National Institute for Public Health
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Ministry of Health, Welfare and Sport

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). 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 Fluorine

1. Substance identification

CAS-number:	7782-41-4
IUPAC name:	Fluorine
Synonyms:	Bifluoriden, fluor, fluorine-19, fluoro
Molecular formula:	F_2
Molecular weight:	38.0 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	-188°C (at 101.3 kPa)
Vapour pressure:	10000 kPa (at 20°C)
Saturated vapor conc:	N/A
Conversion factor:	1 mg/m3 = 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:	H330-H314

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 human toxicity following acute inhalation exposure were identified in which details about both health effects and the exposure have been documented in sufficient detail.
In a volunteer study by Keplinger and Suissa (1968), males exposed to 10 ppm (15.8 mg/m^3) for 15 minutes did not show irritation to eyes, skin or respiratory tract. At 25 ppm (39.5 mg/m^3) for 5 minutes irritation effects were noted, but no respiratory difficulties.

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 fluorine, 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

[1] AEGL2010.

- 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 2 studies were identified -with 8 datasets for 4 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, 4 datasets was/were assigned status B and 4 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies were found in which sensory irritation of fluorine was studied. In the final AEGL it is stated that adaptation to sensory irritation occurs at levels of mild irritation. It is unclear if this statement really refers to sensory irritation or 'typical' irritation effects since no studies were performed to identify effects of sensory irritation, i.e. respiratory rate depression.

5. Probit functions from individual studies

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

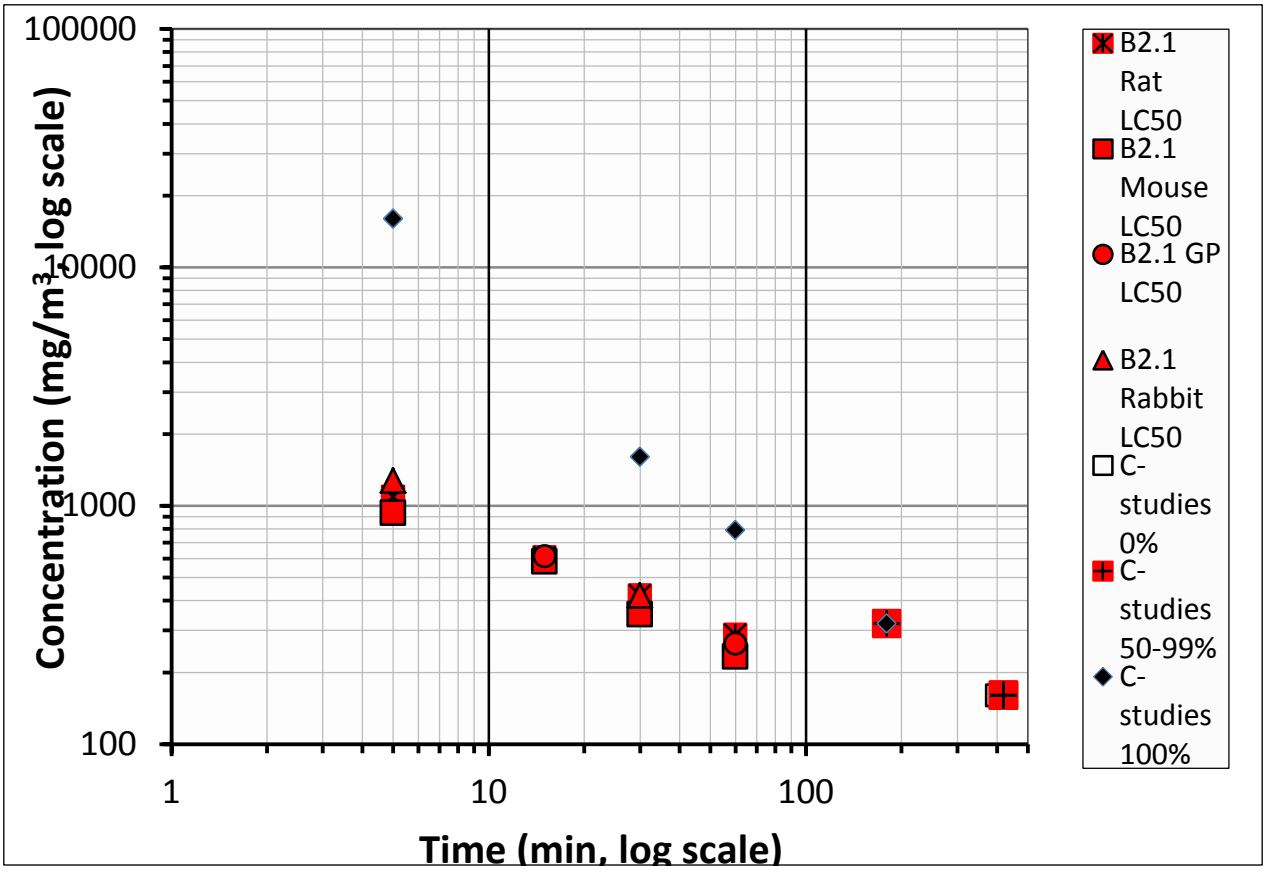


Figure 1 *All available acute lethality data for fluorine.*

The data that were selected for initial analysis of the animal probit function are presented in Table 1 and Figure 2.

Because studies with A or B1 quality were not found, the probit function was derived using data from the study by Keplinger and Suissa (1968) with B2 quality listed in the table below.

Table 1 *Data selected for initial analysis of the animal probit function of fluorine.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (exposure duration)	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B2.1	Rat		1088 (5 min) 606 (15 min) 420 (30 min) 287 (60 min)	420	1.87
	Mouse		932 (5 min) 583 (15 min) 350 (30 min 233 (60 min)	350	1.77
	Guinea Pig		614 (15 min) 264 (60 min)	420 386 GM: 403	
	Rabbit		1274 (5 min) 420 (30 min	420	

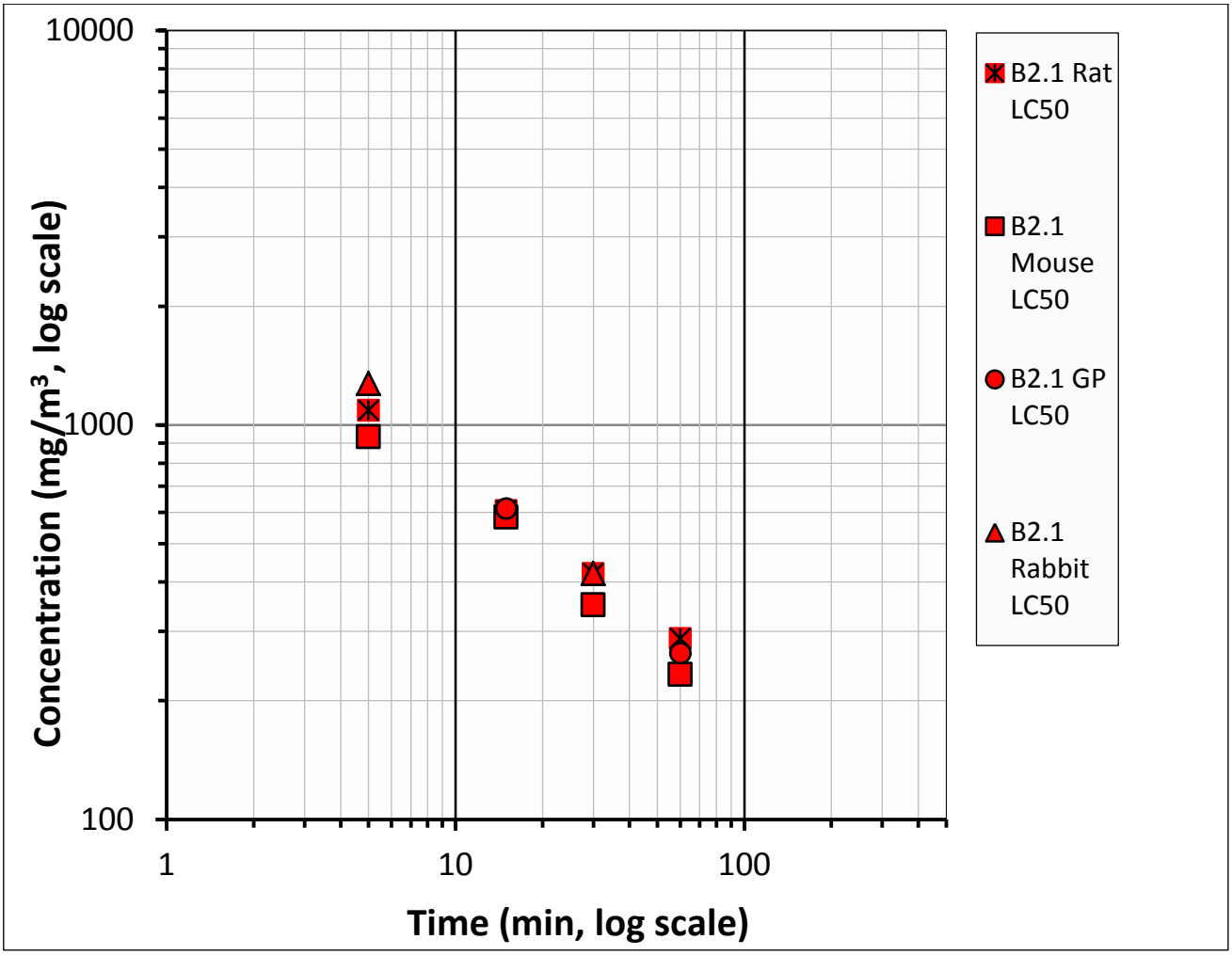


Figure 2 *LC_{50} values of B2.1 datasets for fluorine.*

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.

Based on criteria outlined in the guideline the data from study B2.1 were selected for the final dataset for the derivation of the animal probit function. The B2 study does not report the individual concentration data, making it impossible to evaluate the LC_{50} values derived by the study authors. Otherwise, the study is relatively well described and includes four exposure durations for four species and two exposure durations for two more species. The data for the rat and mouse can qualify as B2 datasets. Since there are no other eligible studies available for probit function derivation it was decided to use the study by Keplinger and Suissa (1968; B2.1). Even though the datasets for the guinea pig and rabbit do not qualify as a B2 dataset since only two exposure durations were reported where three are required, these datasets were included for derivation of the point of departure. The reason is that LC_{50} values for a common exposure duration could be derived for these species, and there is no valid argument that the LC_{50} values for the guinea pig and rabbit are less scientifically sound than those for the rat and mouse as the experimental designs were identical. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 3.

The final data eligible for calculating the animal probit function contains four datasets from one study and includes data from four animal species.

Table 2 *Data selected for the derivation of the animal probit function of fluorine.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (exposure duration)	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B2.1	Rat		1088 (5 min) 606 (15 min) 420 (30 min) 287 (60 min)	420	1.87
	Mouse		932 (5 min) 583 (15 min) 350 (30 min 233 (60 min)	350	1.77
	Guinea Pig		614 (15 min) 264 (60 min)	*420* *386* *GM: 403**	
	Rabbit		1274 (5 min) 420 (30 min	420	

* This value was used to derive the geometric mean of the 30 min LC_{50} value for the different species. There is no scientific reason for either of the two options, i.e. scaling from 15 minutes or from 60 minutes; therefore, the geometric mean 30 min LC_{50} was calculated and used for the guinea pig.

The data of the selected datasets are presented graphically below.

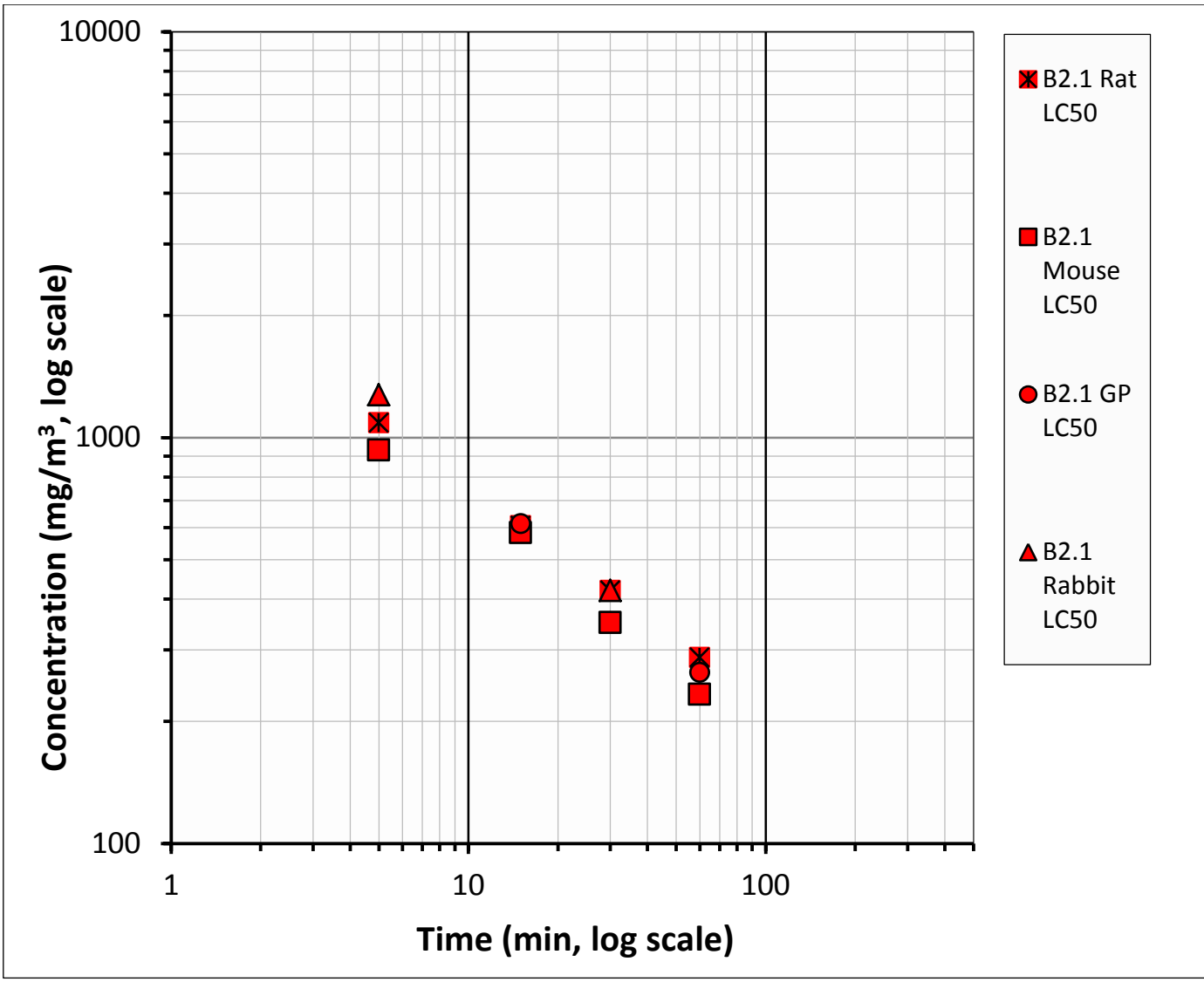


Figure 3 *Final data selected for derivation of the animal probit function of fluorine (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from Keplinger and Suissa (1968; B2.1) have been used to derive a point of departure as outlined above.

First, the arithmetic mean n-value was calculated from studies B2.1.
The species-specific n-value was 1.87 for the rat, 1.77 for the mouse. The arithmetic mean n-value across species is the simple arithmetic mean of the species-specific mean n-values, without weight and was calculated to be 1.82.

Second, the LC_{50}-values of all applicable B2 datasets were used or derived by scaling for a common exposure duration of 30 minutes. To enable this inter-species pooling, the LC_{50}-value of the B2 dataset for guinea pigs was scaled using the overall n-value of 1.82 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 = overall n-value

Finally, a geometric mean overall LC_{50}-value was calculated from the available LC_{50} values (1 per species). The formula for the geometric mean of (time-scaled) LC_{50}-values between species is as follows:

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

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value across species
$LC_{50,j}$ = LC_{50}-value of species j.
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 30-minute geometric mean animal LC_{50} value of 397.2 mg/m^3 and an arithmetic mean n-value of 1.82.

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

Table 3 Rationale for the applied assessment factors.

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	2	The animal to human extrapolation factor was lowered from 3 to 2, because the study by Keplinger and Suissa (1968) showed little differences in LC_{50} values for four species.
Nominal concentration	1	Measured concentrations were used.
Adequacy of database:	2	There is one B2 study available. Overall the database is limited.

The estimated human equivalent 30-minute LC_{50} value is 397.2 / 4 = **99 mg/m^3**.

The experimentally determined n-value was **1.82** (Based on B2.1, see above for explanation). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.10**.

The human probit function is then calculated on the human equivalent 30 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): 5 = a + 1.10 × ln ($99^{1.82}$× 30) resulting in the a-value of **-7.93**.

Pr = -7.93 + 1.10 × ln (C $^{1.82}$ × t) with C in mg/m^3 and t in min.

The derived human probit function has a scientifically weak basis. The probit function is based on one study with B2 quality with four species.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 14 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 21 mg/m^3.

Table 4 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	21	14
1% lethality, this probit	31	21
AEGL-3[2] (2010 final)	30	21
ERPG-3[3] (2009)		32
LBW (2017)	58	40

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are lower than the LBW and comparable to AEGL and ERPG.

[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: B2.1

Author, year: Keplinger and Suissa, 1968

Substance: fluorine

Species, strain, sex: Rat, Osborne-Mendel, sex unspecified; Mouse, Swiss-Webster, sex unspecified; Guinea pigs, New England, sex unspecified; Rabbit, New England, sex unspecified

Number/sex/conc. group: 10 rats, 10 mice, 5 guinea pigs, 5 rabbits

Age and weight: unknown

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	*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*
Type of restrainer	*N/A*
Pressure distribution	*Slight negative pressure in the chamber (0.1 inch of water)*
Homogeneity of test atmosphere in breathing zone of animals	*Air flow entered along the top and left along the bottom of the chamber. No flow rate given. A mixing fan was built in the rear of the chamber to facilitate uniform distribution*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Cannot be calculated*
Start of exposure relative to equilibration	*A sliding drawer was used for rapid entrance or egress of the animals from the exposure chamber. It took approximately one second for entrance or egress.*
Actual concentration measurement	*Yes, colorimetrically. The mean recovery was 99.4% with SD of 2.4%. 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	***B2*** *four exposure durations were tested and corresponding LC_{50} values calculated for rat and mouse data. An n value could be derived based on these data. However, details on concentration groups and response were lacking.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	LC50 value	95% CI		
Rat	1088	(1005-1127)	5	LC50
	606	(570-667)	15	LC50
	420	(367-495)	30	LC50
	287	(224-379)	60	LC50
Mouse	932	(817-1100)	5	LC50
	583	(544-648)	15	LC50
	350	(314-401)	30	LC50
	233	(220-256)	60	LC50
Guinea pig	614	(556-700)	15	LC50
	264	(240-300)	60	LC50
Rabbit	1274	(1153-1454)	5	LC50
	420	(379-490)	30	LC50

Probit function

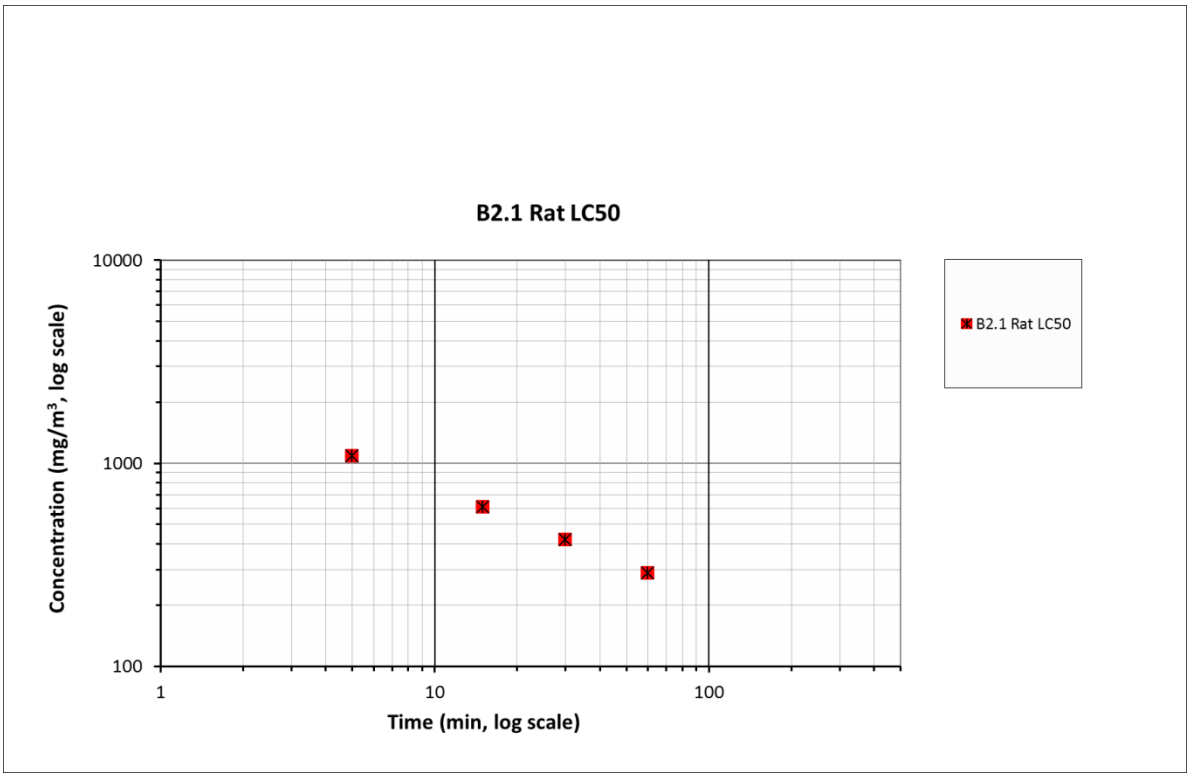
The available information was insufficient to derive a probit relation for the concentration-duration-mortality response to fluorine in the species mentioned in this study. However, as LC50 values were provided for more than two exposure durations for both the rat and mouse n-values could be calculated using the following formula:

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

N-value rat

The calculated n-value was 1.87.

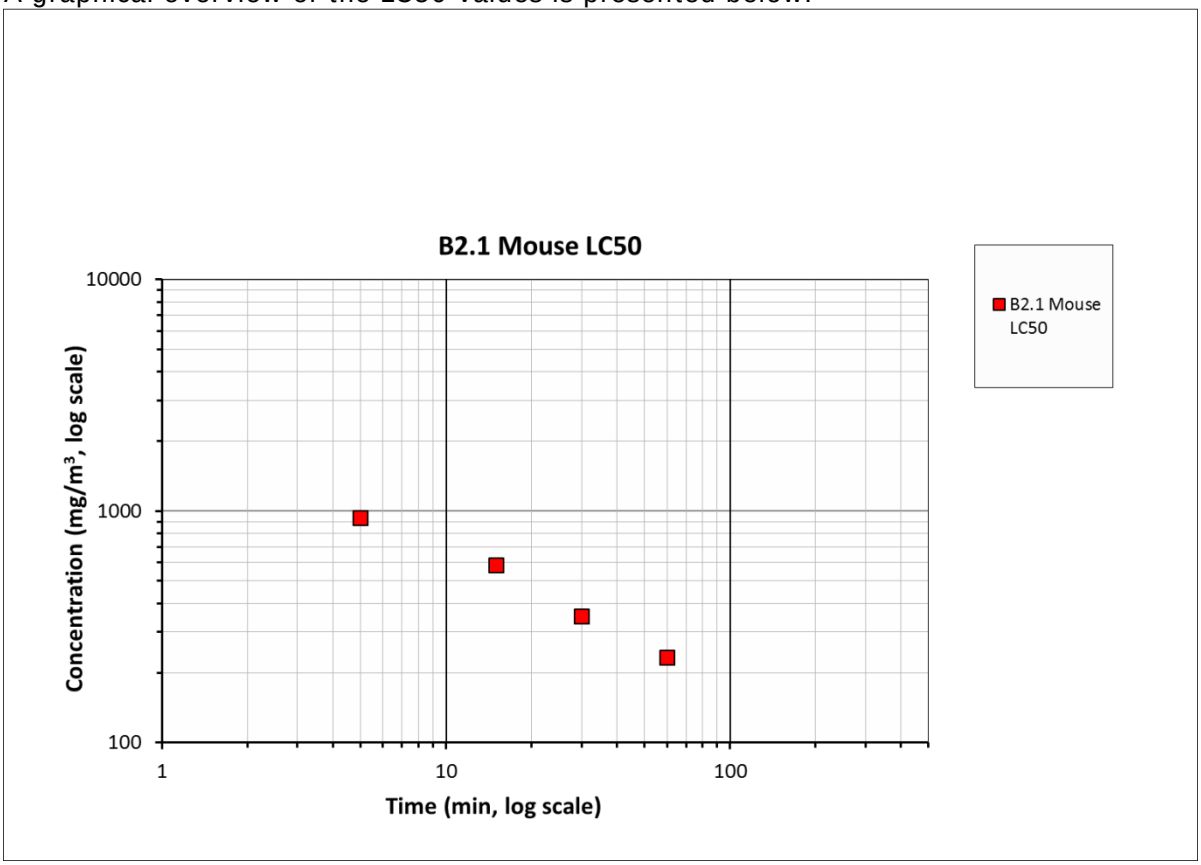
A graphical overview of the LC50 values is presented below.



N-value mouse

The calculated n-value was 1.77.

A graphical overview of the LC50 values is presented below.



Study ID: C studies

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/m3)	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, 2010. National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 8. Washington, DC. The National Academies Press, 2010.

Chemiekaarten. Ed 32. Den Haag. TNO/SDU uitgevers, 2017.

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.

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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.