Probit function technical support document

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substance name	CAS number
Sulfuric Acid **Sulfur trioxide** **Oleum**	**7664-93-9** **7446-11-9** **8014-95-7**

This draft document describes the derivation of a probit function for application in a quantitative risk analysis (QRA).

This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM), and has been assigned the status "proposed". The document is open for discussion by the scientific expert panel on probit functions. Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the e-mail address mentioned above.

If the proposed probit function is approved by the expert panel on scientific grounds, the status of the document and probit function will be raised to "interim".

Subsequently, a committee of governmental representatives will perform a second tier evaluation to decide whether the probit function will be formally implemented. The decision on actual implementation will primarily be based on the results of a consequence analysis.

Detailed information on the procedures for derivation, evaluation and formalization of probit functions is available at http://www.rivm.nl/milieuportaal/bibliotheek/databases/probitrelaties.jsp.

Technical support document Sulfuric Acid

1 Substance identification

CAS-number:	7664-93-9 Sulfuric acid
	7446-11-9 Sulfur trioxide
	8014-95-7 Oleum
IUPAC name:	sulfuric acid
Synonyms:	battery acid, hydrogen sulphate
Molecular formula:	H_2SO_4
** *All physical-chemical data below are for sulfuric acid* **	
Molecular weight:	98.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	330 °C (at 101.3 kPa)
Vapour pressure:	0.0001 kPa (at 20°C)
Saturated vapour conc:	1.0 ppm = 4.08 mg/m^3 (at 20°C and 101.3 kPa)
Conversion factor:	1 mg/m^3 = 0.245 ppm (at 20°C and 101.3 kPa)
	1 ppm = 4.08 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	R: 35

2 Mechanism of action and toxicological effects following acute exposure[1]

Special considerations: Studies of the thermodynamics of clouds generated from spills of SO_3 and oleum (H_2SO_4 containing up to 80% free SO_3) found that while the conversion from SO_3 to H_2SO_4 is very fast, that the content of atmospheric moisture immediately above the pool is insufficient for complete and rapid reaction to sulfuric acid mist. Close to the source clouds will contain SO_3 vapour, H_2SO_4 vapour and H_2SO_4 aerosol. Typically some 50-100 m downwind from the source only sulfuric acid will be present in the aerosol cloud (Kapias and Griffiths 1999).
The probit function in this document is for the sulphuric acid aerosol that ultimately results from an airborne release of any of these 3 substances.
Species specificity: Guinea pigs are far more susceptible to pulmonary damage by sulfuric acid inhalation than other species (mice, rats, monkeys, rabbits). Guinea pigs respond with a reflex airway constriction, mediated by the parasympathetic nervous system. Other effects, in particular desquamation of terminal bronchiolar epithelium in guinea pigs, are related to these parasympathetic reflexes. It was found that sulfuric acid strongly affects the alveolar surface tension in guinea pigs but not in rats, and they suggest that neurogenic inflammation could be involved which may also lead to a potent bronchoconstrictive response (NAC/AEGL, 2008).
For these reasons, the guinea pig is considered not to be a suitable animal model to predict the acute health effects of sulfuric acid inhalation in humans. Therefore, the results of an extensive body of studies in guinea pigs (other than the Treon 1950 study, B1) were not included in this document.
Acute effects: The main target organs and tissues for inhalation exposure to H_2SO_4 are the cornea, conjunctiva, skin and respiratory tract. H_2SO_4dissolves in the mucous membranes of the respiratory tract and eyes to form hydrochloric acid, a strong acid that produces coagulative necrosis. The health endpoints are all related to the irritative and corrosive properties of H_2SO_4. Symptoms of high exposure are laboured breathing, secretions from nose, mouth and eyes and prostration.

[1] Interim AEGL TSD for Sulfuric Acid Dec 2008, AHLS Provider manual 3rd ed.

Damage occurs in the respiratory system, particularly the upper respiratory tract resulting in mucus secretion, upper airway and/or pulmonary oedema and laryngospasm. The resulting hypoxemia will cause CNS and cardiovascular (myocardial ischemia) effects. Lethality results when the respiratory damage proceeds to inflammation, degeneration and necrosis of affected tissue, atelectasis, emphysema and finally death.

Long-term effects: Chronic exposure produces essentially the same type of health effects. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition has been described to develop after single exposure to H_2SO_4. Symptoms occur within minutes to hours after the initial exposure and may persist as non-specific bronchial hyper-responsiveness for months to years. IARC classifies sulphuric acid as carcinogenic to humans (Group 1).

3 Human toxicity data

No reliable and informative studies with details about both human exposure as well as lethality have been identified and described. There is a wealth of human inhalation studies in the lower exposure ranges.

4 Animal acute toxicity data

Animal lethal toxicity data considering acute exposure are described in Appendix 1. A total of 4 studies were identified -with 8 relevant datasets for 4 species- with data on lethality following acute inhalation exposure. Two datasets have been assigned with status A for deriving the human probit function, 5 datasets with status B and 1 has been assessed to be unfit (status C) for human probit function derivation.

During a literature search the following technical support documents and databases have been consulted:

1. AEGL interim TSD and ERPG documents and reference database for sulfuric acid, covering references before and including 1995.
2. An additional search covering publications from 1980 - 2008 was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, RTECS, with the following search terms:
   - Sulfuric acid and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

Sensory irritation

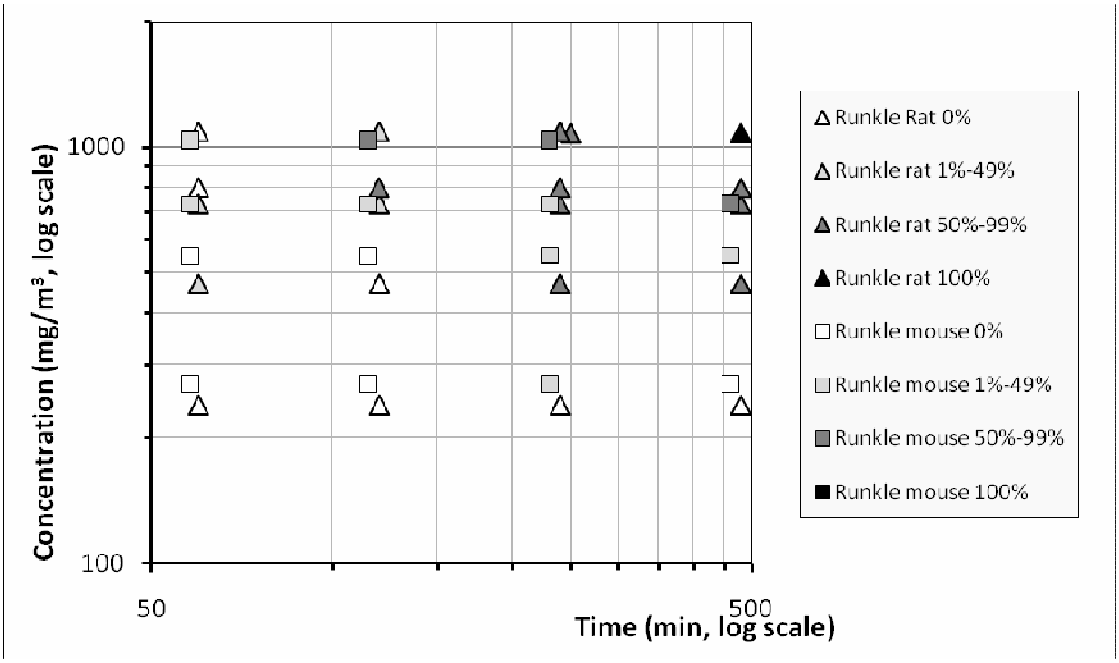
No studies were identified in which sensory irritation of sulfuric acid, sulphur trioxide or oleum was studied.

5 Probit functions

Probit functions have been calculated and reported in Appendix 1 for each of the reported studies. Below the results of the calculations can be found.

Study ID	*Species*	*Probit (C in mg/m³, T in min)*	*LC_{50}, 30 minutes (mg/m³) 95% C.I.*
A.1	*Rat*	*-12.46 + 1.63 ×lnC + 1.28× lnt*	*3083 (1927 - 6600)*
A.2	*Mouse*	*-13.35 + 2.16 ×lnC + 0.72× lnt*	*1573 (1165 - 2441)*

The data of the 2 A studies with rats and mice are presented graphically below.



6 Evaluation

To derive the human probit function the results from Runkle and Hahn (1976, study A.1) have been used to derive a point of departure. This was the only available A study in rats.

As point of departure for deriving the human probit function the 30 min LC_{50} value of 3083 mg/m³ for the rat from the Runkle and Hahn (1976) study was taken. The human equivalent LC_{50} was calculated by applying the following assessment factors:

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	
RD_{50}	1	No RD_{50} data available
Nominal concentration	1	Analytical concentrations available
Adequacy of database:	1	Sufficiently well conducted study

The estimated human equivalent 30-minute LC_{50} value is 3083 / 3 = **1028 mg/m^3**.

The experimentally determined n-value was **1.27 (Runkle and Hahn, 1976)**. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.58**.

The human probit function is then calculated on the human equivalent 30 min LC_{50} and using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.58 \times \ln (1028^{-1.27} \times 30)$ resulting in the a-value of **-14.23**.

$Pr = -14.2 + 1.6 \times \ln (C^{1.3} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically sound basis. The probit function is based on 1 study in the rat with A quality, including 168 animals in 21 concentration-time combinations ranging from 1 to 8 hours.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 143 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 99 mg/m^3.

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
1% lethality, this probit	244	143
0.1% lethality, this probit	169	99
AEGL-3 (2008, interim)	200	160
ERPG-3 (1989)		30
LBW (2007)		20

Comparing to equivalent (inter)national guideline levels as presented in the table above, the derived probit function are in good accordance with the AEGL values which are based on the mouse data from the same study (Runkle and Hahn 1996). The ERPG-3 and LBW are much lower, since they appear to be based on guinea pig lethality data. Guinea pig data have been disqualified for probit development because the validity of the guinea pig model for human lethality is questionable.

Appendix 1 Animal experimental research

Study ID: A.1

Author, year: Runkle and Hahn, 1976

Substance: Sulfuric acid

Species, strain, sex: male and female Fischer F344 rats

Number/sex/concentration group: 4 animals/sex/group

Age and weight: 6-7 weeks old, weight unspecified

Observation period: 21 days

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*Insufficient details to assess compliance with (then non existing) OECD guideline 403*
Stability of test compound in test atmosphere	*Aerosol formation present*
Use of vehicle (other than air)	*Air, relative humidity maintained at 40%*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body.*
Pressure distribution.	*No information provided.*
Homogeneity of test atmosphere at breathing zone of animals	*SO_3 gas was mixed with humid air to produce H_2SO_4 droplets.*
Number of air changes per hour	*Air flow was 10 cubic feet/min (17 m^3/h) into a 27-inch Rochester chamber (approx volume 410 ℓ), which equals 41 air changes/h.*
Actual concentration measurement	*Not exactly specified. In two elaborate studies describing the atmosphere generation system and chamber airflow distribution (resulting in modifications to the chambers to achieve a uniform concentration distribution), actual concentrations were determined with a wet-bench method as well as conductivity measurements after concentration of aerosol in a Mercer cascade impactor.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Approximately 1.1-1.4 µm MMAD (GSD 1.6-2.2)*
Assessment of Reliability	***A***

Lethality occurred over the whole observation period, with some animals dying more than 14 days after exposure.

157 **Results**
158

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			exposed	fatal
Rat	240	60	8	0
	240	120	8	0
	240	240	8	0
	240	480	8	0
	470	60	8	1
	470	120	8	0
	470	240	8	5
	470	480	8	7
	730	60	8	1
	730	120	8	3
	730	240	8	5
	730	480	8	7
	800	60	8	0
	800	120	8	5
	800	240	8	6
	800	480	8	7
	1080	240	8	7
	1080	480	8	8
	1090	60	8	0
	1090	120	8	3
	1090	240	8	5

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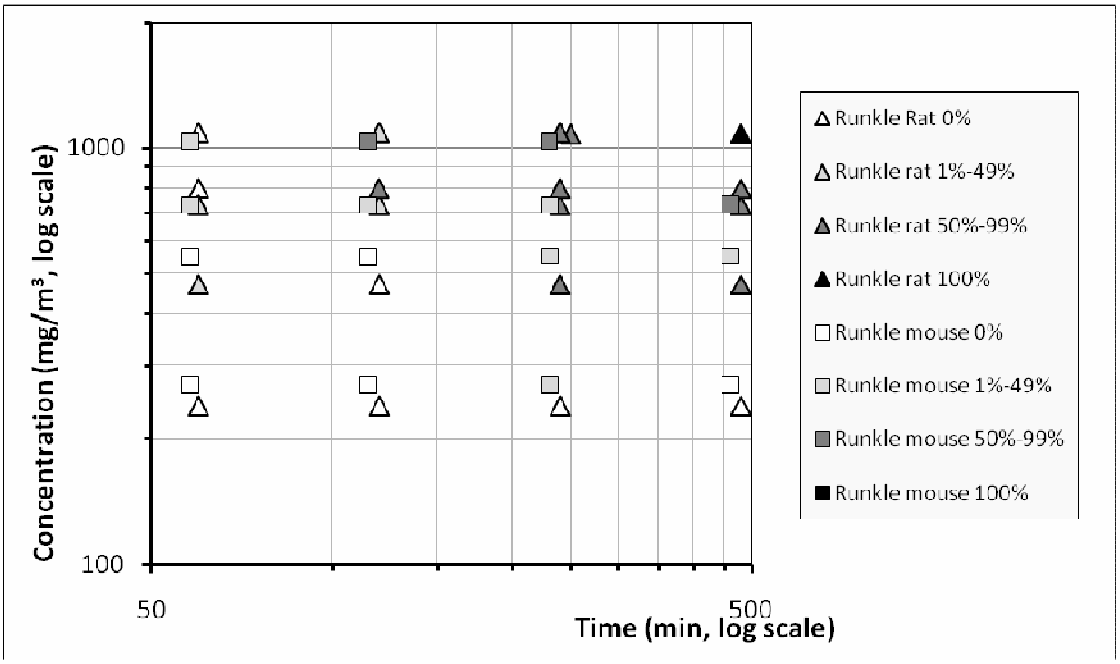
161 **Probit function**
162 The probit function and associated LC-values have been calculated using the
163 DoseResp program by Wil ten Berge (version December 2006) as
164 $Pr = a + b \times \ln C + c \times \ln t$
165 with C for concentration in mg/m^3 and t for time in minutes.
166

Probit function	*Species*	*A*	*b*	*c*	*d*	*n-value*
Sexes combined	*Rat*	*-12.46*	*1.63*	*1.28*		*1.27 (0.82 - 1.73)*

167
168 There is no information on sex differences in the response.
169

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***Combined***
10	7303 (3542 - 23690)
30	3083 (1927 - 6600)
60	1789 (1304 - 2965)

A graphical overview of the data is presented below. Each concentration-time combination (with 4 male and 4 female rats) represents one point in the plot. Mouse data (study A.2) are also plotted.



Study ID: A.2

Author, year: Runkle and Hahn, 1976

Substance: Sulfuric acid

Species, strain, sex: male and female CD-1 mice

Number/sex/concentration group: 5-7 animals/sex/group

Age and weight: 6-7 weeks old, weight unspecified

Observation period: 21 days

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*Insufficient details to assess compliance with (then non existing) OECD guideline 403*
Stability of test compound in test atmosphere	*Aerosol formation present*
Use of vehicle (other than air)	*Air, relative humidity maintained at 40%*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body.*
Pressure distribution.	*No information provided.*
Homogeneity of test atmosphere at breathing zone of animals	*SO_3 gas was mixed with humid air to produce H_2SO_4 droplets.*
Number of air changes per hour	*Air flow was 10 cubic feet/min (17 m^3/h) into a 27-inch Rochester chamber (approx volume 410 ℓ), which equals 41 air changes/h.*
Actual concentration measurement	*Not exactly specified. In two elaborate studies describing the atmosphere generation system and chamber airflow distribution (resulting in modifications to the chambers to achieve a uniform concentration distribution), actual concentrations were determined with a wet-bench method as well as conductivity measurements after concentration of aerosol in a Mercer cascade impactor.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Approximately 0.85-2.0 µm MMAD (GSD 1.6-2.0)*
Assessment of Reliability	***A***

Most of the fatalities occurred during exposure or 1-2 days afterwards.

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			exposed	fatal
Mouse	270	60	10	0
	270	120	10	0
	270	240	10	1
	270	480	10	0
	550	60	10	0
	550	120	10	0
	550	240	10	2
	550	480	10	4
	730	60	10	3
	730	120	10	1
	730	240	10	3
	730	480	10	7
	1040	60	12	4
	1040	120	14	8
	1040	240	14	11

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program by Wil ten Berge (version December 2006) as

$Pr = a + b \times \ln C + c \times \ln t$

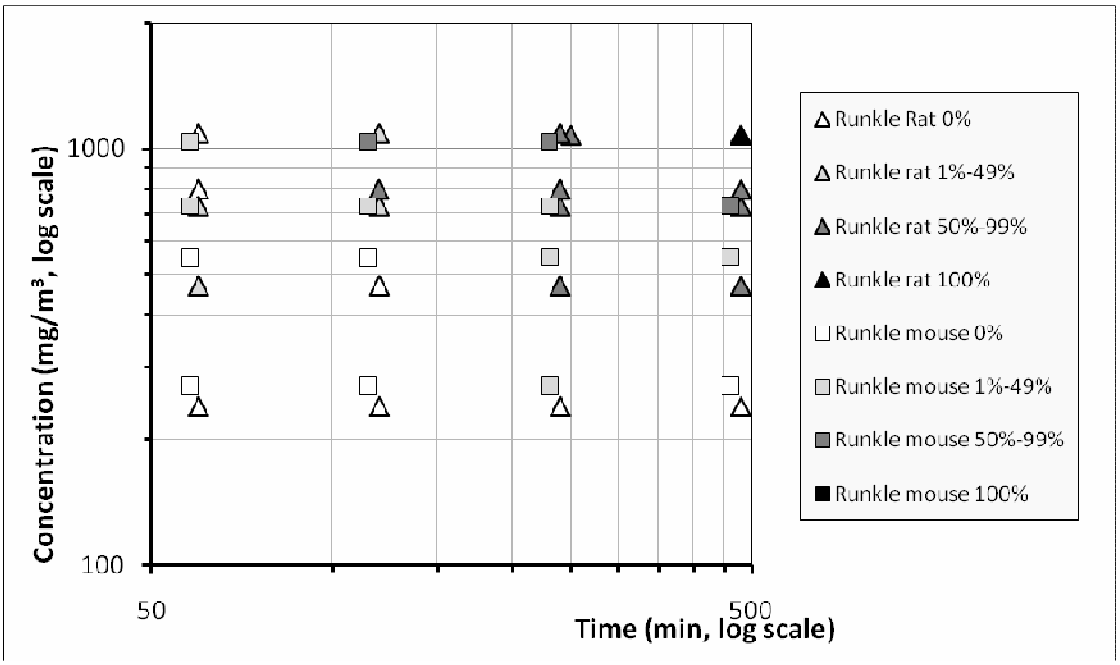
with C for concentration in mg/m^3 and t for time in minutes.

Probit function	*Species*	*a*	*b*	*c*	*d*	*n-value*
Sexes combined	*Rat*	*-13.35*	*2.16*	*0.72*		*3.00 (1.51 - 4.50)*

There is no information on sex differences in the response.

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***Combined***
10	2268 (1428 - 4363)
30	1573 (1165 - 2441)
60	1249 (1017 - 1705)

A graphical overview of the data is presented below. Each concentration-time combination (with 5-7 male and 5-7 female mice) represents one point in the plot. Rat data (study A.1) are also plotted.



Study ID: B.1

Author, year: Treon 1950

Substance: Sulfuric acid mist

Species, strain, sex: guinea pig, mouse, rat and rabbit, sex and strain unspecified

Number/sex/concentration group: usually 2-3 guinea pigs, 5 mice, 2 rats and 2 rabbits

Age and weight: unspecified

Observation period: unspecified; publication mentions time of death at 5 days post exposure, as well as sacrifice 48 hours after the last period of exposure (may apply only for repeated exposure regimens)

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*Insufficient details to assess compliance with (then non existing) OECD guideline 403*
Stability of test compound in test atmosphere	*Aerosol formation present (i.e. generated)*
Use of vehicle (other than air)	*Air, relative humidity not controlled*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body. It appears that 2-3 guinea pigs, 5 mice, 2 rats and 2 rabbits were exposed simultaneously.*
Pressure distribution.	*No information provided.*
Homogeneity of test atmosphere at breathing zone of animals	*Aerosols were generated by spraying compressed air through an orifice fed with an aqueous solution (10-60%) through a capillary. A 'large fan' circulated the test atmosphere in the exposure chamber.*
Number of air changes per hour	*3.2-34.5 ℓ/min in a 223 ℓ chamber, which equals 0.86-9.3 air changes/h.*
Actual concentration measurement	*Sampling location unspecified. Six samples for 7 hour periods, 3-4 samples for 1-3 hour periods and 2 samples for 30 minute periods. Material was collected in a 2-stage absorption train and analysed photometrically (after chemical reaction with BaCl) and acidity.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Diameter of 93-99% of the particles was < 2 µm as determined with thermal precipitation.*
Assessment of Reliability	***B*** *Difference in H_2SO_4 concentration of test material which results in different particle sizes, uncertain homogeneity and low exchange rate of test atmosphere. Insufficient number of tested exposure durations.*

Results

Concentration (mg/m^3)	Exposure duration (min)	Lethality			
		Guinea pig	Mouse	Rabbit	Rat
1610	420		3/5	1/2	2/2
1470	210		2/5	1/2	2/2
699	420		2/5	0/2	2/2
715	210		3/5	0/2	0/2
549	210		2/5	0/2	0/2
461	420		0/5	0/2	0/2
218	420	2/2	0/5	0/2	0/2
190	420	3/3	0/5	0/2	0/2
206	180	2/3			
178	60	2/3			
178	30	1/2			
165	15	1/2			
121	60	0/3			
120	30	0/3			
116	15	0/3			
90	165	3/3	0/5	0/2	0/2

Probit function

The probit function and associated LC-values have been calculated for each species using the DoseResp program by Wil ten Berge (version December 2006) as

$Pr = a + b \times \ln C + c \times \ln t$

with C for concentration in mg/m^3 and t for time in minutes.

For rats and rabbits the probit function could not be estimated. The probit functions for guinea pigs and mice were meaningless, with non-physiological results (such as negative n-values) and a large variance that did not allow to calculate confidence intervals.

The extrapolation far beyond the range of the actual data required to calculate LC_{50} values in the 10-60 minute range renders these LC_{50} values almost meaningless. Therefore such LC_{50} values were not calculated.

Study ID: B.2

Author, year: Zwart 1984

Substance: Sulfuric acid mist

Species, strain, sex: Male Wistar rats

Number/sex/concentration group: 10 animals per group

Age and weight: age unspecified, average weight 172 grams

Observation period: 14 days post exposure

Criteria	*Comment*
Study carried out according to GLP	*GLP statement provided*
Study carried out according to guideline(s)	*No statement of compliance with OECD guideline 403 provided. Many conditions prescribed in the guideline appear to be met.*
Stability of test compound in test atmosphere	*Test atmosphere was generated as an aerosol.*
Use of vehicle (other than air)	*Air saturated with water*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body, individually placed in 700mℓ glass tubes*
Pressure distribution.	*No information on pressure distribution provided.*
Homogeneity of test atmosphere at breathing zone of animals	*Test atmosphere was generated by passing saturated air through a nebulizer fed with 97% H_2SO_4. Large particles were removed with a cyclone. The sulphuric acid content in the mist was approximately 56%.*
Number of air changes per hour	*Flow was 2 ℓ/min/animal from a centrally generated sulphuric acid mist, or about 170 air changes/h.*
Actual concentration measurement	*5-11 samples per exposure period were taken at an unspecified location.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Particle size was not determined.*
Assessment of Reliability	***B*** *Insufficient number of concentration-time combinations to calculate a reliable probit function, particle size not determined, information derived from a secondary source*

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			exposed	fatal
Rat	3540	60	10	5
	3610	150	10	7
	3870	105	10	10
	3940	60	10	9

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program by Wil ten Berge (version December 2006) as

$Pr = a + b \times \ln C + c \times \ln t$

with C for concentration in mg/m^3 and t for time in minutes.

Probit function	*Species*	*a*	*b*	*c*	*n-value*
Males	*Rat*	*-122*	*15.3*	*0.46*	*33.1 (-52.3 - 118)*

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***Male***
10	3753 (2994 - 4962)
30	3630 (3137 - 4082)
60	3555 (2930 - 3623)

While the data allowed to calculate a concentration-time-response probit function, the model fit was poor, the n-value unrealistically high. Extrapolation beyond the range of observation is not recommended, and only provided for the sake of consistency.

Study ID: C studies

In a publication with toxicological data on many chemicals Vernot (1977) reported 1-hour LC_{50} values for sulphuric acid of 1714 mg/m^3 for males and 1416 mg/m^3 for females. Many relevant details of the study design were not provided.

Appendix 2 Reference list

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