Probit function technical support document

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substance name	CAS number
Fluorine	**7782-41-4**

This 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). The contents of this document, including the probit function, have been approved by the scientific expert panel on probit functions on scientific grounds. The status of this document was therefore raised to "interim", pending a decision on its formal implementation.

Subsequently the Ministry of Housing, Spatial Planning and the Environment (VROM) 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.

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.

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 Fluorine

1 Substance identification

CAS-number:	7782-41-4
IUPAC name:	Fluorine
Synonyms:	Bifluoriden, fluor, fluorine-19, fluoro
Molecular formula:	F_2
Molecular weight:	37.99 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	-188°C (at 101.3 kPa)
Vapour pressure:	> 1013 kPa (at 20°C)
Conversion factor:	1 mg/m^3 = 0.633 ppm (at 20°C and 101.3 kPa)
	1 ppm = 1.58 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	R8, R26, R35

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

Acute effects: The main target organ and tissue for inhalation exposure to fluorine is the respiratory system, in particular the lungs. Fluorine is severely irritating to the eyes, mucous membranes, skin and lungs. It may cause lung oedema, emphysema and haemorrhage. Damage to the respiratory tract is due to the hygroscopic character of fluorine which will cause it to react with moist mucous membranes.
Long-term effects: Fluorine mainly affects the eyes and tissues of the respiratory tract. The concentration of fluorine in the inhaled air rather than the absorbed dose is considered to be the main determinant of its toxic effects.

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.

4 Animal acute toxicity data

Animal lethal toxicity data considering acute exposure are described in Appendix 1. A total of 8 studies were identified -with 8 datasets for 4 species- with data on lethality following acute inhalation exposure. No datasets have been assigned status A for deriving the human probit function, 4 datasets were assigned status B and 4 have 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 final TSD and ERPG documents and reference database for fluorine, covering references before 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, RTECS, with the following search terms:
   - Fluorine and synonyms

[1] Interim Acute Exposure Guideline Levels (AEGLs) Formaline, February 2002

- CAS number
- lethal*
- mortal*
- fatal*
- LC_{50}, LC
- probit

3. Industry data were sought through networks of toxicological scientists.

Sensory irritation

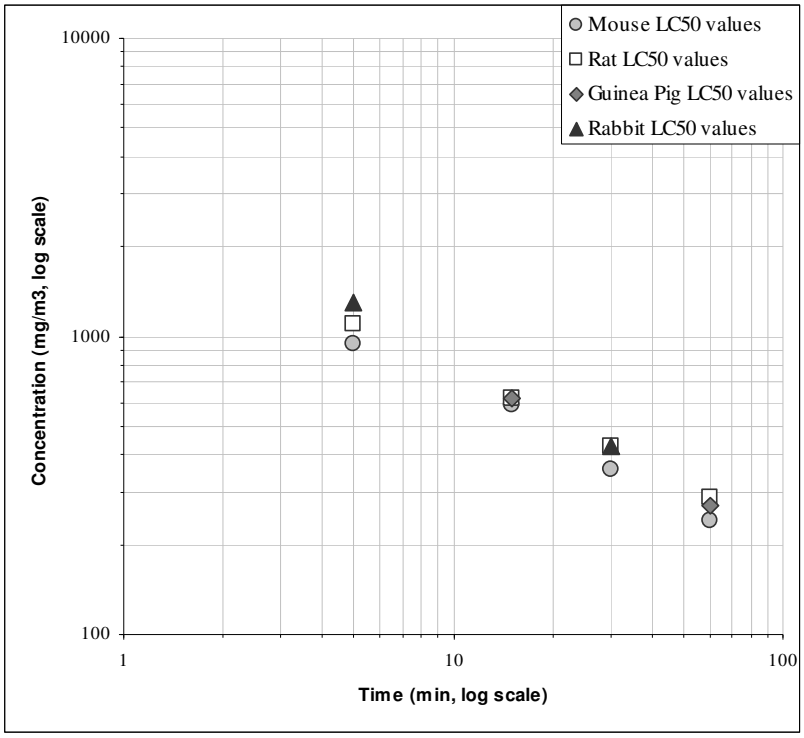
No studies were found in which sensory irritation of fluorine was studied

5 Probit functions

The available data were insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in experimental animals. However, as LC_{50} values were provided for different (> 2) exposure durations in the rat and the mouse n-values could be calculated for two available B studies (i.e. B.1 and B.2), as reported in Appendix 1. Below the results of the calculations can be found.

Study ID	*Species*	*LC_{50}, 30 minutes (95% C.I.) (mg/m^3) (study data)*	*n-value (calculated)*
B.1	*Rat*	420 (361-487)	*1.85*
B.2	*Mouse*	350 (310-395)	*1.51*

The data (LC_{50} values) of the B studies are presented graphically below.



6 Evaluation

To derive the human probit function the results from the study by Keplinger and Suissa (1968) were used. Because rat data are preferred over mouse data as point of departure for deriving the human probit function the 30 min LC_{50} value of 420 mg/m^3 for the rat from the B.1 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	Standard value
RD_{50}	1	No RD_{50} available
Nominal concentration	1	Measured concentrations
Adequacy of database:	1	One B-study, similar results for four species.

The estimated human equivalent 30-minute LC_{50} value is 420/3 = **140 mg/m^3**.

The experimentally determined n-value for rats, calculated from LC_{50} values, was **1.85** (Study B.1, value calculated excluding the < 10 minute data[2]). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.08**.

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): $5 = a + 1.08 \times \ln(140^{1.85} \times 30)$ resulting in the a-value of **– 8.56**.

$$Pr = -8.56 + 1.08 \times \ln(C^{1.85} \times t)$$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically reasonable basis. The probit function is based on a study in the rat with B quality, using 10 animals per group and 4 exposure durations. No data were available to derive a probit function using the DoseResp program by Wil ten Berge. However, in the available B study, LC_{50} values were derived for different time points, allowing the calculation of an n-value that could be used to derive a probit function assuming b * n = 2. Data were provided for 4 species, showing little species variability in lethality.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 30 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.93) is 21 mg/m^3.

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
1% lethality, this probit	44	30
0.1% lethality, this probit	30	21
AEGL-3 (interim, 2002)	30	21
ERPG-3 (1998)	-	32
LBW (2007)	-	20

[2] As a general rule, data from exposure durations less than 10 minutes are excluded because uncertainties in chamber conditions and the ability of animals to temporarily reduce their minute volume.

Compared to equivalent (inter)national guideline levels as presented in the table above, the derived lethal levels with this probit function are almost identical. The same study was used as point of departure, which explains the similarity.

Appendix 1 Animal experimental research

Study ID: B.1

Author, year: Keplinger and Suissa, 1968

Substance: fluorine
Species, strain, sex: Rat, Osborne-Mendel, sex unspecified
Number/sex/concentration group: 10
Age and weight: unknown
Observation period: 14 days

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	*Not specified*
Use of vehicle (other than air)	*5-10% fluorine in nitrogen was mixed with air in a mixing chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Pressure distribution.	*Slight negative pressure in the chamber (0.1 inch of water)*
Homogeneity of test atmosphere at breathing zone of animals	*A mixing fan was built in the rear of the chamber to facilitate uniform distribution*
Number of air changes per hour	*Not specified*
Actual concentration measurement	*Yes, colorimetrically. No further details were provided*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B;*** *4 exposure durations were tested and corresponding LC_{50} values calculated. An n value could be derived. However, details on concentration groups and response were lacking.*

Results

Species	Concentration (95% C.I.) (mg/m^3)	Exposure duration (min)	Lethality
Rat	1088 (989-1197)	5	LC_{50}
Rat	606 (561-656)	15	LC_{50}
Rat	420 (361-487)	30	LC_{50}
Rat	287 (220-372)	60	LC_{50}

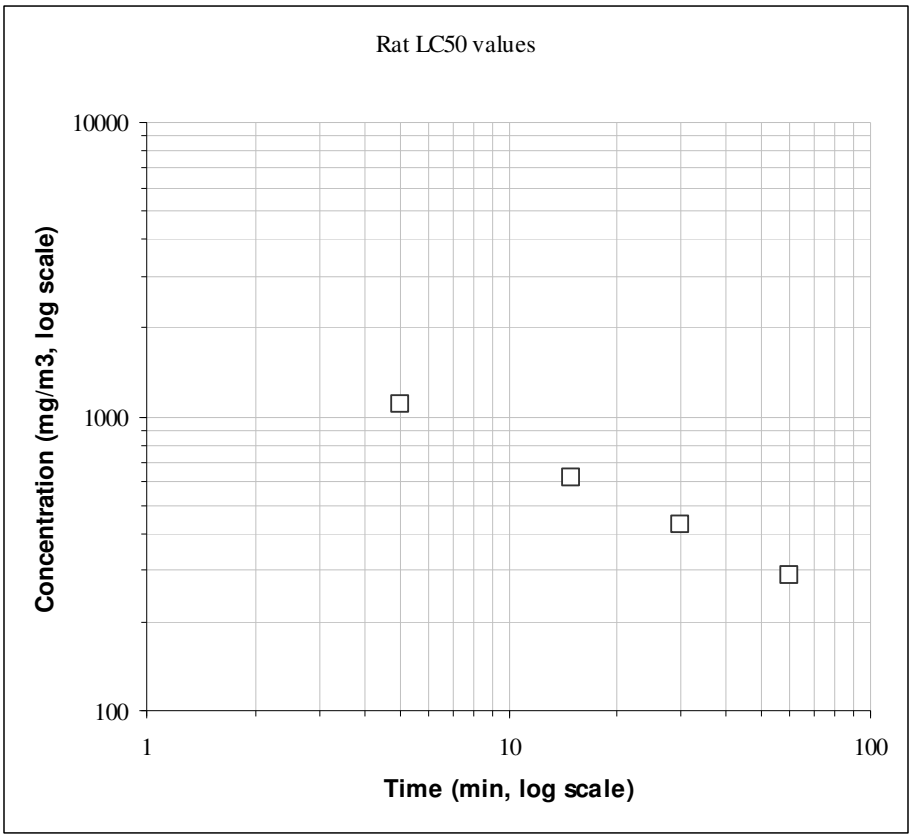
n-value

The available information was insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in the rat. However, as LC_{50} values were provided for different exposure durations an n-value could be calculated using the following formula:

$$-n = \frac{N\sum(\log t)^2 - (\sum \log t)^2}{N\sum(\log t)(\log C) - (\sum \log t)(\sum \log C)}$$

The calculated n-value was 1.85. This value was calculated excluding the 5-minute data because of possible uncertainties in chamber conditions and the ability of animals to temporarily reduce their minute value. However, including the 5-minute data resulted in a calculated n-value of 1.87.

A graphical overview of the LC_{50} values is presented below.



Study ID: B.2

Author, year: Keplinger and Suissa, 1968

Substance: fluorine

Species, strain, sex: Mouse, Swiss-Webster, sex unspecified

Number/sex/concentration group: 10

Age and weight: unknown

Observation period: 14 days

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	*Not specified*
Use of vehicle (other than air)	*5-10% fluorine in nitrogen was mixed with air in a mixing chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Pressure distribution.	*Slight negative pressure in the chamber (0.1 inch of water)*
Homogeneity of test atmosphere at breathing zone of animals	*A mixing fan was built in the rear of the chamber to facilitate uniform distribution*
Number of air changes per hour	*Not specified*
Actual concentration measurement	*Yes, colorimetrically. No further details were provided*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B;*** *4 exposure durations were tested and corresponding LC_{50} values calculated. An n value could be derived. However, details on concentration groups and response were lacking.*

Results

Species	Concentration (95% C.I.) (mg/m^3)	Exposure duration (min)	Lethality
Mouse	932 (803-1081)	5	LC_{50}
Mouse	583 (535-637)	15	LC_{50}
Mouse	350 (310-395)	30	LC_{50}
Mouse	233 (216-252)	60	LC_{50}

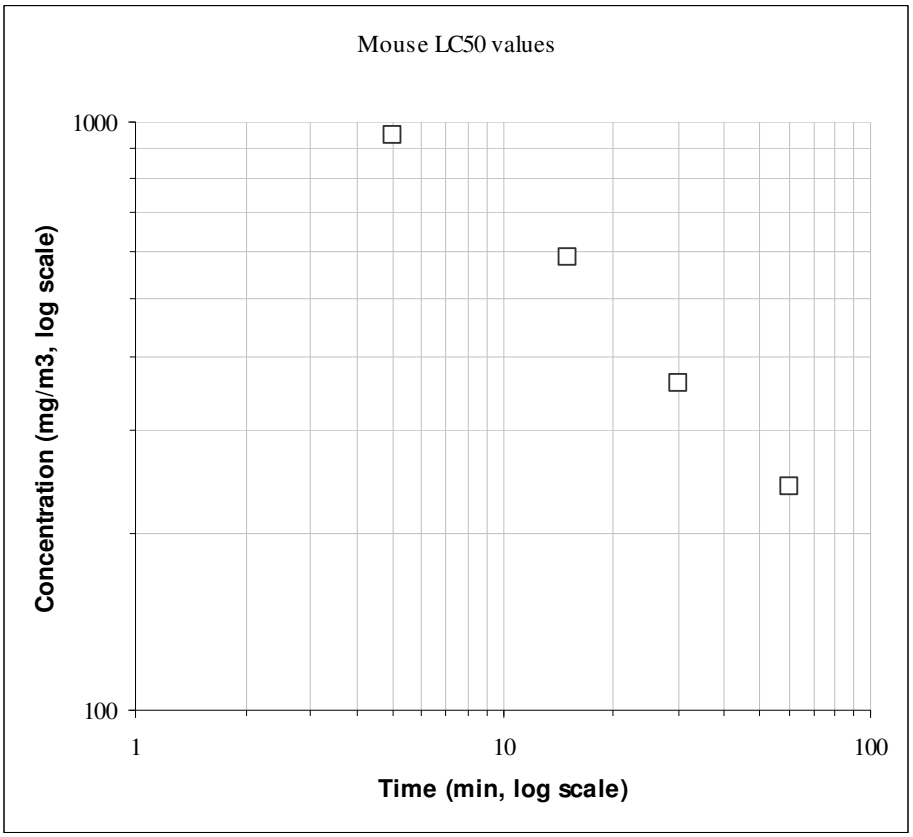
n-value

The available information was insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in the mouse. However, as LC_{50} values were provided for different exposure durations an n-value could be calculated using the following formula:

$$-n = \frac{N\sum(\log t)^2 - (\sum \log t)^2}{N\sum(\log t)(\log C) - (\sum \log t)(\sum \log C)}$$

The calculated n-value was 1.51. This value was calculated excluding the 5-minute data because of possible uncertainties in chamber conditions and the ability of animals to temporarily reduce their minute value. However, including the 5-minute data resulted in a calculated n-value of 1.77.

A graphical overview of the LC_{50} values is presented below.



Study ID: B.3

Author, year: Keplinger and Suissa, 1968

Substance: fluorine

Species, strain, sex: Guinea pigs, New England, sex unspecified

Number/sex/concentration group: 5

Age and weight: unknown

Observation period: 14 days

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	*Not specified*
Use of vehicle (other than air)	*5-10% fluorine in nitrogen was mixed with air in a mixing chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Pressure distribution.	*Slight negative pressure in the chamber (0.1 inch of water)*
Homogeneity of test atmosphere at breathing zone of animals	*A mixing fan was built in the rear of the chamber to facilitate uniform distribution*
Number of air changes per hour	*Not specified*
Actual concentration measurement	*Yes, colorimetrically. No further details were provided*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B;*** *Only 2 exposure durations were tested and corresponding LC_{50} values calculated.*

Results

Species	Concentration (95% C.I.) (mg/m^3)	Exposure duration (min)	Lethality
Guinea pig	614 (547-689)	15	LC_{50}
Guinea pig	264 (236-295)	60	LC_{50}

Probit function

The available information was insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in the guinea pig.

Study ID: B.4

Author, year: Keplinger and Suissa, 1968

Substance: fluorine

Species, strain, sex: Rabbit, New England, sex unspecified

Number/sex/concentration group: 5

Age and weight: unknown

Observation period: 14 days

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	*Not specified*
Use of vehicle (other than air)	*5-10% fluorine in nitrogen was mixed with air in a mixing chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Pressure distribution.	*Slight negative pressure in the chamber (0.1 inch of water)*
Homogeneity of test atmosphere at breathing zone of animals	*A mixing fan was built in the rear of the chamber to facilitate uniform distribution*
Number of air changes per hour	*Not specified*
Actual concentration measurement	*Yes, colorimetrically. No further details were provided*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B;*** *Only 2 exposure durations were tested and corresponding LC_{50} values calculated.*

Results

Species	Concentration (95% C.I.) (mg/m^3)	Exposure duration (min)	Lethality
Rabbit	1274 (1134-1429)	5	LC_{50}
Rabbit	420 (373-482)	30	LC_{50}

Probit function

The available information was insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in the rabbit.

Other studies (C quality)

In the AEGL and ERPG technical dossiers on fluorine the studies by Eriksen (1945) and Stokinger (1949), which appear to be the same study, are described. The original report was not available to us.

In the study rats, mice, guinea pigs and rabbits have been exposed to various concentrations of fluorine for 5, 30, 60, 180 or 420 minutes. The results of the study are listed in the table below. It was not possible to derive an animal probit function based on the data, because in most cases 100% mortality was observed.

Species	Concentration (mg/m^3)	Exposure duration (min)	Exposed	Responded
Rat	16000	5	45	100%
Rat	1600	30	45	100%
Rat	790	60	45	100%
Rat	320	180	45	100%
Rat	160	420	45	54%
Mouse	16000	5	45	100%
Mouse	1600	30	45	100%
Mouse	790	60	45	100%
Mouse	320	180	45	100%
Mouse	160	420	45	96%
Guinea pig	16000	5	20	100%
Guinea pig	1600	30	20	100%
Guinea pig	790	60	20	100%
Guinea pig	320	180	20	90%
Guinea pig	160	420	20	0%
Rabbit	16000	5	8	100%
Rabbit	1600	30	8	100%
Rabbit	790	60	8	100%
Rabbit	320	180	8	100%
Rabbit	160	420	8	88%

Appendix 2 Reference list

AEGL 2002, Fluorine, Interim Acute Exposure Guideline Levels (AEGLs) for NAS/COT Subcommittee for AEGLs February 2002

Eriksen, N. 1945. A Study of the Lethal Effect of the Inhalation of Gaseous Fluorine (F2) at Concentrations from 100 ppm to 10,000 ppm. DOE/EV/03490-T3, United States Atomic Energy Commission, Pharmacology Report 435. University of Rochester, Rochester, NY. NTIS DE85-010190.

Keplinger, M.L., Suissa, L.W.: Toxicity of Fluorine Short-Term Inhalation. Am. Ind. Hyg. Assoc. J. 1968; 29: 10-18.

Stokinger, H.E. 1949. Toxicity following inhalation of fluorine and hydrogen fluoride, Chapter 17. In: Pharmacology and Toxicology of Uranium Compounds, C. Voegtlin and H.C. Hodge, eds. NewYork: McGraw-Hill Book Company.