12. Male rats exposed to air containing 14 mg/m^3 HCl for life developed hyperplasia in larynx and trachea, but no cancer. The incidences of laryngeal and tracheal hyperplasia were 22 % and 26 % compared with 2 % and 6 % among the controls. No other level of exposure was tested (212). In a previous study with equal exposure level and duration, no nasal cancer was observed (10).

Human studies

Effects of occupational exposure are presented in Tables 15-16.

In a hot dip zinc galvanising plant, 90 % of 38 examined workers in the pickling process in which a 15 % HCl solution was used had grade 1-2 dental erosion of the incisor teeth. Exposure levels (geometric mean) ranged from 1.8 to 12.4 mg/m^3. The dental effect could not be causally linked to the HCl exposure due to the lack of control group and the small number of workers, which made dose-response analysis impossible (191).

In a report from steel pickling facilities, chronic bronchitis was reported after exposure to approximately 30 mg/m^3 for years. It was also stated (no further information given) that no damage to the teeth occurred at average concentrations of 4.5-7.7 mg/m^3 (165). The study does not comply with current standards.

IARC concluded in 1992 that HCl was not classifiable as to its carcinogenicity to humans.

12.3 Nitric acid

Toxicity data from low-level exposures to nitric acid are presented in Table 20.

12.3.1 Single/short-term exposure

Animal studies

Details are presented in Chapter 10 (Tables 6 and 10).

The lowest effect levels reported concern the rabbit lung defence. A reduced production of superoxide anions by alveolar macrophages was observed after 4 weeks of exposure to ≥ 0.05 mg/m^3. At ≥ 0.15 mg/m^3, reduced bronchial responsivity to smooth muscle constrictor challenge and reduced TNFα activity were seen (207). Decreased superoxide anion production in rat pulmonary macrophages was also observed after a 4-day repeated exposure to 0.25 mg/m^3, the only dose tested, as well as increased elastase inhibitory capacity of lung lavage fluid (175).

No bronchoconstriction was seen in normal sheep exposed for 4 hours to 4.1 mg/m^3. However, in allergic sheep this concentration caused increased airway hyperreactivity to carbachol (2).

[1] Chemical Industry Institute of Toxicology (1984). *90-Day inhalation study of hydrogen chloride gas in B6C3F1 mice, Sprague-Dawley rats, and Fischer-344 rats.* ToxiGenics, Inc for CIIT Research Triangle Park, NC, USA, CIIT Docket No. 20915.

Table 20. No observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for low-level inhalation exposures to nitric acid.

NOAEL (mg/m^3)	LOAEL (mg/m^3)	Species/ subjects	Exposure duration	Effects	Reference
Animal studies					
-	0.05	Rat	40 wk	Elevated stress-inducible heat-shock protein 70 in the lungs.	(164, 215, 248)
-	0.05	Rabbit	4 wk	Decreased superoxide anion production in alveolar macrophages.	(207)
0.05	0.15	Rabbit	4 wk	Reduced *in vitro* bronchial responsivity to smooth muscle constrictor challenge and TNFα activity in alveolar macrophages.	(207)
-	0.25	Rat	4 h/d, 4d	Decreased superoxide anion production in isolated pulmonary macrophages. Increased elastase inhibitory capacity of lung lavage fluid.	(175)
4.1 (n, a)		Sheep	4 h	No bronchoconstriction.	(2)
4.1 (n)	4.1 (a)	Sheep	4 h	Hyperreactivity (carbachol).	(2)
Human studies					
0.125		Adolescent asthmatics	40 min	No effects on pulmonary function.	(137)
-	0.2	Healthy	2 h	Alveolar macrophage function effected (increased phagocytic activity and resistance to infection, and decreased superoxide anion production.	(25)
0.5		Healthy	4 h	No effect on symptom scores, no proximal airway and distal lung injuries assessed by pulmonary function measurements, lavage and biopsies.	(17)

a: allergic, n: normal, TNF: tumour necrosis factor.

At repeated exposure to much higher levels (190-320 mg/m^3), impaired pulmonary function, histopathological findings such as chronic inflammation of smaller airways, and hyperresponsiveness to histamine were observed in dogs (85, 185).

Human studies

Pulmonary function parameters were not affected in adolescent asthmatics (n=28), 12-19 years old, after inhalation of a combination of 0.05 ppm (0.125 mg/m^3) HNO_3, 0.12 ppm O_3 and 0.30 ppm NO_2 for 90 minutes via a mouthpiece (137).

Exposure of 9 healthy subjects to 0 and 0.2 mg/m^3 of HNO_3 vapour for 2 hours, did not affect pulmonary function, subjective symptoms or indicators of airway injury and inflammation. However, there was an effect of HNO_3 on alveolar macrophage function (increased phagocytic activity and resistance to infection, and decreased superoxide anion production) (25).

In 10 healthy volunteers, no effects on symptoms or pulmonary function were seen after exposure to 0.5 mg/m^3 HNO_3 for 4 hours (17) nor after exposure for 2 hours to 0.4 mg/m^3 (16), the only levels tested.

In an old study, exposure to 11-12 ppm (27-30 mg/m^3) for more than 1 hour was considered intolerable and dangerous to human health. Exposure to 84 ppm (210 mg/m^3) was tolerated for only 2-3 minutes. The results were based on only 1-2 individuals (Diem[1], cited in (66)).

Inhalation of high, but unknown, concentrations of HNO_3 fumes has caused numerous deaths; death can be delayed several days. Contact with concentrated acid causes severe skin burns and corneal injury leading to blindness.

12.3.2 Long-term exposure

Animal studies

Elevated stress-inducible heat shock protein 70 was observed in lungs from rats exposed to HNO_3 vapour at 0.05 mg/m^3 for 40 weeks. Body weight, lung poly-amine contents and lung clearance was not affected (164, 215, 248). No other concentrations were tested.

Human studies

No quantitative human data on effects from long-term exposure to HNO_3 have been found in the peer-reviewed literature.

12.4 Phosphoric acid

Apart from an LC_{50} of > 850 mg/m^3 (Table 6) no quantitative data on effects from exposure to H_3PO_4 have been found in the peer-reviewed literature.

H_3PO_4 is a mild irritant of the eyes, upper respiratory tract and the skin, and the dust is especially irritating to skin in the presence of moisture. Severe reactions including death have been described after excessive exposure.

13. Previous evaluations by national and international bodies

13.1 Sulphuric acid

The *Nordic Expert Group for Documentation of Occupational Exposure Limits* (previous name for NEG) concluded in 1992 that the critical effect of acid aerosols is acute and chronic irritation of the airways. NEG stated further that some human volunteer studies (not replicated by others, NEG claims in 1992) indicated that H_2SO_4 aerosols in the one-micron size range may induce moderate increase of airway resistance in asthmatics at concentrations around 0.1 mg/m^3 and even lower, and that submicron long-term exposures to H_2SO_4 aerosols in the 0.1-0.5 mg/m^3 range induced changes in airways and lungs in animal models.

[1] Diem L. *Untersuchungen über die Einatmung von Saltpetersäure-dämpfen* (thesis). Würzburg, 1907.

Long-term acid aerosol exposures in doses found in several industries should be suspected as a causative factor for laryngeal cancer (142).

In 1992, *IARC* classified occupational exposure to strong inorganic acid mists containing H_2SO_4 as carcinogenic to humans (Group 1) (116).

The Agency for Toxic Substances and Disease Registry (*ATSDR*) (1998) was not able to derive a minimal risk level (MRL) for inhalation exposure in humans to H_2SO_4. ATSDR argued that physiological factors and conditions are just as important as the exposure concentration, and that the response depends on individual factors. Because the occupational studies identified NOAELs higher than LOAELs in acute-duration studies in animals, they were not considered appropriate for MRL derivation (19).

The German Research Foundation (*DFG*) evaluation of H_2SO_4 for MAK-values concluded in 2001 that the most sensitive endpoint for the local effects in man has proved to be the alterations in mucociliary clearance seen after exposure to concentrations of 0.3 mg/m^3 or more (67).

The US National Toxicology Program (*NTP*) published a Report on Carcinogens (RoC) in 2002 titled "Strong inorganic acid mists containing sulfuric acid". In the report, H_2SO_4 was identified as a carcinogen (180).

The Dutch Expert Committee on Occupational Standards (*DECOS*) conducted an evaluation of carcinogenicity and genotoxicity of strong inorganic acid mists containing H_2SO_4 in 2003, and concluded it to be carcinogenic to humans (comparable with EU category 1), acting as non-stochastic genotoxic carcinogens (meaning that an OEL can be derived using a threshold model) (106).

The American Conference of Governmental Industrial Hygienists (*ACGIH) (2004)* has recommended an 8-hour threshold limit value (TLV) of 0.2 mg/m^3 for H_2SO_4 (thoracic particulate fraction) to avoid mucociliary clearance and pulmonary function changes, and also other effects (6).

The Scientific Committee on Occupational Exposure Limits (*SCOEL*) in the European Union concluded in 2007 that experimental studies in a range of animals suggest respiratory tract effects from repeated exposure to concentrations around 0.3 mg/m^3, with the possibility of effects of some health significance even at concentrations as low as 0.1 mg/m^3. SCOEL emphasised the human carcinogenicity data and the larynx as a site of particular concern. SCOEL stated that the presumed mechanism by which laryngeal cancer arose in workers is chronic inflammation of the epithelium in this region, caused by the acidity of H_2SO_4 aerosols, a hypothesis that links with the findings of the rat inhalation study of Kilgour *et al* (2000). A threshold would apply to this presumed carcinogenic mechanism, that being the dose at which the buffering capacity of the epithelial cells is overwhelmed and a significant fall in cellular pH occurs. SCOEL concluded that long-term exposure should be maintained below 0.1 mg/m^3 and hence recommended an 8-hour TWA limit of 0.05 mg/m^3 (210).

13.2 Hydrochloric acid

The International Programme on Chemical Safety (*IPCS)* considered in 1982 sensory irritation and objective changes in pulmonary function to be likely critical effects from exposure to chlorine and HCl, but was unable to establish a value for the protection from effects from HCl (117).

IARC stated in 1992 that HCl is not classifiable as to its carcinogenicity to humans (Group 3) (115).

ACGIH recommended in 2003 that a TLV-Ceiling of 2 ppm (2.8 mg/m^3) for HCl should be based on the NOAEL from Stevens *et al* (228) of 1.8 ppm (2.52 mg/m^3) in human volunteers exposed for 45 minutes with intermittent exercise. The asthmatic subjects in this study showed no adverse respiratory health effects of inhalation of this low exposure. The recommended TLV should prevent acute irritation (5).

The *DFG* evaluation of HCl for MAK-values (Germany) concluded in 1982 that it could not be excluded that long-term exposure of workers to the current MAK-value of 5 ppm (dated 1958) could cause changes in respiration mechanics and possible effects on lung function should be investigated (65). Later, the MAK-value was reduced from 5 ppm to 2 ppm (2004) based on the 2-year studies in rats exposed to 10 ppm HCl by inhalation, and the finding of hyperplasia in larynx and trachea (10, 212). Linear interpolation was carried out between the incidence at 10 ppm and that of controls. This resulted in 2 ppm HCl as an estimated concentration at which the incidence of hyperplasia was not significantly different from the controls (68).

13.3 Nitric acid

The *DFG* evaluation of HNO_3 (Germany) concluded in 1992 that the MAK-value should be lowered to 2 ml/m^3 (2 ppm) to protect against irritation of the airways and lungs and be regarded as a provisional value. HNO_3 was classified in category I for the limitation of exposure peaks because it is a local irritant (66).

The *European commission* recommended in 1996 a short-term exposure limit (STEL) of 1 ppm to protect against acute irritation. The limit value was based on the study by Sackner and Ford in which inhalation of 1.6 ppm (4.2 mg/m^3) for 10 minutes was without effects on the pulmonary function in healthy volunteers and an old study from 1907 indicating that humans are more sensitive than cats and rabbits (75).

IPCS summarised the studies of pulmonary response to HNO_3 vapour in sheep (Section 10.2) and in rats (Section 10.3) (118) in 1997. Sheep exposed head-only to 4.12 mg/m^3 for 4 hours showed decreased specific pulmonary flow resistance "indicating the absence of any bronchoconstriction". Effects on alveolar macrophages and elastase inhibitory capacity of bronchoalveolar lavage were seen in rats exposed for 4 hours to 1 mg/m^3, or for 4 hours/day for 4 days to 0.25 mg/m^3.

ACGIH recommended in 2001 a TLV-TWA of 2 ppm and a TLV-STEL of 4 ppm for HNO_3. The values were considered sufficiently low to prevent ocular and upper respiratory tract irritation and also dental corrosion (3).

SCOEL in the European Union recommended an 8-hour TWA of 1 ppm (2.6 mg/m^3) and a STEL of 2 ppm (5.2 mg/m^3) in 2001 (209), based on the ACGIH-document and an abstract from Sackner and Ford (1981, not fully published) (3). Sackner and Ford briefly described a study on healthy volunteers exposed to 1.6 ppm (4.2 mg/m^3) for 10 minutes with no effect on pulmonary function.

13.4 Phosphoric acid

Based on data presented as brief communication to ACGIH, *the European Commission* concluded in 1992 that fumes of phosphorous pentoxide are unlikely to produce significant irritation at concentrations 0.8-5.4 mg/m^3. It was also noted that phosphorous pentoxide is a powerful dehydrating agent combining with atmospheric moisture or in the respiratory tract to produce H_3PO_4. Since this reaction generates heat and desiccates tissues it is likely to cause more tissue damage than pre-formed H_3PO_4. Applying the results of studies on phosphorous pentoxide would therefore supply an adequate margin of safety (74).

Based on analogy from comparable experience and data for H_2SO_4 (they recommended 1 mg/m^3 at the time), *ACGIH* recommended in 2001 a TLV-TWA of 1 mg/m^3 and a TLV-STEL of 3 mg/m^3 for H_3PO_4. The TLV-TWA was said to be below the concentration that causes throat irritation among unacclimated workers (4).

14. Evaluation of human health risks

14.1 Assessment of health risks

Sulphuric, hydrochloric and nitric acids (H_2SO_4, HCl, HNO_3) are strong mineral acids, whereas phosphoric acid (H_3PO_4) is weaker. HNO_3 and H_2SO_4 are also oxidants of which HNO_3 is the stronger. Acute toxicity data (Table 6) suggests that these two acids have a higher acute toxicity than HCl and possibly also than H_3PO_4. All acids are hygroscopic. The more volatile HCl and HNO_3 will appear in air as vapours or aerosols, whereas the less volatile H_2SO_4 and H_3PO_4 will be present in air primarily as aerosols. Droplet size is usually the critical factor governing the site of deposition and hence the respiratory response to the acid aerosols. Industrial aerosols can have MMADs as large as 14 µm (160).

All four acids are direct irritants causing adverse effects at the site of contact. Severe reactions including corrosion and destruction of body tissues from burns leading to ulcers, as well as blindness and death have been described after contact with skin, eyes, and mucous membranes. Repeated or prolonged skin exposure to dilute solutions may cause dermatitis.

There are no data describing dermal absorption but the polarity of the acids suggests little absorption via an intact skin barrier.

Following absorption, the toxic effects of the acids will mainly be from their protolysis, yielding H^+ dissolved in the mucosa. The protons will lower the local pH and induce cell membrane injuries and ulcerations. The anions are essential and enter the body pool. No systemic effects are expected at relevant exposure levels. However, effects from both protons and anions such as acidosis, cyanosis, hyperphosphataemia and hypocalcaemia may occur after excessive exposure.

No sensitising effects have been reported after exposure to any of the acids.

The risk for dental erosion has been shown to increase with increasing concentration of acids or with exposure time and duration of employment.

Low pH has produced positive responses such as clastogenic effects and DNA-damage in some *in vitro* mutagenicity assays. There are no *in vivo* data.

An excess risk of laryngeal cancer has been found among workers exposed to strong inorganic acid mists containing H_2SO_4 and this exposure has also been classified by IARC as carcinogenic to humans (Group 1). It is not possible to conclude as to the carcinogenicity of the other acids.

NOAELs and LOAELs for low-level inhalation exposures are presented in Tables 18-20.

Except for H_2SO_4, the number of studies is limited, and many studies are old. The validity regarding exposure measurements of the acids in both older and in some more recent field studies is uncertain.

Sulphuric acid

H_2SO_4 is hygroscopic enough to char the skin. The reaction with water is rapid and liberates sufficient heat to produce burns similar to thermal burns. The potent dehydrating ability combined with the heat generation means that H_2SO_4 causes more tissue damage than expected from acidity alone.

The effect of H_2SO_4 aerosols on pulmonary defence mechanisms has been investigated in both animals and humans. In some animal studies, tracheo-bronchial mucociliary or alveolar clearance of inert particles has been affected and in humans, an effect on bronchial mucociliary clearance has been reported in several studies. Both decreases and increases in clearance have been observed. The outcome seems to depend on acid dose and the sizes of the H_2SO_4 aerosol droplets (hence of deposition sites) and of the inert test particles, respectively.

Alterations in bronchial mucociliary clearance after single exposures in healthy volunteers were reported at 0.1 mg/m^3 in a few studies (lowest dose tested) and in experimental animals after short- and long-term exposure at the same or even lower levels. Changes in the phagocytic capacity and in biological modifiers critical for maintaining pulmonary immunocompetence (such as reduced super-oxide anion production and TNFα release in pulmonary macrophages) as well as increased hyperresponsiveness have also been observed in animals at these low levels.

In humans, tracheal clearance or tracheal transport rates were affected only in one study in which exposure was to larger droplets (MMAD 10.3 µm).

Cellular changes in the respiratory tract have been shown after H_2SO_4 exposure. Alterations in the nasal mucosa have been observed in workers after long-term exposure at > 0.2 mg/m^3. Epithelial secretory cell hyperplasia in the small airways of rabbits has been reported after long-term exposure to 0.125 and 0.25 mg/m^3 (same daily doses). Minimal squamous metaplasia in ciliated epithelium of the larynx not accompanied by cell proliferation occurred in rats after a 28-day exposure at 0.3 mg/m^3. The severity of the lesions increased after exposure at higher air levels. The changes observed at 0.3 mg/m^3 were regarded as an adaptive response and suggest a risk of respiratory tract epithelial changes following exposures of longer duration. In monkeys, long-term exposure to submicrometer droplets (MMD 0.54 µm) at 0.48 mg/m^3 produced no alterations of pulmonary structures whereas droplets with MMD 2.15 µm at 0.38 mg/m^3 produced slight histological changes (bronchiolar epithelial hyperplasia and thickening of walls of respiratory bronchioles and alveoli) and an increased respiratory frequency, indicating that droplet size was the important factor.

Overall, the above-mentioned results correspond well with data reviewed by Wanner 1996, who concluded that short-term exposure to cigarette smoke, atmospheric pollutants (including H_2SO_4) and oxygen at low to intermediate concentrations/doses may cause transient ciliostimulation, mucous secretion, and stimulation of mucociliary clearance. In contrast, long-term exposure to low to intermediate concentrations or short-term exposure to high concentrations can produce changes of the airway mucosa with disruption of the ciliated epithelium, mucous cell hyperplasia and metaplasia, hypersecretion and impaired clearance.

In healthy volunteers, the LOAEL for upper and lower respiratory symptoms was 0.5 mg/m^3 after a single exposure to large droplets (VMD 10 µm) in a humid atmosphere. Smaller particles (MMAD 0.9 µm) did not induce respiratory symptoms in healthy subjects even at 1 mg/m^3. In occupationally exposed, respiratory and eye irritation were reported at 0.1-0.5 mg/m^3 in one study.

Bronchial hyperreactivity in healthy subjects were demonstrated in a study after a 16-minute exposure to 1 mg/m^3. However, pulmonary function has in general not been affected after single exposures up to 1 mg/m^3 although some studies indicate that asthmatics, especially adolescent asthmatics, may be more vulnerable. Thus, FEV_1 was reduced in asthmatics (13-18 years) exposed for 45 minutes to 0.035 and 0.07 mg/m^3, significantly so at the lower dose. No effect on lung function was seen when the same subjects were exposed for 90 minutes. Exposure to 0.1 mg/m^3 produced significant changes in lung function in 10 adolescent asthmatics after exercise. Thus, the LOAEL for impaired pulmonary function in adolescent asthmatics may be at or even below 0.1 mg/m^3. At the same level (0.1 mg/m^3) impaired pulmonary function was reported in guinea pigs exposed for 1 hour. Enhanced bronchoconstriction was observed in adult asthmatics exposed to 0.45 mg/m^3 at rest, and, following exercise at 0.35 mg/m^3 in combination with low oral

ammonia levels. Other studies have shown no pulmonary function effects in adult asthmatics exposed to up to 1 mg/m^3 or above.

In workers, a reduced FVC was observed at an average exposure to 0.21 mg/m^3 (cumulative exposure above 15 mg/m^3 × months) whereas no effect was seen at an average exposure of 0.10 mg/m^3 (cumulative exposure < 7 mg/m^3 × months).

Tooth etching and erosion in workers has been shown after exposure to approximately 0.2 mg/m^3 and above. At an estimated average exposure of 0.23 mg/m^3, the earliest cases of etching and erosion, respectively, occurred after 4 and 30 months.

An excess risk of laryngeal cancer has been found among workers exposed to strong inorganic acid mists containing H_2SO_4. Although H_2SO_4 was the commonest exposure, the levels of H_2SO_4 were poorly characterised in the studies and the validity regarding past measurements of the acid is uncertain. It is therefore not possible to associate an increased cancer incidence with a particular exposure level.

The development of cancer seems to be secondary to the tissue damage caused by the acid. Thus a threshold is likely, i.e. induction of laryngeal cancer will only occur at exposure levels surpassing the buffering capacity of the epithelial cells.

Hydrochloric acid

The toxicological database is small.

In asthmatics, no airway irritation or pulmonary function changes were reported after exposure to up to 2.5 mg/m^3 for 45 minutes.

In a report not complying with current standards regarding performance and scientific documentation, it was stated that no irritation of the mucous membranes was observed among workers in steel pickling facilities exposed to 3-4.5 mg/m^3 but initial mild irritation of the airway mucosa, which regressed rapidly, at 5.2 mg/m^3. Slight irritation was observed at 7-11 mg/m^3 and breathing difficulties at 26-34 mg/m^3. In the same report, it was also stated that no damage to the teeth occurred at average concentrations of 4.5-7.7 mg/m^3. Dental erosion was indicated in a study of workers (prevalence 90 %) where average exposure levels ranged from 1.8 to 12.4 mg/m^3. The lack of control group, however, weakens the result.

Hyperplasia in larynx and trachea, but no cancer, was reported after life-time exposure of male rats at 14 mg/m^3 HCl, the only level tested. Incidences of laryngeal and tracheal hyperplasia were 22 % and 26 %, respectively, compared with 2 % and 6 % among the controls.

Nitric acid

The documentation of health effects from exposure to HNO_3 is scarce.

Pulmonary function parameters were not affected in adolescent asthmatics inhaling a combination of 0.125 mg/m^3 HNO_3, 0.12 ppm O_3 and 0.30 ppm NO_2 for 90 minutes via a mouthpiece.

In healthy volunteers, NOAELs for effects on pulmonary function and inflammatory response was reported after exposure to 0.5 mg/m^3 HNO_3 for 4 hours, the only level tested, and after a similar exposure for 2 hours at 0.4 mg/m^3.

Following a 2-hour exposure to 0.2 mg/m^3 HNO_3, defence functions of alveolar macrophages were affected (increased phagocytic activity and resistance to infection, decreased superoxide anion production) (25).

Like for H_2SO_4, the lowest reported effect levels after short- or long-term exposure in animals relate to pulmonary defence mechanisms. At 0.05-0.25 mg/m^3, reduced level/production of superoxide anion and TNFα activity in alveolar macrophages, increased elastase inhibitory capacity of lung lavage fluid, reduced bronchial responsivity to smooth muscle constrictor challenge and elevated stress-inducible heat shock protein 70 were observed. Heat-shock proteins are highly active within the immune system (168) but the relevance of this latter finding is unclear.

Irritation of the airways seen as bronchoconstriction in sheep exposed to 4.1 mg/m^3 for 4 hours is reported.

In an old study based on only 2 individuals, exposure to 27-30 mg/m^3 for more than 1 hour was considered intolerable and dangerous to human health.

Phosphoric acid

No relevant studies were identified. Severe effects including death have been reported after excessive exposure.

14.2 Groups at extra risk

Data indicate that asthmatics, especially adolescent asthmatics are more susceptible to respiratory effects from H_2SO_4 exposure.

Incidents with extremely polluted air containing H_2SO_4 aerosols have caused increased mortality, e.g. among persons with chronic respiratory tract disease.

Subjects with chronic bronchitis and smokers may be at extra risk, but little is known about their susceptibility to the four acids.

14.3 Scientific basis for an occupational exposure limit

Sulphuric acid

The toxicological databases from short- and long-term animal and human exposures are quite consistent although a clear-cut overall NOAEL is difficult to identify from the available data.

Based on short- and long-term exposure data in both animals and humans, the critical effects are effects on bronchial mucociliary clearance, pulmonary function, and airway and eye irritation. The effects appear at approximately 0.1 mg/m^3. The impairment of pulmonary function at this level has been observed in adolescent asthmatics. At slightly higher levels, dental erosion, and pathological changes in the nasal mucosa have been reported in humans. In animals, cellular changes of the respiratory tract epithelium have occurred in rats, rabbits and monkeys at repeated exposure to concentrations in the range 0.125-0.38 mg/m^3. An excess risk of laryngeal cancer has been found among workers exposed to strong inorganic acid mists containing H_2SO_4. The development of laryngeal cancer from

H_2SO_4 exposure is likely to have a threshold and thought to be secondary to local irritation and damage of the respiratory epithelium. Damage to the respiratory tract epithelium resulting in cancer development is unlikely at exposure levels below those affecting mucociliary clearance.

The reliable measurement of exposure around the lowest effect levels is non-problematic for 8-hour samplings when only H_2SO_4 aerosol is present, but challenging when sampling times are short.

Hydrochloric acid

The critical effect is airway irritation. Initial mild irritation of the airway mucosa, which regressed rapidly, was reported at 5 mg/m^3 (LOAEL) in workers. No airway irritation was observed at 2.5 mg/m^3 (NOAEL) in asthmatics exposed 45 minutes.

Tracheal and laryngeal hyperplasia observed after chronic exposure of rats at 14 mg/m^3 is regarded secondary to airway irritation in analogy with H_2SO_4.

A higher prevalence of dental erosion among battery and galvanising workers exposed to H_2SO_4 and HCl has been found but the HCl level at which it appears is not known.

Nitric acid

There is a general lack of data that could serve as the scientific basis for an occupational exposure limit for HNO_3.

In healthy volunteers, a NOAEL for effects on pulmonary function and inflammatory response was reported after exposure to 0.5 mg/m^3 HNO_3 for 4 hours, the only level tested. Following a 2-hour exposure to 0.2 mg/m^3, results indicating a stimulatory as well as an inhibitory effect on the defence functions of alveolar macrophages were obtained.

Based on animal acute toxicity data, the potency of HNO_3 seems to be similar to that of H_2SO_4.

Phosphoric acid

No relevant studies that could serve as the basis for an occupational exposure limit have been identified.

The assessment must be based on the conclusion made by the European commission in 1992 that fumes of phosphorous pentoxide at concentrations 0.8-5.4 mg/m^3 are unlikely to produce significant irritation. It was also noted that phosphorous pentoxide is a powerful dehydrating agent combining with atmospheric moisture or in the respiratory tract to produce H_3PO_4 in a reaction generating heat and is likely to cause more tissue damage than H_3PO_4 itself. Thus, applying the NOAEL for irritation for phosphorous pentoxide would supply an adequate margin of safety.

15. Research needs

- Repeated inhalation exposure studies on HCl, HNO_3 and H_3PO_4 in animals and human volunteers focusing on pulmonary function, sensory irritation, respiratory effects and, in addition, animal studies on cytotoxicity and laryngeal cancer.
- Epidemiological studies on dental etching and erosion, pulmonary effects and laryngeal cancer with better exposure data, or the assessment of past exposure by developing job-exposure matrices in relevant industries.
- Studies of the mechanism behind the carcinogenic effect of strong inorganic mists containing H_2SO_4.

16. Summary

van der Hagen M, Järnberg J. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 140. Sulphuric, hydrochloric, nitric and phosphoric acids.* Arbete och Hälsa 2009;43(7):1-122.

Sulphuric, hydrochloric, nitric and phosphoric acids are common inorganic or mineral acids. The first three acids are strong, whereas phosphoric acid is weaker. They are all important industrial chemicals used in a variety of applications, e.g. in the manufacture of chemicals and metal or food products. The relatively non-volatile sulphuric and phosphoric acids will occur in air primarily as aerosols and the more volatile hydrochloric and nitric acids as vapours or aerosols. Following absorption, the toxic effects of the acids will be mainly from protolysis yielding protons in the mucosa. The reaction between sulphuric acid and water generates heat.

Except for sulphuric acid, the toxicological database is poor or very poor.

The acids are corrosive and will cause chemical burns when in contact with eyes, skin and mucous membranes. Acid vapours and aerosols are respiratory tract irritants and may cause pulmonary impairment, as well as dental erosion, and laryngeal cancer.

Sulphuric acid: The critical effects are alterations in bronchial mucociliary clearance, lung function effects and airway and eye irritation. The effects begin to appear at approximately 0.1 mg/m^3 in humans. At slightly higher levels, dental erosion and pathological changes of the nasal mucosa have been reported. Cellular changes of the respiratory tract epithelium have been observed in animals after repeated exposures to concentrations in the range 0.125-0.38 mg/m^3. An excess risk of laryngeal cancer has been found among workers exposed to strong inorganic acid mists containing H_2SO_4. The mechanism of laryngeal cancer from acid mist exposure seems to be secondary to the local airway irritation caused by the acid.

Hydrochloric acid: The critical effect is airway irritation. No airway irritation at 2.5 mg/m^3 was reported in asthmatics but mild irritation, which regressed rapidly, at 5 mg/m^3 in workers. Tracheal and laryngeal hyperplasia observed in animals after chronic exposure to 14 mg/m^3 is regarded secondary to airway irritation in analogy with sulphuric acid.

Nitric acid: There is a general lack of data. In healthy volunteers, no effects on pulmonary function and inflammatory response were noted after a single exposure to 0.5 mg/m^3 but defence functions of alveolar macrophages were affected at 0.2 mg/m^3. The potency of nitric acid seems to be similar to that of sulphuric acid.

Phosphoric acid: As data are lacking, the assessment has to be based on comparison with the stronger irritant phosphorous pentoxide, which is converted to the acid in the airways.

Keywords: aerosol, hydrochloric acid, hyperplasia, irritation, laryngeal cancer, nitric acid, occupational exposure limit, phosphoric acid, respiratory tract, review, risk assessment, sulphuric acid, toxicity

17. Summary in Norwegian

van der Hagen M, Järnberg J. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 140. Sulphuric, hydrochloric, nitric and phosphoric acids.* Arbete och Hälsa 2009;43(7):1-122.

Svovelsyre, saltsyre, salpetersyre og fosforsyre er vanlige uorganiske syrer (mineralsyrer). De er alle viktige industrikjemikalier i bruk til ulike formål som produksjon av industrikjemikalier, metaller og matvarer. Alle unntatt fosforsyre er sterke syrer. Svovelsyre og fosforsyre er mindre flyktige og finnes primært som aerosoler. Saltsyre og salpetersyre er mer flyktige og kan forekomme som damp eller aerosol. Etter at stoffene er absorbert er den toksiske virkningen knyttet til proteolyse og frigjøring av protoner i slimhinnen. Reaksjonen mellom svovelsyre og vann frigjør varme.

Databasen har tilstrekkelig informasjon om svovelsyre, mens det er lite informasjon om de andre syrene. De er etsende og kan føre til kjemiske brannskader når de kommer i kontakt med øyne, slimhinner og hud. Syredamper og aerosoler kan føre til irritasjon i luftveiene og nedsatt lungefunksjon. Det er også dokumentert økt risiko for tannerosjon og strupekreft.

Svovelsyre: Kritiske effekter er endringer i slimheisfunksjonen, lungefunksjon, samt irritasjon i luftveier og øyne. Disse fremkommer ved eksponeringer omkring 0,1 mg/m^3. Ved litt høyere konsentrasjoner oppstår tannerosjoner og vevsforandringer i neseslimhinnen, Celleskade i respiratorisk epitel oppstår hos dyr eksponert for 0,125-0,38 mg/m^3. Det er påvist økt risiko for kreft i strupen blant arbeidere eksponert for sterk uorganiske tåke som inneholder H_2SO_4. Mekanismen for kreftutviklingen synes å være sekundær til luftveisirritasjonen forårsaket av syren.

Saltsyre: Kritisk effekt er luftveisirritasjon, rapportert som mild og raskt forbigående hos arbeidstakere ved en konsentrasjon på 5 mg/m^3. Ingen irritasjon ble vist hos astmapasienter ved 2,5 mg/m^3. Fortykkelse av slimhinnen i hovedluftrør og strupe ble påvist ved kronisk eksponering for 14 mg/m^3, bedømt som sekundært til luftveisirritasjon.

Salpetersyre: Det er få data i litteraturen. Hos en gruppe friske frivillige ble det ikke påvist utfall i lungefunksjon eller betennelsesrespons etter en engangseksponering på 0,5 mg/m^3. Det ble også påvist endringer i alveolare makrofagers forsvarsevne ved 0,2 mg/m^3. Evnen til å forårsake effekt synes sammenliknbar med svovelsyre.

Fosforsyre: Det finnes ikke data som gir grunnlag for å vurdere kritisk effect. I dette dokumentet er det foreslått å vurdere den i forhold til den sterkere irritanten fosforpentoksid som omdannes til syre i luftveiene.

Nøkkelord: administrative norm, aerosol, fosforsyre, hyperplasi, irritasjon, luftveier, review, risikovurdering, salpetersyre, saltsyre, strupekreft, svovelsyre, toksisitet

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19. Data bases used in the literature search

The major literature searches were performed in January 2006. The following databases were used:

Arbline
Cheminfo
CISDOC
HSELINE
MHIDAS
NIOSHTIC2
OSHLINE
PubMed
RILOSH
RTECS
Toxline

A final search in PubMed and Toxline was performed on October 29, 2008.

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Appendix 1. Occupational exposure limits

Occupational exposure limits (mg/m^3) for the inorganic acids in different countries as time-weighted averages.

Country	Sulphuric acid		Hydrochloric acid		Nitric acid		Phosphoric acid		Reference
	8-h	STEL	8-h	STEL	8-h	STEL	8-h	STEL	
Denmark	1	2	7 [a]	-	1.3	2.6	1	2	(1)
Finland	0.2	1	-	7.6	1.3	2.6	1	2	(2)
Germany (DFG)	0.1 [b]	0.1 [b] 0.2 [a, b]	3	6	-	-	2 [b]	4 [b]	(3)
The Netherlands	-	-	8	15	-	1.3	1	2	(4)
Norway	0.1	0.3	7 [a]	-	5	10	1	3	(5)
Sweden	1	3	8 [a]	-	5	13	1	3	(6)
United Kingdom	-	-	2	8	-	2.6	1	2	(7)
US (ACGIH)	0.2 [c]	-	-	2.8 [a]	5	10	1	3	(8)
US (NIOSH)	1	-	7 [a]	-	5	10	1	3	(9)
US (OSHA)	1	-	7 [a]	-	5	-	1	-	(9)
EU	-	-	8	15	-	2.6	1	-	(10, 11)

[a] Ceiling value.
[b] Inhalable fraction.
[c] Thoracic fraction.
STEL: short-term exposure limit, OSHA: Occupational Safety and Health Administration.

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Appendix 2. Previous NEG criteria documents

NEG criteria documents published in the scientific serial Arbete and Hälsa (Work and Health):

Substance/Agent	*Arbete och Hälsa issue*
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium	1992:45, 1993:1*
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*

Substance/Agent	*Arbete och Hälsa issue*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7

Substance/Agent	*Arbete och Hälsa issue*
Phenol	1984:33
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

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D = collaboration with the Dutch Expert Committee on Occupational Standards (DECOS).
N = collaboration with US NIOSH.

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