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Probit function technical support document

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substance name	CAS number
Hydrogen Fluoride	**7664-39-3**

This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have had the opportunity to comment on the derivation of the proposed probit function. The status of this document has now been raised to "interim", pending a decision on its formal implementation.

The decision on actual implementation depends on the results of a further consequence analysis.

Detailed information on the procedures for the derivation, evaluation and formalization of probit functions is available at
http://www.rivm.nl/en/Topics/P/Probit_functions

Technical support document Hydrogen Fluoride

1. Substance identification

CAS-number:	7664-39-3
IUPAC name:	hydrogen fluoride
Synonyms:	hydrofluoric acid (anhydrous form), fluorine, fluoride
Molecular formula:	HF
Molecular weight:	20 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	19.5°C (at 101.3 kPa)
Vapour pressure:	103 kPa (at 20°C)
Saturated vapor conc:	N/A (gas at 20°C)
Conversion factor:	1 mg/m^3 = 1.20 ppm (at 20°C and 101.3 kPa)
	1 ppm = 0.83 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H300-310-314-330

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

Acute effects: The main target organs and tissues for inhalation exposure to hydrogen fluoride are the respiratory tract and the epithelial tissues, as well as the heart. The health endpoints are irritation of the airways, eye irritation, headache, coughing, shortness of breath, and nausea. Symptoms of high exposure are severe irritation, oedema, and lung haemorrhages. Fluoride sequesters calcium, and produces systemic hypocalcaemia, hypomagnesemia and hyperkalaemia with the associated cardiac dysrhythmias. Deaths were attributed to pulmonary oedema and cardiac arrhythmias. It should be noted that airborne exposure may also result in severe dermal lesions and electrolyte imbalance due to dermal fluoride uptake.
Long-term effects: Chronic exposure produces similar effects as observed from short term exposures. Short term exposures could result in long term effects due to tissue damage in the lungs.

3. Human toxicity data

No informative reports on health effects in humans following acute inhalation exposure were identified. Such reports are considered informative if both health effects as well as the exposure have been documented in sufficient detail.

Accident reports as well as human volunteer studies with HF are available. Cited from the AEGL document on HF: “Three documented cases of accidental release of HF were located. A fourth accident was cited in an EPA (1993) report. Over a 48-h period, approximately 24,000 kg of anhydrous HF and 3000 kg of isobutane were released from a petrochemical plant in Texas in October, 1987 (Wing et al. 1991). Outdoor samples taken downwind (distance not stated) 1 h after the release contained 10 ppm HF (8.3 mg/m^3); samples obtained after 2 h contained “minimal traces” of HF. The most prevalent symptoms were eye irritation (41.5%), throat burning (21.0%), headache (20.6%), shortness of breath (19.4%), throat soreness (17.5%), chest pain (16.9%), cough (16.4%), and nausea (15%). Although substantial improvements in health were apparent 2 years after the accident, some symptoms persisted, notably breathing problems and eye symptoms.

In another incident, a cloud of gases was released from an oil refinery near Tulsa, Oklahoma, on March 19, 1988 (Himes 1989). The major constituent of the cloud was HF, which may have reached an airborne concentration of 20 ppm (16.6 mg/m^3). A

[1] AEGL final volume 4, 2004

total of 36 people, including emergency personnel responding to the incident, were treated at area hospitals for acute chemical exposure. There were no fatalities. No measurements were taken and no further details of the incident were given.

In a third incident, 13 workers at an oil refinery were exposed to hydrofluoric acid mist at a maximum concentration of 150-200 ppm (125-166 mg/m^3) for approximately 2 min (Lee et al. 1993). Prompt treatment with nebulized calcium gluconate was administered. The workers were medically evaluated within an hour of exposure, at which time the only symptoms were minor upper respiratory tract irritation.

EPA (1993) cited a study by Trevino (1991) that described an industrial accident in Mexico that resulted in exposure of seven workers at approximately 10,000 ppm (8,300 mg/m^3) for several minutes. Periodic examinations for up to 11 y after exposure revealed no long-term or delayed effects. No measurement methods and no further details of the study were provided."

The volunteer study with the highest reported concentration was by Machle et al. (1934) who exposed two male volunteers to concentrations of HF at 100, 50, and 26 mg/m^3 for very short exposure periods. Inhalation of HF at 100 mg/ m^3 produced marked conjunctival and respiratory irritation within 1 min and smarting of the exposed skin. At 50 mg/ m^3, eye and nasal irritation were marked, but smarting of the skin was not reported. Irritation of the eyes and nose was mild at 26 mg/ m^3, and that concentration was "tolerated" with discomfort. At all concentrations, irritation of the larger airways and a sour taste in the mouth were present. Repeated exposures (undefined) failed to produce adaptation.

4. Animal acute toxicity data

During the literature search the following technical support documents and databases were consulted:

1. AEGL final TSD, ERPG document and EU RAR and reference database for hydrogen fluoride, covering references before and including 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA, RTECS, IRIS and ToxNet with the following search terms:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

Animal lethal toxicity data focused on acute exposure are described in Appendix 1. A total of 13 studies were identified -with 23 datasets for 5 species- with data on lethality following acute inhalation exposure. One dataset was assigned status A for deriving the human probit function, 7 datasets were assigned status B and 15 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of 2 studies were identified in which sensory irritation was studied. In these studies the following RD_{50} value were observed:

Table 1 *Sensory irritation data for hydrogen fluoride*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
Mouse	125 (NS)	15	EU RAR, 2001 (secondary source, original ICI, 1990)
Mouse	110 (NS)	30	EU RAR, 2001 (secondary source, original Schorsch, 1995)

NS: not specified if a plateau in response was reached.

5. Probit functions from individual studies

All available acute lethality data on hydrogen fluoride are displayed in Figure 1.

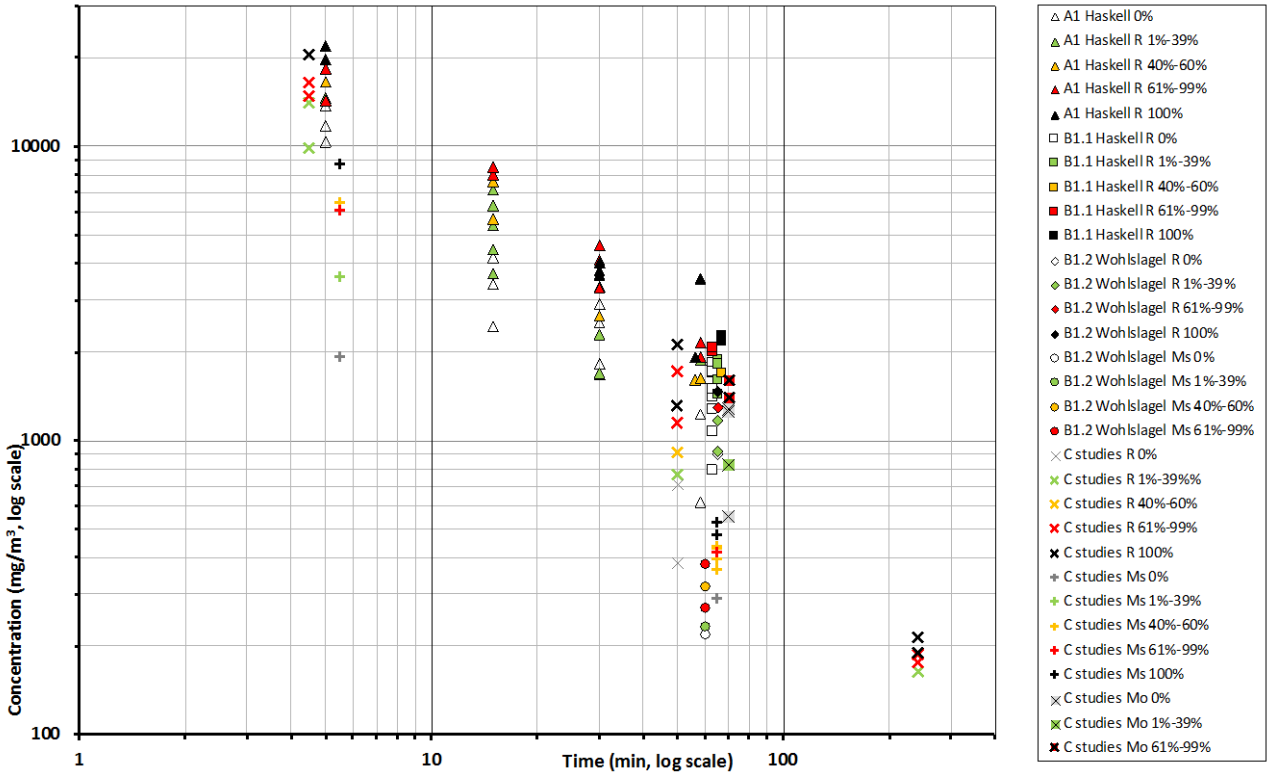


Figure 1 *All available acute lethality data for hydrogen fluoride. R = rat, Ms = Mouse, Mo = Monkey.*

The data that were selected for initial analysis of the animal probit function are presented in Table 2 and Figure 2.

All A and B1 studies were selected for derivation of the animal probit function for hydrogen fluoride.

To enable intra-species pooling, 60-min LC_{50}-values of A and B1-studies were used, including the scaled 30-min LC_{50} value of the A.1 study with gaseous HF (which is essentially treated as a B1 study), using the n-value of 1.094 derived from the C×t dataset in the A.1 study.

Probit functions have been calculated and reported in Appendix 1 for each of the reported studies. The results of the calculations are presented in Table 2.

Table 2 *Data selected for initial analysis of the animal probit function of hydrogen fluoride.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 60 minutes (mg/m^3) 95% C.I.	LC_{50}, 30 minutes (mg/m^3) 95% C.I.	n-value 95% C.I.
A.1	Rat, anhydrous HF, dry air Rat, HF gas	-30.5 + 3.18×lnC + 2.91×lnt	1709 (1519–1918) *1233*	3170 (2931 – 3435) 2287 (1383 – 3460)	1.09 (1.00-1.19) N/A
B1.1	Rat	*60-min LC_{50}*	1906 (1799 – 2062)		N/A
B1.2	Rat Mouse	*60-min LC_{50}* *60-min LC_{50}*	1159 (1073 – 1250) 284 (261 – 315)		N/A

The data of the A study and two B1 studies are presented graphically below.

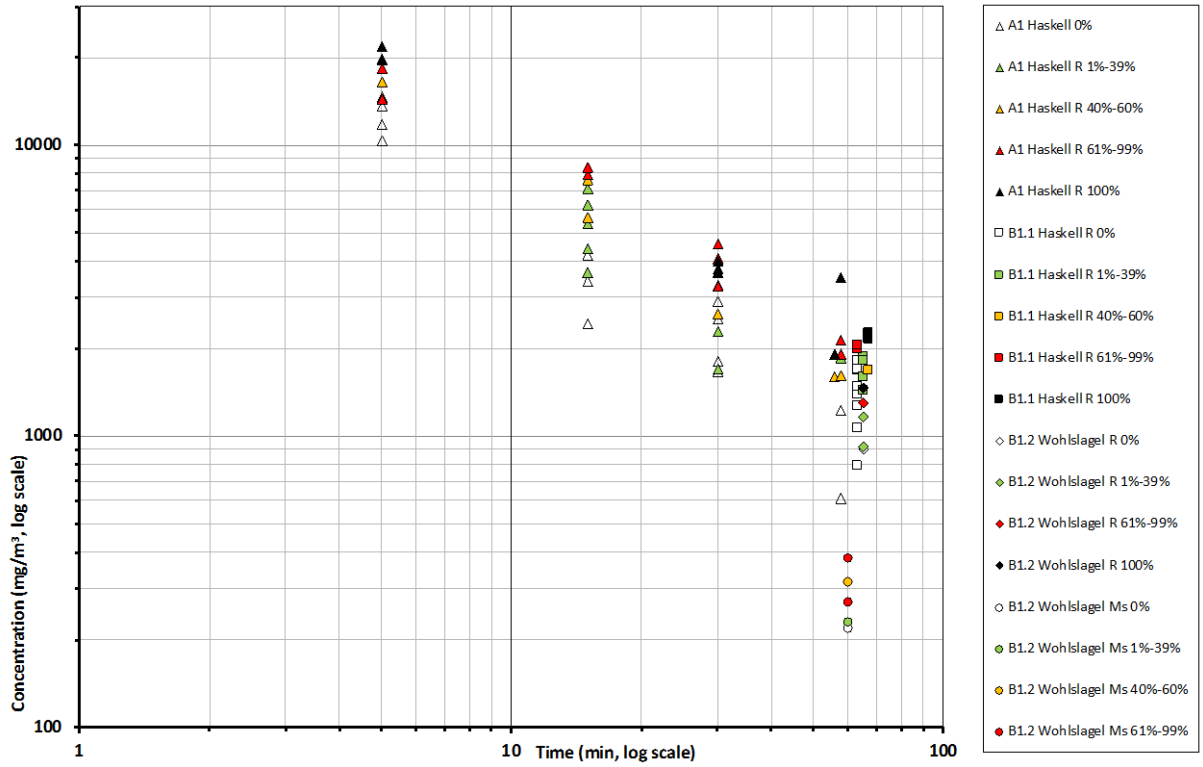


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of hydrogen fluoride. R = rat, Ms = Mouse.*

Based on criteria outlined in the guideline, the data from studies A.1, B1.1 and B1.2 were selected for the final dataset for the derivation of the animal probit function. Figure 3 provides an overview of LC_{50} values and LC_{50}-time relationships for all datasets in the final analysis. The data that were selected for final analysis of the animal probit function are presented in Table 3 and Figure 4.

The final data eligible for calculating the animal probit function contains 5 datasets from 3 studies and includes data from 2 animal species.

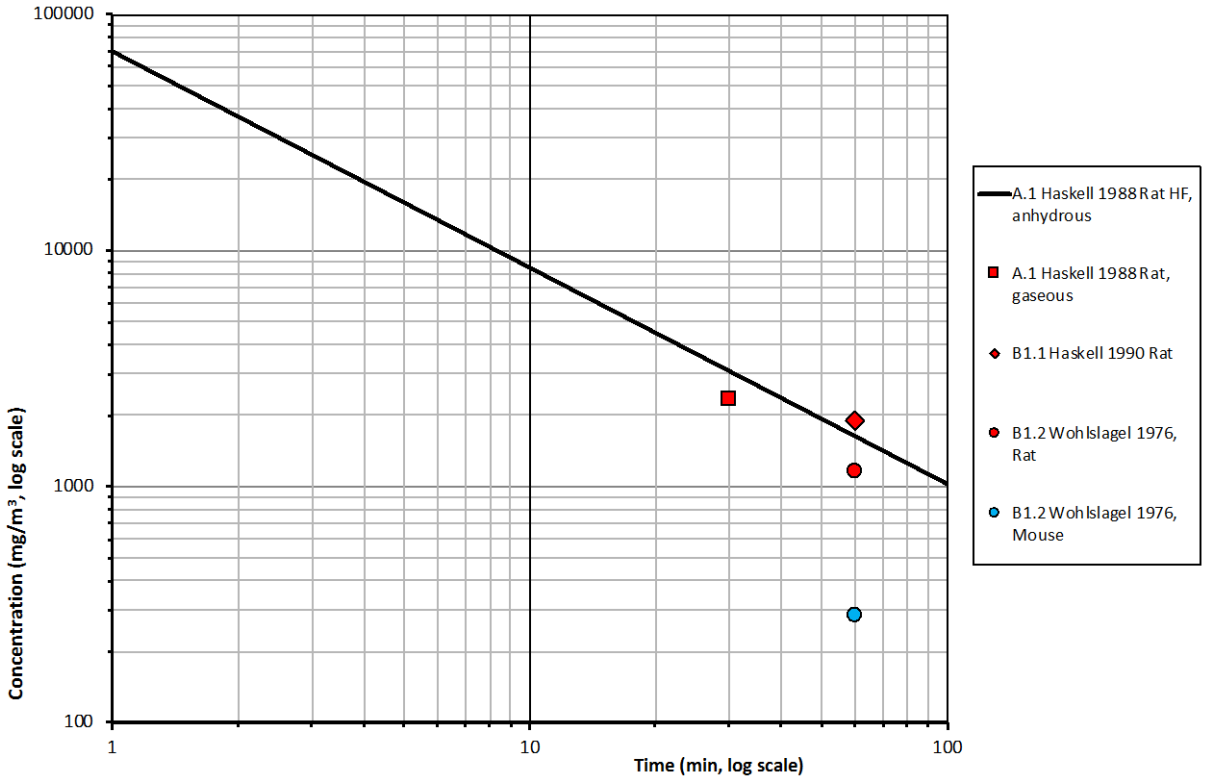


Figure 3 *LC_{50} values of A and B1 datasets for hydrogen fluoride, over time where available.*

The data of the datasets selected for the for the derivation of the animal probit function are presented graphically below in figure 4 and table 3.

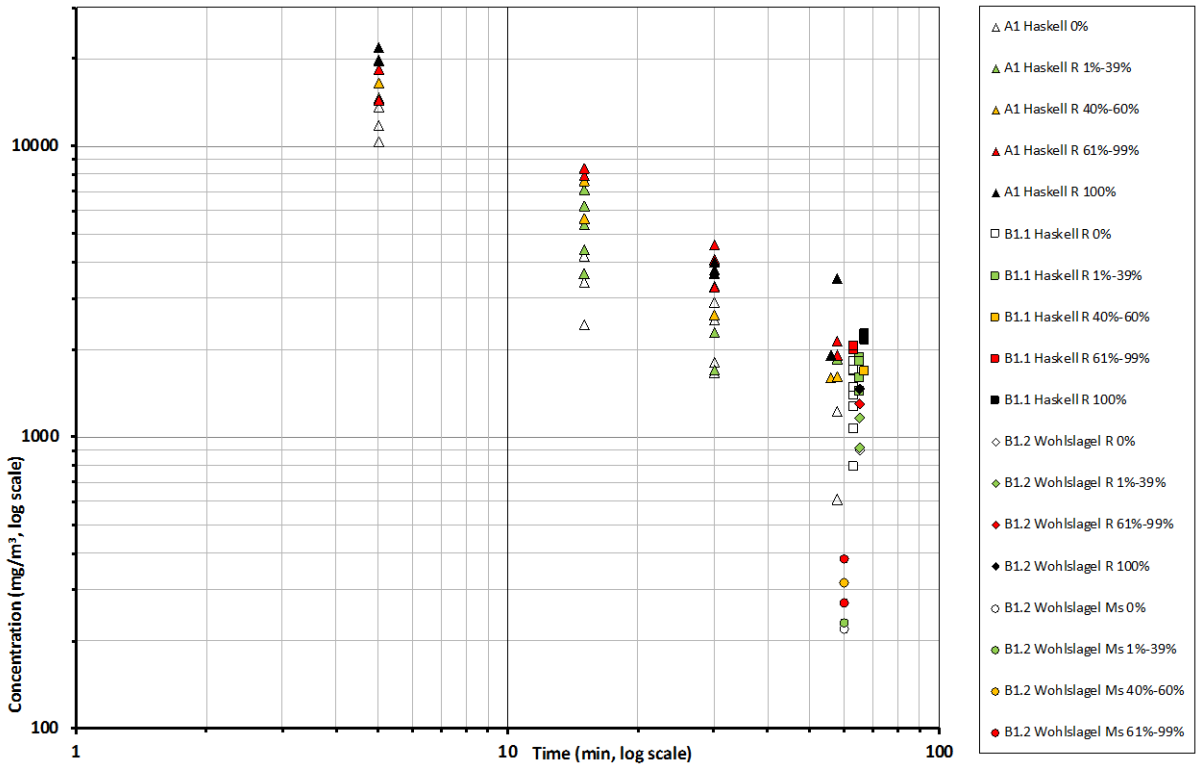


Figure 4 Final data selected for derivation of the animal probit function of hydrogen fluoride (identical to figure 2). *R = rat, Ms = Mouse.*

Table 3 *Data selected for the derivation of the animal probit function of hydrogen fluoride, identical to table 2.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 60 minutes (mg/m^3) 95% C.I.	LC_{50}, 30 minutes (mg/m^3) 95% C.I.	n-value 95% C.I.
A.1	Rat, anhydrous HF, dry air Rat, HF gas	-30.5 + 3.18×lnC + 2.91×lnt	1709 (1519 – 1918) *1233*	3170 (2931 – 3435) 2287 (1383 – 3460)	1.09 (1.00-1.19) N/A
B1.1	Rat	*60-min LC_{50}*	1906 (1799 – 2062)		N/A
B1.2	Rat Mouse	*60-min LC_{50}* *60-min LC_{50}*	1159 (1073 – 1250) 284 (261 – 315)		N/A

6. Derivation of the human probit function

To derive the human probit function the results from Haskell, 1988 (A.1), Haskell, 1990 (B1.1) and Wohlslagel et al. 1976 (B1.2) have been used to derive a point of departure as outlined above. Stavert et al. 1991 and Dalbey et al. 1998 showed that mouth breathing rats (cannulated) were more susceptible to HF exposure than nose breathing rats. By by-passing the nasal region in the cannulated rats, damage to the trachea was observed and mortality occurred at lower exposure concentrations, whereas in the nose breathing rats only damage in the nasal region was seen. It is yet unclear which of these 2 models provides a better prediction of the response in humans, and whether or not data with nose breathing rats may underestimate human toxicity. However, the data by MacEwen and Vernot (1970) indicate that the LC_{50} value in the rhesus monkey following HF exposure is similar to or slightly higher than the LC_{50} values in rats and mice. Therefore, all rodent data were used without any adjustment or weight in the derivation of the probit function for humans.

First, the n-value was derived from C×t dataset in study A.1 with rats, i.e. 1.094.

Second, the LC_{50}-values of all applicable A- and B1-studies were calculated for a common exposure duration of 60 minutes. To enable this intra-species pooling, the 30-min LC_{50}-value of the dataset of the gaseous HF of study A.1 was scaled to 60 minutes using the n-value of 1.094 with the following formula:

$$LC_{50,c} = LC_{50,test}\left(\frac{t_{test}}{t_c}\right)^{(1/n)}$$

With $LC_{50,c}$ = scaled LC_{50} value for common exposure duration t_c
$LC_{50,test}$ = observed LC_{50} value for tested exposure duration
t_c = common exposure duration for intra-species pooling
t_{test} = tested exposure duration
n = n-value = 1.094

Finally, the species-specific geometric mean LC_{50}-values were calculated from all available (time-scaled) LC_{50} values of studies Haskell, 1988 (A.1), Haskell, 1990 (B1.1) and Wohlslagel et al. 1976 (B1.2). The species-specific 60-min LC_{50}-value were 1469 mg/m^3 for the rat and 284 mg/m^3 for the mouse. Finally, a geometric mean overall LC_{50}-value was calculated. The overall formula for the geometric mean of time-scaled LC_{50}-values is as follows:

$$\overline{LC_{50}} = \left[\prod_{j=1}^{s}\left(\prod_{i=1}^{m} LC_{50,i}\right)^{1/m}\right]^{(1/s)}$$

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value across species
$LC_{50,i}$ = LC_{50}-value of study i.
m = number of observations on LC_{50}-values within a species (i=1…m).
s = number of species for which LC_{50}-values are pooled (j= 1…s).

The Point of Departure for the human probit function is a 60-minute geometric mean animal LC_{50} value of 646 mg/m^3 and an n-value of 1.09.

The human equivalent LC_{50} was calculated by applying the following assessment factors:

Table 4 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	Standard assessment factor. This approach may produce a slightly conservative probit since in a comparative study, monkeys appeared to be slightly less susceptible to HF inhalation than rats and mice.
Nominal concentration	1	Analytical concentrations were determined in all eligible studies.
Adequacy of database:	1	One A study and two eligible B1 studies were available for probit function derivation.

The estimated human equivalent 60-minute LC_{50} value is 646 / 3 = **215 mg/m^3**.

The experimentally determined n-value was **1.094** (A.1, Haskell 1988). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.828**.

The human probit function is then calculated on the human equivalent 60 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.828 \times \ln(215^{1.094} \times 60)$ resulting in the a-value of **-13.23**.

$Pr = -13.2 + 1.83 \times \ln(C^{1.09} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a sound basis. The probit function is based on 3 studies (one with A and 2 with B1 quality), including in total 84 C x t combinations in rats and mice, with supportive data from rats, mice, rabbits, Guinea pigs and rhesus monkeys.
The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 46 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 67 mg/m^3.

Table 5 *LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
0.1% lethality, this probit	86	46
1% lethality, this probit	126	67
AEGL-3[2] (2004, final)	51	37
ERPG-3[2] (1999)		42
LBW (2016)	51	36

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are higher.

[2] AEGL and ERPG values were converted from ppm to mg/m^3 with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m^3 can deviate slightly from those reported in the AEGL and ERPG TSDs.

Appendix 1 Animal experimental research

Study ID: A.1

Author, year: ***Haskell 1988***
Substance: gaseous and anhydrous hydrogen fluoride
Species, strain, sex: Rat, Crl:CD BR, male
Number/sex/conc. group: 4
Age and weight: 8 weeks old, weighing between 224-304 grams
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes*
Study carried out according to OECD 403 guideline(s)	*No statement of compliance with OECD guideline 403 provided*
Stability of test compound in test atmosphere	*The test substance was assumed to be stable throughout the exposure phase of the study. The authors further state: in high relative humidity possible aerosol formation.*
Use of vehicle (other than air)	*Drierite® dried air for exposure to 2% HF in nitrogen, dry (0-9%) or humid air (40-60%) for exposure to liquefied HF**
Whole body / nose-only (incl. head/nose-only) exposure	*Head-only*
Type of restrainer	*Perforated Teflon coated stainless steel cylinders fitted with conical nose pieces (Lucite tubes).*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*Gaseous HF: test atmosphere was generated by metering the gas (2% HF in N_2) into an exposure chamber (internal volume approx. 23.2 L) fitted with 4 restrainer tubes.* *Liquefied HF: The test substance cylinders were placed in temperature-controlled water-baths. Obtained HF vapor (metered) was then mixed with dry or humid air. To avoid condensation the stainless-steel tubes where insulated and heated.*
Number of air changes per hour	*Airflow through the exposure chamber was 12 L/min (31 Air Changes/Hour).*
Equilibration time (t95)	*5.8 minutes for the internal volume.*
Start of exposure relative to equilibration	*No information.*
Actual concentration measurement	*Analytical concentrations were determined in the breathing zone at regular intervals (5 minutes). Analyses were performed using a fluoride specific ion electrode*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*Was not performed.*

Assessment of Reliability	***A*** *The dataset with dry air included multiple exposure durations and was well performed, this dataset was assigned the A status (see also comment below this table).*

** This study started exposure with gaseous HF (2% in N_2). HF in N_2 was mixed with dried household air (typically <10% before desiccation).*

The supply of gaseous HF was limited which required the switch to anhydrous HF during the study. Therefore the second part of this study (Haskell 1988) included measurements of lethality following HF atmospheres generated with liquefied HF delivered with dry (0-9%) or humid air (40-60%). The outcomes were widely different: the LC_{50} values were approx. 3 times lower for humid air than for dry air at exposure durations of 15-min. and up, and approx. 1.4 times lower for the 5-min exposure duration. The authors were uncertain if this was a valid finding.

To validate this finding, Haskell performed a second study in 1990 (study B1.1) to verify the different lethal response with dry and humid air. Based on the findings in 1990 (see study B1.1) it was concluded that the results in this 1988 study with humid air were caused by technical errors, could not be related to possible aerosol formation and should not be used for risk assessment. For this reason, only the full dataset for dry air is presented and will be used for probit derivation. For the exposures with humid air only the summary data will be provided, and these data will not be used for probit derivation. The data from exposure with 2% HF in N_2 were also performed with dried air and will be used as a separate (in essence a B1 quality) dataset.

A second finding of the 1990 study was that the analytical techniques of this 1988 study systematically underestimated the HF air concentrations in dry air by 28%. Therefore, all concentrations of this 1988 study were adjusted by multiplication with a factor 1.28 for the probit calculations. The authors of study B1.1 also recalculated the LC_{50} value from this 1988 study with the same adjustment factor of $\times$1.28.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Gaseous HF, dried air					
Rat	749	965	30	0/4	
	808	1042	30	1/4	
	979	1263	30	0/4	
	1162	1498	30	0/4	
	1560	2012	30	0/4	
	1602	2066	30	1/4	
	2034	2622	30	3/4	
	2092	2697	30	2/4	
	2316	2986	30	4/4	
	2390	3082	30	3/4	
	3237	4174	30	4/4	
	3478	4484	30	4/4	

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Liquefied HF, dry air					
Rat	8076	10413	5	0/4	
	9130	11772	5	0/4	
	10624	13699	5	0/4	
	11122	14341	5	3/4	
	11371	14662	5	1/4	
	12782	16481	5	2/4	
	14276	18408	5	3/4	
	15355	19799	5	4/4	
	17015	21939	5	4/4	
	1884	2429	15	0/4	
	2639	3403	15	0/4	
	2855	3682	15	1/4	
	3254	4195	15	0/4	
	3445	4441	15	1/4	
	4183	5394	15	1/4	
	4399	5672	15	2/4	
	4864	6271	15	1/4	
	5503	7096	15	1/4	
	5893	7599	15	2/4	
	6167	7952	15	3/4	
	6565	8465	15	3/4	
	1295	1670	30	0/4	
	1320	1702	30	1/4	
	1411	1819	30	0/4	
	1776	2290	30	1/4	
	1776	2290	30	0/4	
	1959	2526	30	0/4	
	2050	2643	30	2/4	
	2258	2911	30	0/4	
	2556	3296	30	3/4	
	2573	3318	30	1/4	
	2830	3649	30	4/4	
	2922	3767	30	4/4	
	3104	4003	30	4/4	
	3179	4099	30	3/4	
	3586	4623	30	3/4	
	478	616	60	0/4	
	955	1231	60	0/4	
	1245	1605	60	2/4	
	1262	1627	60	2/4	
	1453	1873	60	1/4	
	1486	1916	60	4/4	
	1494	1926	60	3/4	
	1668	2151	60	3/4	
	2739	3532	60	4/4	

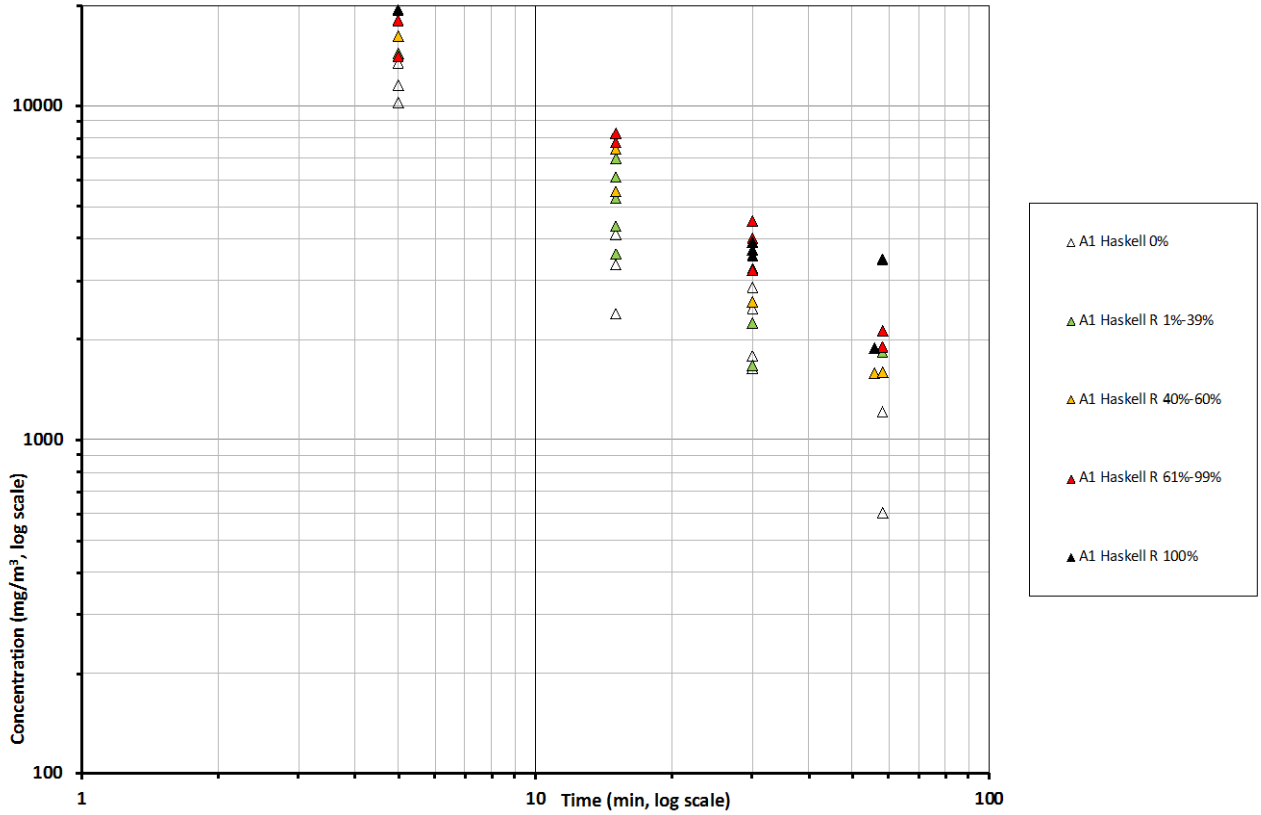
The primary dataset from this study was the C×t dataset of anhydrous HF delivered with dry air. The dataset with gaseous HF in N_2 will be treated as a separate (in essence a B1) dataset.
The study authors reported 5-, 15-, 30-, and 60-min LC_{50} values of 10,700, 2470, 1110, and 541 ppm (8881, 2050, 921, and 449 mg/m^3, without the 26% concentration adjustment) *for humid air conditions*. These data will not be used for the derivation of the probit function.

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as
Pr = a + b×lnC + c×lnt
with C for concentration in mg/m^3, t for time in minutes.

Probit function	Species	a	b	c	n-value
Gaseous HF	Rat	-16.1	2.73	-	-
Anhydrous HF, dry air	Rat	-30.5	3.18	2.91	1.094 (1.00 – 1.19)

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Gaseous HF, dry air	LC_{50} (mg/m^3) 95%-C.I. Anhydrous HF, dry air
10	-	8794 (8070 – 9655)
30	2324 (1405 – 3515)	3220 (2977 – 3490)
60	-	1709 (1519 – 1918)



Study ID: B1.1

Author, year: ***Haskell 1990***
Substance: anhydrous hydrogen fluoride
Species, strain, sex: Rat, Crl:CD BR, male
Number/sex/conc. Group: 4
Age and weight: 8 weeks old, weighing between 240-307 grams
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*No GLP statement provided, however study has been internally audited.*
Study carried out according to OECD 403 guideline(s)	*No statement of compliance with OECD guideline 403 provided*
Stability of test compound in test atmosphere	*The test substance was assumed to be stable throughout the exposure phase of the study.*
Use of vehicle (other than air)	*Dry air or humid air.*
Whole body / nose-only (incl. head/nose-only) exposure	*Head-only*
Type of restrainer	*Perforated Teflon coated stainless steel cylinders fitted with conical nose pieces (Lucite tubes).*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*The test substance cylinders were placed in temperature-controlled water-baths. Obtained HF vapour (metered) was then mixed with dry or humid air. The anhydrous HF was then introduced to the exposure chamber (internal volume approx. 23.2 L). The chamber was fitted with 4 restrainer tubes. To avoid condensation the stainless-steel tubes where insulated and heated.*
Number of air changes per hour	*Airflow through exposure chamber was 13.5 L/min*
Equilibration time (t95)	*5.16 minutes for the internal volume.*
Start of exposure relative to equilibration	*No information.*
Actual concentration measurement	*Analytical concentrations were determined in the breathing zone at regular intervals (2-3 min. sampling with 10-20 min. intervals). Analyses were performed using a fluoride specific ion electrode. The sampling flow rate was investigated. The previous studies do not provide the sampling flow rate, however, the authors note that the 1.4 L/min sampling rate collected approx. 12% more HF than with 0.2 L/min.* *The glass impingers were modified by inserting a Teflon PTFE tube into the inlets and outlets as previously (in the*

	former Haskell studies 1976, 1988) the tubes eroded. These modified impingers had a better collection efficiency, especially under dry air conditions (though differences are not significant). The combined effect of all technical adjustments in this study resulted in a 2 times higher analytical-to-nominal ratio for dry air tests compared with the 1988 study, and a 4-fold difference for humid air.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*Several filter types were applied to evaluate the possibility of HF aerosol formation. The authors conclude that "aerosols were not a major contributor to the total amount of HF present."*
Assessment of Reliability	***B1*** *Well performed study, limited to one exposure duration.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
RAT					
Dry air	791	NA	60	0/4	
	1284	NA	60	0/4	
	1404	NA	60	0/4	
	1438	NA	60	1/4	
	1492	NA	60	0/4	
	1687	NA	60	0/4	
	1690	NA	60	2/4	
	1877	NA	60	1/4	
	2006	NA	60	3/4	
	2269	NA	60	4/4	
Humid air	1071	NA	60	0/4	
	1606	NA	60	1/4	
	1712	NA	60	0/4	
	1828	NA	60	1/4	
	1837	NA	60	0/4	
	2067	NA	60	3/4	
	2172	NA	60	4/4	

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C + d \times H$

with C for concentration in mg/m^3 and H for humidity (0 = dry air, 1 = humid air).

Probit function	Species	a	b	d	n-value
Humidity as covariate	Rat	-50.2	7.34	-0.43	-
	Rat	-47.4	6.94		-

The LC_{50} values for both humidity conditions did not differ by more than a factor of 2. This does not support the proposition that differences exist in the lethal response. For this reason the data from both humidities were pooled and analysed to derive the animal probit function.

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Dry air	LC_{50} (mg/m^3) 95%-C.I. Humid air	LC_{50} (mg/m^3) 95%-C.I. Combined
60*	1848 (1710 – 2043)	1959 (1809 – 2164)	
60	1861 (1711 – 2138)	1940 (1806 – 2180)	1906 (1799 – 2062)

*results based on probit function with humidity as covariate

No C × t probit function could be calculated from these data alone.

Study ID: B1.2

Author, year: ***Wohlslagel et al. 1976***
Substance: hydrogen fluoride
Species, strain, sex: rats, male CFE (Sprague-Dawley derived), mice, female CF-1 (ICR derived)
Number/sex/conc. group: 10 males per group (rats), 10 females per group (mice)
Age and weight: weight 250-325 grams (rats), 25-32 grams (mice)
Observation period: 14 days

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*Either pure liquid HF or gaseous HF in nitrogen was used as source. Mixing occurred in partially dried air (23% humidity).*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body, 22.1 cubic feet (appr. 625 L) chamber*
Type of restrainer	*N/A*
Pressure distribution.	*No information*
Homogeneity of test atmosphere at breathing zone of animals	*Test atmosphere is generated by mixing the partially dried air with the pure liquid form from steel tanks or from gas cylinders of a 1% HF concentration in dried nitrogen. Metering of HF was accomplished with mass flowmeters*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Cannot be determined.*
Start of exposure relative to equilibration	*No information.*
Actual concentration measurement	*Continuous analyses. Known volumes of chamber atmosphere were mixed in a gas scrubber column with aqueous reagent absorbers and then passed through flow cells containing ion and reference electrodes. The electrodes were calibrated prior to exposure.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B1*** *Reasonably well performed study with some uncertainty about the dosing system. Uncertain if HF generation was identical for rats and mice. Only one exposure duration was tested.*

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			Male	
rat	902	60	0/10	
	920	60	2/10	
	1166	60	3/10	
	1299	60	8/10	
	1465	60	10/10	

The study authors reported an LC_{50} value (95% CI) of 1158 (1081-1241) mg/m^3. The study authors derived a probit relation for 60-min exposure as follows (equation was edited by author of this TSD in conformity to the other equation provided here):
Pr = -41.928 + 6.481(lnC)

Note that C for concentration is in ppm.

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
				Female
Mouse	218	60		0/10
	231	60		1/10
	269	60		7/10
	316	60		6/10
	380	60		9/10

The study authors reported an LC_{50} value (95% CI) of 284 (261-309) mg/m^3. The authors derived a probit relation for 60-min exposure as follows (equation was edited by author of this TSD in conformity to the other equation provided here):
Pr = -24.618 + 5.075(lnC). Note that C for concentration is in ppm.

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, December 2016) as
Pr = a + b×lnC
with C for concentration in mg/m^3

Probit function	*Species*	*a*	*b*	*n-value*
	Rat	*-40.7*	*6.48*	-
	Mouse	*-23.7*	*5.09*	-

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***Rat***	*LC_{50} (mg/m^3) 95%-C.I.* ***Mouse***
60	1159 (1073 – 1250)	284 (261 – 315)

No C × t probit function could be calculated from these data alone.

Study ID: B2.1

Author, year: ***Rosenholtz et al. 1963***
Substance: hydrogen fluoride
Species, strain, sex: Rats, Wistar derived, males; Guinea pigs, Hartley derived, males.
Number/sex/conc. group: unknown
Age and weight: Rats: 100-120 g; Guinea pigs: 340-360 g.
Observation period: 14 days

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*stable*
Use of vehicle (other than air)	
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body (400-liter chamber)*
Type of restrainer	*N/A*
Pressure distribution.	*No information*
Homogeneity of test atmosphere at breathing zone of animals	*Test atmosphere was generated by passing a metered HF vapour from a cylinder at 88°C in an oil bath through a manometer containing kerosene into a paraffin coated glass-mixing bowl and then introduced in the chamber.*
Number of air changes per hour	*Air flow of 200 liters per minute which corresponds to 30 ACH.*
Equilibration time (t95)	*6 minutes*
Start of exposure relative to equilibration	*At start of concentration build-up*
Actual concentration measurement	*One or two samples taken before exposure and one (5 and 15-min exposure) to three (30 and 60-min exposure) samples during exposure. Samples were collected in glass bottles (1L or 3L) or absorbers. Sampling rate was from 0.4 to 1 liter per minute. Analysis for fluoride according to Willard and Winter (1933).*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B2*** *Only LC_{50} values presented for a number of exposure durations. No details on concentration-time combinations.*

1 **Results**

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
rat	4.06×10^3 ($3.805\text{-}4.472 \times 10^3$)	5	LC_{50}	
	2.2×10^3 ($1.990\text{-}2.503 \times 10^3$)	15	LC_{50}	
	1.67×10^3 ($1.578\text{-}1.819 \times 10^3$)	30	LC_{50}	
	1.07×10^3 ($1.006\text{-}1.17 \times 10^3$)	60	LC_{50}	
Guinea pig	3540 (3325-3878)	15	LC_{50}	

2

3 The n-value calculated from these LC_{50} values is 1.90.

4

5

Study ID: C

Author, year: ***MacEwen and Vernot, 1970***
Substance: hydrogen fluoride
Species, strain, sex: rhesus monkeys male and female, Male Wistar rats and male ICR mice.
Number/sex/conc. group: 4 monkeys, 8 rats and 5 mice per group
Age and weight: unspecified
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*The cylinder was wrapped with heating tape to avoid polymerisation of the HF vapour.*
Use of vehicle (other than air)	*None*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body, it seems that animals were placed in 'domes'.*
Type of restrainer	*N/A*
Pressure distribution	*Negative pressure in animal housing dome. It seems that exposures took place here as well but is unclear from the reports.*
Homogeneity of test atmosphere in breathing zone of animals	*HF vapour was metered from a cylinder wrapped with heating tape. In the study report it is described that an oxidising system is used. However, it is unclear how test atmosphere was transferred from the cylinder to the dome.*
Number of air changes per hour	*It seems to be at least 9 ACH, however unclear if this relates to housing conditions and/or exposure conditions.*
Equilibration time (t95)	*Cannot be determined.*
Start of exposure relative to equilibration	*Animals were present at start of the concentration build-up.*
Actual concentration measurement	*Nominal concentrations are reported. After the study, continuous analysis of HF by using fluoride ion specific electrodes were developed and conducted. HF is absorbed in citrate-acetate buffer and delivered to the electrode. Calibration of the system, probably without animals in the exposure dome, before and after analysis showed approx. 4% precision.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*

Assessment of Reliability	***C*** The study description is unclear on important points concerning the exposure settings (size of chamber and delivery of the substance) but provides information on exposure concentrations and how the dome was kept 'clean' from contaminants and remaining exposures. Only one exposure duration tested. No actual concentrations presented, but nominal concentrations calculated.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Nominal	Adjusted*		Male	both
Rhesus monkey	573	550	60		0/4
	859	825	60		1/4
	1307	1255	60		0/4
	1328	1275	60		0/4
	1453	1394	60		3/4
	1660	1594	60		3/4
Rats	398	382	60	0/8	
	797	765	60	2/8	
	1195	1147	60	5/8	
	1793	1721	60	7/8	
	2200	2112	60	8/8	
Mice	415	398	60	3/5	
	457	438	60	3/5	
	498	478	60	5/5	

* Adjustment is made based on the 4% imprecision. It is assumed that the nominal concentrations are all overestimating the actual exposure by 4%.

The authors calculated 60-min LC_{50} values (C.I.) of 1472 (1241-1747) mg/m^3 for rhesus monkeys, 1059 (860-1300) mg/m^3 for rats, and 416 (295-585) mg/m^3 for mice.

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

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

with C for concentration in mg/m^3

Probit function	Species	a	b	n-value
	Rhesus monkey	-11.9	2.32	N/A
	Rat	-13.4	2.65	N/A
	Mouse	-40.9	7.66	N/A

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Rhesus monkey	LC_{50} (mg/m^3) 95%-C.I. Rat	LC_{50} (mg/m^3) 95%-C.I. Mouse
60	1500 (no reliable CI)	1016 (759 – 1260)	397 (no reliable CI)

No C × t probit function could be calculated from these data alone.

Study ID: C

Author, year: ***MacEwen and Vernot, 1974***
Substance: hydrogen fluoride
Species, strain, sex: Male Sprague-Dawley rats, female CF-1 mice
Number/sex/conc. group: rats 5/group, mice 10/group.
Age and weight: age unknown, rats weight 250-300 grams, mice 30-35 grams
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*Dry nitrogen*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body, 120 liter plexiglass chamber*
Type of restrainer	*N/A*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by heating a mixture of sulfuric acid and calcium fluoride. Control of the generation rate was achieved by changing the temperature. A 500cc/min carrier flow of dry nitrogen was passed through the Monel vessel and carried the reaction product HF to the plexiglass exposure chamber.*
Number of air changes per hour	*No information on air flow in chamber.*
Equilibration time (t95)	*Cannot be determined.*
Start of exposure relative to equilibration	*The exposure chamber was fitted with a sliding cage drawer which allowed rapid insertion and withdrawal of test animals.*
Actual concentration measurement	*Continuous analysis of chamber concentration was provided by passing a sample of test atmosphere through an aqueous reagent absorber, with subsequent measurement of F^- ions in the absorber using specific electrode in a flow cell of unspecified material.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***C*** *Uncertainties about the exposure generation; possible co-exposure to sulfuric acid. Material of flow cell possibly glass, which may cause a bias.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Mice	291	NA	60		0/10
	364	NA	60		5/10
	419	NA	60		9/10
	430	NA	60		6/10
	525	NA	60		10/10
Rats	704	NA	60	0/5	
	911	NA	60	3/5	
	1308	NA	60	5/5	

The authors calculated 60-min LC_{50} values and C.I. of 378 (354-406) mg/m^3 for the mouse and 802 (652-986) mg/m^3 for the rat.

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times lnC$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Mouse	-36.3	6.96	-
	Rat	-69.7	11.0	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. **Mouse**	LC_{50} (mg/m^3) 95%-C.I. **Rat**
60	379 (346-405)	890 (no reliable CI)

No C × t probit function could be calculated from these data alone.

Study ID: C

Author, year: ***MacEwen and Vernot, 1971; DiPasquale and Davis, 1971; Higgins et al. 1972 ****

Substance: hydrogen fluoride

Species, strain, sex: Wistar rats, ICR mice, sex not specified

Number/sex/conc. group: 10 rats per group and 15 mice per group

Age and weight: Rats: 250-275 g; Mice: 30-35 g.

Observation period: 7 days

* It is unclear who published the original data. In literature, references can be found to the authors as stated above, all referring to the same dataset.

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution.	*No information*
Homogeneity of test atmosphere at breathing zone of animals	*No information on test atmosphere generation.*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Cannot be determined*
Start of exposure relative to equilibration	*When the desired hydrogen fluoride concentrations were obtained, the animals were introduced by sliding the Rochester chamber into the exposure chamber. After 5 minutes the chamber was slid out again.*
Actual concentration measurement	*Concentrations were monitored by specific ion electrodes and analysed by aqueous reagent solutions.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***C*** *Little information on the test method. 5-minute exposures only and a too short observation period of 7 days. In a study by Haskell (1988) animals died 10 days post-exposure.*

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
Rat	10325	5	1/10	
	14620	5	3/10	
	15421	5	8/10	
	17247	5	7/10	
	21323	5	10/10	
Mouse	2058	5	0/15	
	3735	5	5/15	
	6320	5	10/15	
	6756	5	8/15	
	9138	5	15/15	

The study authors reported 5-min LC_{50} values of 15160 mg/m^3 (13251-17221 mg/m^3) and 5185 mg/m^3 (3975-6764 mg/m^3) for rat and mouse, respectively.

Study ID: C

Author, year: ***Machle et al. 1934***
Substance: hydrogen fluoride
Species, strain, sex: New Zealand white Rabbits (most of them), Guinea pigs
Number/sex/conc. group: 3/group
Age and weight: 4 to 6 months, 1800-3900 g. Guinea pigs: 500-1300 g.
Observation period: Unknown. Some animals kept for up to 15 weeks.

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*Considered stable under static exposure conditions. Authors limited the duration to 30 minutes for static conditions.*
Use of vehicle (other than air)	*air*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body; 24000 L inhalation chamber, provided with an air lock of appr. 1,500 L.*
Type of restrainer	*N/A*
Pressure distribution.	*No information*
Homogeneity of test atmosphere at breathing zone of animals	*A fan was used in the exposure chamber to evenly distribute the test substance. Homogeneity was shown by taking samples at various locations in the exposure chamber. At five different locations the range of HF was 0.016-0.022 mg/L. Unknown if this applied to both static and dynamic conditions.* *Weighed quantities of gas were passed directly into the chamber (static conditions).* *A metered air flow (by measuring pressure) was applied in the dynamic conditions.* *Rabbits and guinea pigs were exposed simultaneously.*
Number of air changes per hour	*Not provided.*
Equilibration time (t95)	*Cannot be determined.*
Start of exposure relative to equilibration	*At low exposures the animals were placed in the chamber after the desired exposure was obtained, whereas at high exposures the animals were placed in the chamber before administration of HF.*
Actual concentration measurement	*At minimum 2, normally 4, at longer durations 8 to 12 sampling apparatuses (a glass bulb) were put in the chamber, wherein HF can be absorbed. Following titration the concentrations could be*

	determined, but only once during the experiment per exposure duration, representing only the mean concentration during that exposure duration. A measuring error of max 10% was found by the authors.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***C*** *The data of the rabbits and guinea pigs are aggregated in the graphs below, no individual animal data provided. Study design is well described but lacks information on concentration-time combinations except for a graph and observation periods.*

Results

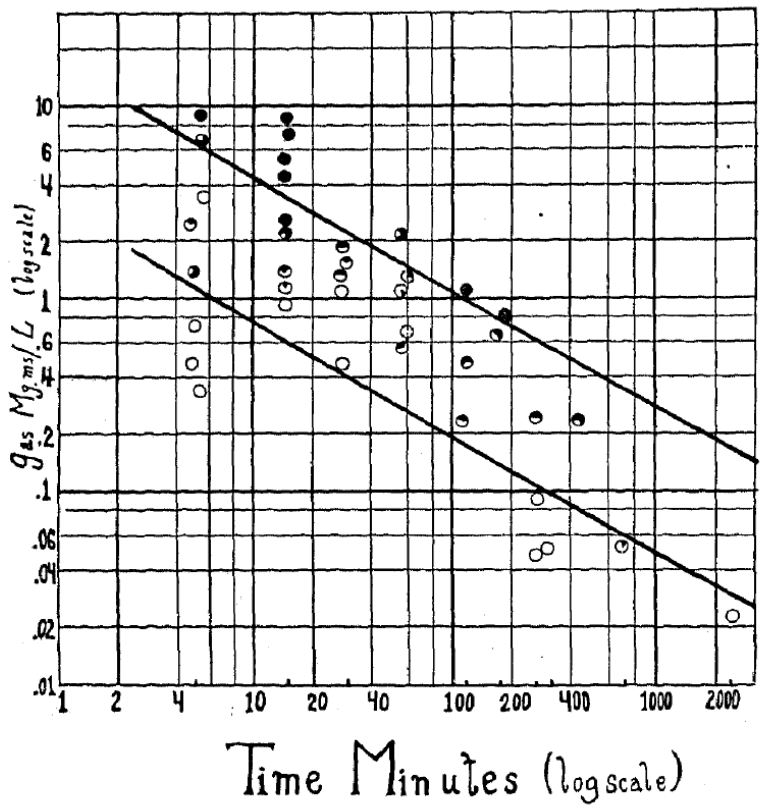


FIG. 4.—Effects of Exposure of Animals to Hydrofluoric Acid in Air. ● ● Death All Animals. ◐ ◐ Proportional Deaths in Group. ○ ○ No Deaths in Group.

Probit function

Not possible to derive a probit function based on graphical representation of the data.

Study ID: C

Author, year: ***Haskell 1976***
Substance: gaseous hydrogen fluoride
Species, strain, sex: Rat, male Crl:CD, male
Number/sex/conc. group: 6
Age and weight: age unknown, weight 250-270 grams
Observation period: at least 24 hours

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*stable*
Use of vehicle (other than air)	
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*The test atmosphere was generated by metering gaseous HF through a stainless steel micromotor valve and was mixed with air. The air was directed to the top of a 20-L cylinder.*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Cannot be determined*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Samples were collected according to HEW publication No. (NIOSH) 75-121, though with modifications at the (higher) test levels by covering equipment with Teflon tape. Samples were taken by syringe and analysed using a fluoride specific ion electrode.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***C*** *Important study details are lacking, and the duration of the observation period is not specified.*

.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Rat	164		240	2/6	
	176		240	5/6	
	187		240	3/6	
	188		240	5/6	
	190		240	6/6	
	215		240	6/6	

Study ID: other C studies

In another C study, exposure of rats to fluoride at 148 mg/m^3 (HF at 190 ppm) for 6 h resulted in 100% mortality within 3 h post-exposure (Morris and Smith 1982; as cited in AEGL 2004). Discharge of fluid from the external nares was observed prior to death, but no lung lesions were present.

Hilado and Machado (1977) cited a study by Carson et al. 1961 where LC_{50} values for white rats and white guinea pigs are reported. A 5-min LC_{50} of 4970 ppm (4125 mg/m^3), 15-min LC_{50} of 2689 ppm (2232 mg/m^3), 30-min LC_{50} of 2042 ppm (1695 mg/m^3) and a 60-min LC_{50} of 1307 ppm (1085 mg/m^3) where reported for rats. A 15-min LC_{50} of 4327 ppm (3591 mg/m^3) was reported for the guinea pig. Unfortunately, no full reference was provided and no other links to Carson et al. 1961 could be found.
It is noted that this dataset is reported by Rosenholtz et al. 1963 above.

Mortality comparison between nose breathing and mouth breathing (cannulated) rats

There are two studies, i.e. by Stavert et al. 1991 and by Dalbey et al., 1998, that have studied the difference in effects, amongst which mortality, between nose breathing rats and cannulated rats (mouth breathing). By cannulating rats, the scrubbing effect in the nose of the obligatory nose-breathing rats is bypassed. Although the studies appear to be of good quality, it usefulness for probit function derivation is limited because the observation periods were either too short (24 hours) or in case of Dalbey et al. 1998, contained only two dose groups at 10 minute exposures that did have a 14 day observation period.

Stavert et al. (1991) exposed an unknown number of male Fischer 344 Rats to 1300 ppm (1097 mg/m^3) for 30 minutes. The nose breathing rats did not show mortality, whereas the mouth breathing rats showed 25% mortality (at 24 h post-exposure).

Dalbey et al. (1998) exposed 20 female rats (strain not given) to various concentrations for 2, 10 or 60 minutes. The results are given in the table below:

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		MB	NB
				Mortality %	Mortality %
Rat	7155		2	5	
	5305		2		0
	4048		2	10	
	1319		2	0	
	492		2	0	
	5822		10	80*	0*
	3193		10	50*	0*
	1464		10	5	
	1385		10		0
	1207		10	0	
	789		10	0	
	225		10	0	
	112		10	0	
	1692		60		10*

	1016		60		0*
	40		60	0	
	28		60		0
	17		60	0	

* animals were observed for 2 weeks after exposures; without asterisk 1 day observation period.

Based on these results it was observed that the LCt_{50} for mouth-breathers and nose-breathers were approximately 40,000 ppm x min and well above 70,000 ppm x min (from the graph, a rough estimate is 80,000 ppm x min), respectively. This would roughly indicate a two-fold difference. See also the copied Figure 1 from Dalbey et al. 1998, which also includes results from other studies.

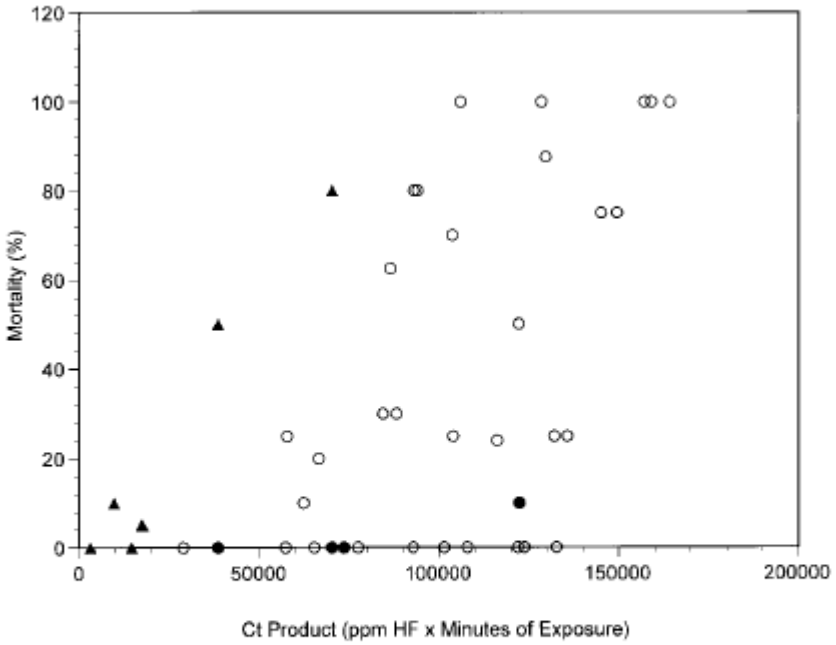


FIG. 1. Mortality (%) in published studies with NB rats acutely exposed to HF (open circles) and with the present exposures with both NB (closed circles) and MB (triangles) groups. Groups sacrificed at both 1 day and 2 weeks in the present work are included.

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