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
Acrylonitrile	**107-13-1**

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.

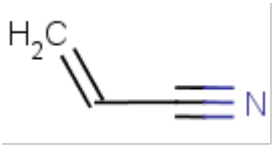
The decision on actual implementation depends on the results of a further consequence analysis.

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 Acrylonitrile

1. Substance identification

CAS-number:	107-13-1
IUPAC name:	acrylonitrile, acrylnitril, 2-propenenitril
Synonyms:	acrylnitril, 2-propene nitril, vinyl cyanide, AN
Molecular formula:	C_3H_3N
Molecular weight:	53.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	77°C (at 101.3 kPa)
Vapour pressure:	11.5 kPa (at 20°C)
Saturated vapor conc:	115,000 ppm = 254 g/m^3 (at 20°C and 101.3 kPa)
Conversion factor:	1 mg/m^3 = 0.452 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.21 mg/m^3 (at 20°C and 101.3 kPa)
Labelling :	H: 350, 331, 311, 301, 335, 315, 318, 317



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

Acute effects: The main target organs and tissues for inhalation exposure to acrylonitrile are the respiratory tract, the central nervous system and cardiovascular system. The health effects following acute inhalation exposure to acrylonitrile appear to be irritation of the respiratory tract and health effects resulting from the metabolism of acrylonitrile to cyanide, such as loss of consciousness and inhibition of the respiratory system. Acrylonitrile-induced neurological effects in laboratory animals appear to involve the parent compound and the cyanide metabolite.
Symptoms of high exposure are irritation, headaches, respiratory discomfort, seizures and clonic convulsions. Lethality results from respiratory arrest.
Long-term effects: Chronic exposure produces similar effects as acute exposure, where insomnia is often mentioned in addition.

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.
Schwanecke (1966) report a 1hr-LCLo (meaning a lethal concentration resulting in an unknown mortality rate) of 452 ppm (999 mg/m^3) without further information.
In a human volunteer study subjects were exposure up to 10 mg/m^3 for 8 hrs (three 10 minute breaks), without any symptoms. In a 10-year epidemiological study in workers daily exposed to 5 ppm (11 mg/m^3) complaints of headache, fatigue, nausea, and insomnia were mentioned.
Toxicokinetic information provided in the AEGL 2014 document on acrylonitrile indicates that the concentration of acrylonitrile and the toxic metabolite cyanoethylene oxide can be a factor 2 higher in humans than in rats, based on a pharmaco-kinetic model (Sweeney et al. 2003; as cited in AEGL final 2014). A PBPK model by Takano et al. (2010; as cited in AEGL final 2014) using in vitro metabolism data showed peak blood acrylonitrile concentrations 2-fold higher in rats than in humans. This motivated an toxicokinetic factor of 2 in the interspecies factor used to derive the AEGL values for acrylonitrile. However, as the data above shows some inconsistencies as to whether humans are more or less susceptible than rats, no adjustment of the default intraspecies factor was applied.

[1] AEGL final, 2014.

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 acrylonitrile, 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 considering acute exposure are described in Appendix 1. A total of 4 studies were identified -with 9 datasets for 6 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, one dataset in one study was assigned status B1, two datasets were assigned B2, and six datasets from two studies were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies on sensory irritation were found.

5. Probit functions from individual studies

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

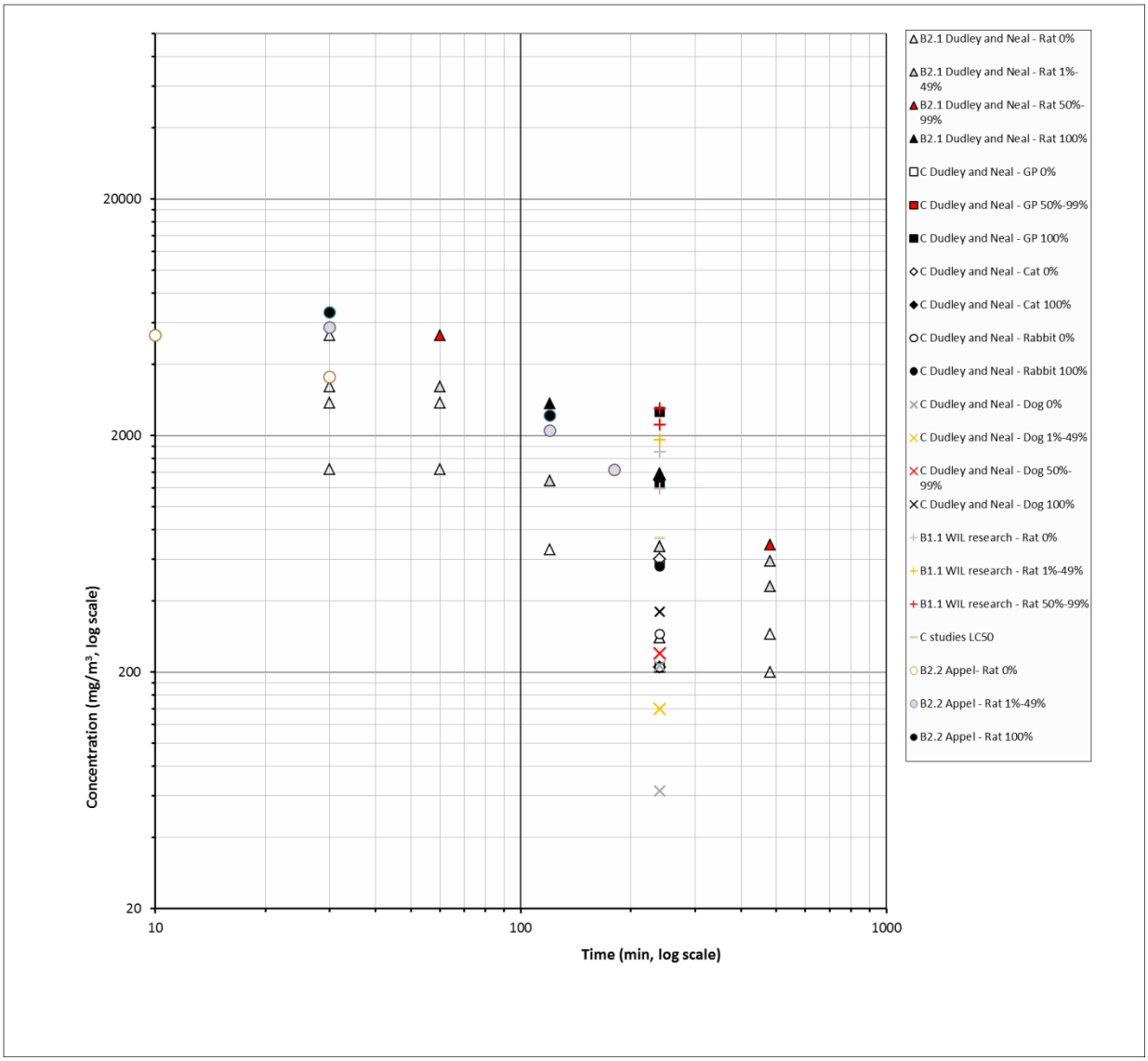


Figure 1 *All available acute lethality data for acrylonitrile.*

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

In accordance with the criteria laid down in the guideline a concentration time relationship was derived from the 4-hour LC_{50} value of the B1 study combined with the average n-value from the two B2 studies.

It was possible to derive a probit function for acrylonitrile based on the available study with B1 quality. Therefore, the probit function was derived using data from the study with B1 quality, which did not enable to produce a concentration-time-lethality relationship. Two B2 studies with a concentration-time-lethality relationship were used to derive the n-value.

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (specify exposure duration)	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B1.1	Rat	*240 min LC_{50}*	2090	-	N/A
B2.1	Rat	-43.5 + 3.96×lnC + 3.83×lnt	-	7670 (6270-9874)	1.03 (0.92-1.15)
B2.2	Rat	-144 + 13.3×lnC + 9.91×lnt	-	5858 (4836-6330)	1.34 (1.21-1.47)

The data of the B1 and B2 studies with rats are presented graphically below.

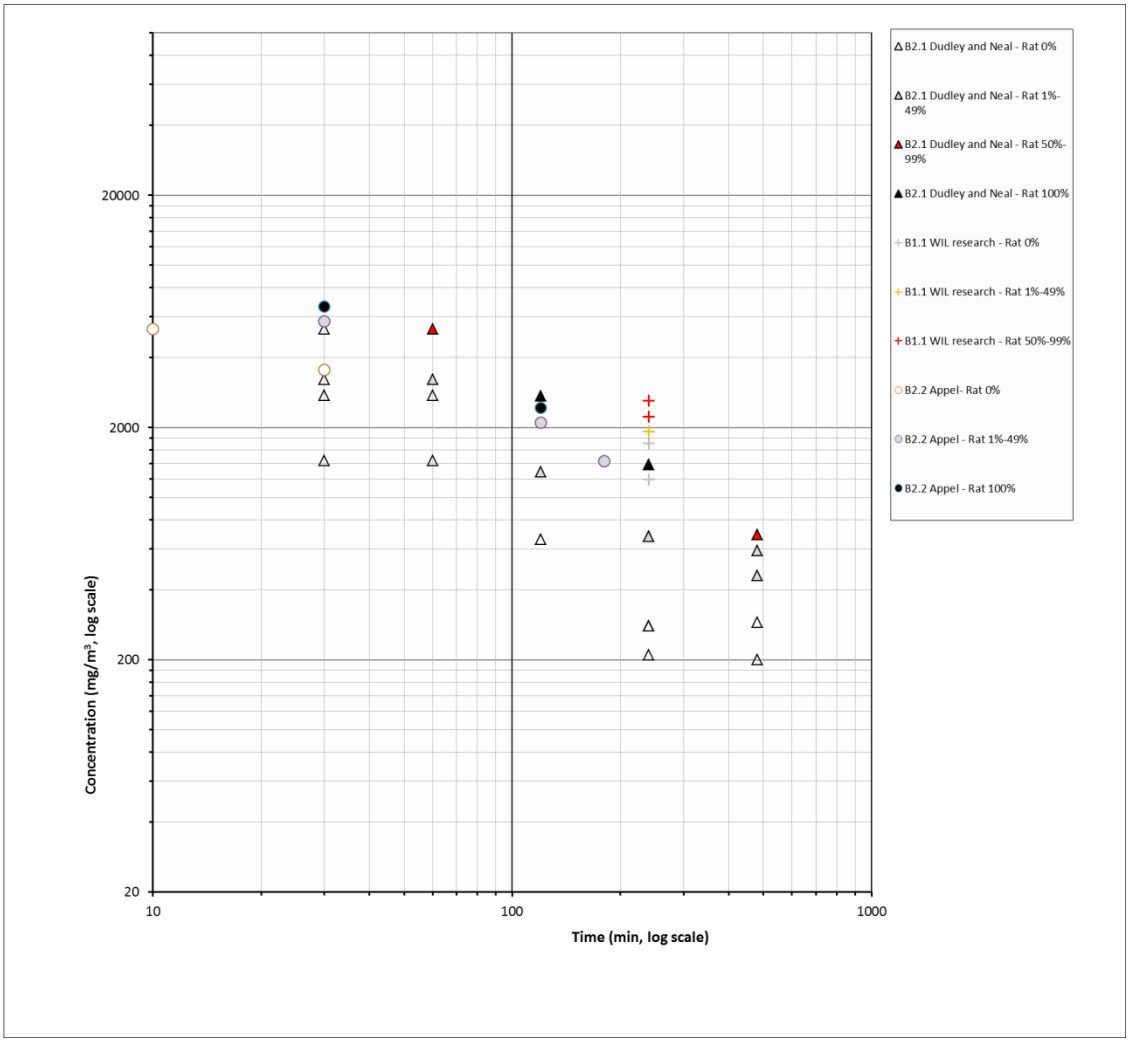


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of acrylonitrile.*

Based on criteria outlined in the guideline the data from studies B1.1, B2.1 and B2.2 were selected for the final dataset for the derivation of the animal probit function. The data that were selected for final analysis of the animal probit function, including the B2 studies used to derive the n-value, are presented in Table 3 and Figure 3.

The final data eligible for calculating the animal probit function contains three datasets from three studies and includes data from one animal species, i.e. the rat.

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (specify exposure duration)	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B1.1	Rat	*240 min LC_{50}*	2090	-	N/A
B2.1	Rat	-43.5 + 3.96×lnC + 3.83×lnt	-	7670 (6270-9874)	1.03 (0.92-1.15)
B2.2	Rat	-144 + 13.3×lnC + 9.91×lnt	-	5858 (4836-6330)	1.34 (1.21-1.47)

The data of the selected datasets are presented graphically below.

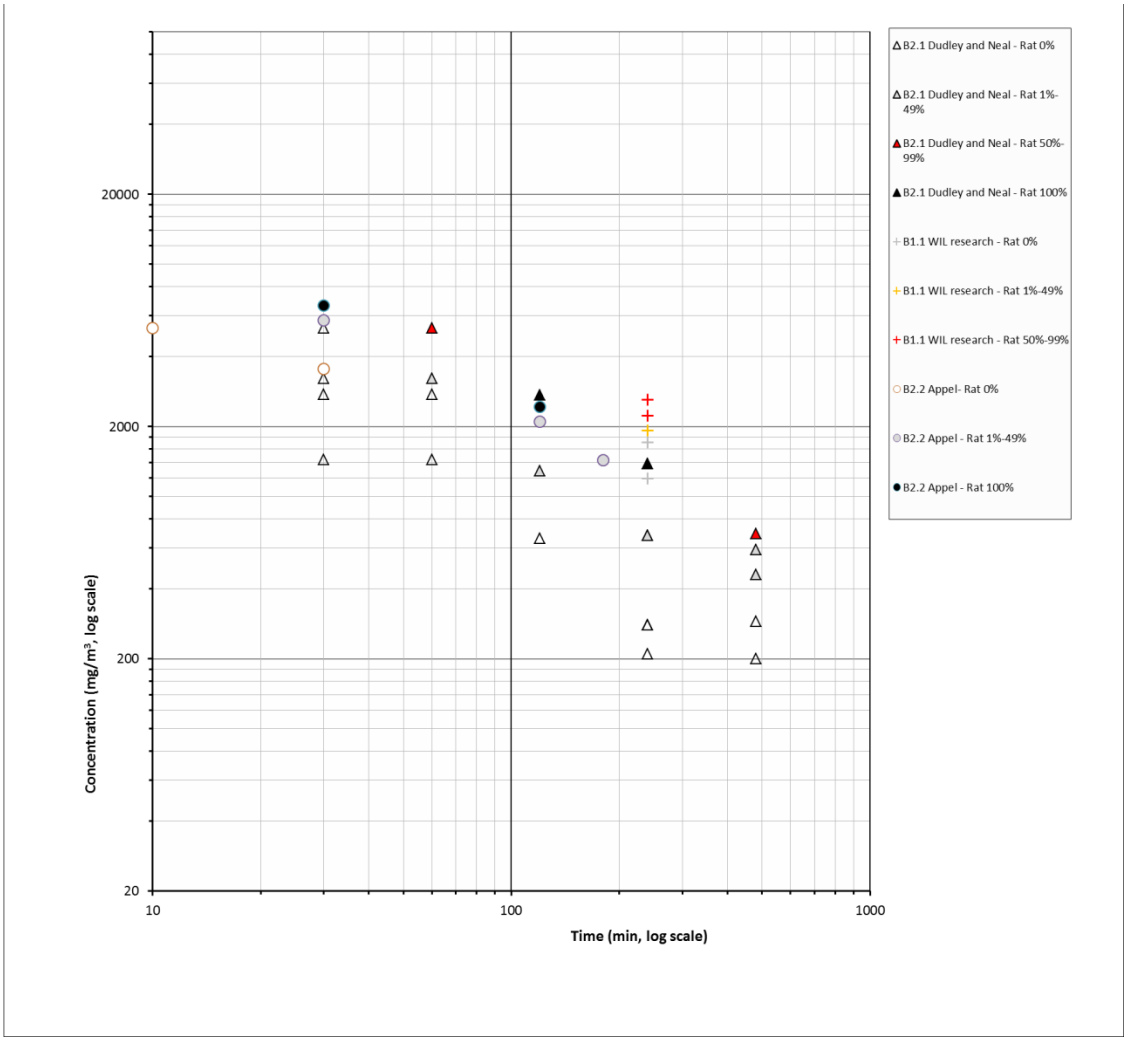


Figure 3 *Final data selected for derivation of the animal probit function of acrylonitrile (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from WIL Research Laboratories, 2005 (B1.1) have been used to derive a point of departure for the animal LC_{50} as outlined above.

First, the arithmetic mean n-value was calculated from studies B2.1 (Dudley and Neal, 1942) and B2.2 (Appel et al., 1981).

The arithmetic mean species-specific (rat) n-value was calculated to be 1.185.

Second, the LC_{50}-value of the B1-study was calculated to be 2090 mg/m^3 for 240 minutes.

The Point of Departure for the human probit function is a 240-minute animal LC_{50} value of 2090 mg/m^3 and an arithmetic mean n-value of 1.19.

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:	3	Default value, see also section 3.
Nominal concentration	1	The concentrations were measured analytically in the B1.1 study.
Adequacy of database:	1	One B1 study and two B2 studies are available.

The estimated human equivalent 240-minute LC_{50} value is 2090 / 3 = **697 mg/m^3**.

The experimentally determined n-value was **1.19** (arithmetic mean of two n-values from studies B2.1 and B2.2). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.69**.

The human probit function is then calculated on the human equivalent 240 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.69 \times \ln(697^{1.19} \times 240)$ resulting in the a-value of **-17.34**.

$Pr = -17.3 + 1.69 \times \ln(C^{1.19} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically acceptable basis. The probit function is based on three studies in the rat with B1 and B2 quality, including 50 animals tested in the B1 study and 26 C x t combinations in the two B2 studies combined.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 451 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 658 mg/m^3.

Table 4 *LC-vales 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	807	451

1% lethality, this probit	1178	658
AEGL-3[2] (2014, final)	111	62
ERPG-3[2] (1997)		166
LBW (2016)	440	220

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

[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: B1.1

Author, year: WIL Research Laboratories, 2005

Substance: acrylonitrile
Species, strain, sex: Crl:CD/(SD) rats, males and females
Number/sex/concentration group: 5
Age and weight: 8-12 weeks old; Females 242-264 g. Males: 264-297 g.
Observation period: 14 days

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*yes*
Study carried out according to guideline(s)	*yes, with OECD guideline 403*
Stability of test compound in test atmosphere	*stable.*
Use of vehicle (other than air)	*nitrogen*
Whole body / nose-only (incl. head/nose-only) exposure	*nose only*
Type of restrainer	*No information*
Pressure distribution.	*No information*
Homogeneity of test atmosphere at breathing zone of animals	*Test atmosphere was generated by using a heated glass gas-washing bottle through which compressed nitrogen was supplied, where it then bubbled to generate a vapour of the test substance. By dilution with compressed air the mixture was administered to the nose-only system.*
Number of air changes per hour	*The generation air flow rates ranged from 164-300 mL/min. The dilution air flow rates ranged from 19-24 L/min.*
Equilibration time (t95)	*No information*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Samples were taken at least every 20-30 minutes. Analysis by gas-chromatography.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Particle detection took place by light scattering techniques. No aerosol formation observed.*
Assessment of Reliability	***B1*** *Well conducted study. Study was not given the A status, because one exposure duration was used.*

Results

Species	Concentration (analytical, mg/m^3)	Concentration (analytical, mg/m^3) adjusted	Exposure duration (min)	Lethality	
				Male	Female
Rat	1191	N/A	240	0/5	0/5
	1713		240	0/5	0/5
	1925		240	1/5	3/5
	2223		240	3/5	4/5
	2610		240	5/5	4/5

The study report provided 4-hr LC_{50} values of 964 ppm (857-1085 ppm confidence interval) (2130 (1894-2398 mg/m^3)) for males, 920 ppm (807-1050 ppm confidence interval) (2033 (1783-2321 mg/m^3)) for females, and 946 ppm (866-1032 ppm 95% confidence interval) (2091 (1914-2281 mg/m^3)) combined.

Probit function

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

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

with C for concentration in mg/m^3

Probit function	*Species*	*a*	*b*
	Rat, males and females combined	*-48.8*	*7.04*
	Rat, males	*-74.0*	*1.03*
	Rat, females	*-36.2*	*5.40*

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

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***Combined***	*LC_{50} (mg/m^3) 95%-C.I.* ***Males***	*LC_{50} (mg/m^3) 95%-C.I.* ***Females***
240	2090 (1938-2267)	2131 (1945-2378)	2034 (1696-2414)

Study ID: B2.1

Author, year: Dudley and Neal, 1942

Substance: Acrylonitrile
Species, strain, sex: rats, Albino Osborne-Mendel, gender not specified
Number/sex/concentration group: 16 per concentration group
Age and weight: adults, average weight 295 g
Observation period: Unclear, dogs exposed in the same study were observed up to 15 days after exposure.

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)	*N/A*
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	*Test atmosphere was generated by bubbling air through test substance (with a boiling point of 76-77°C) and mixing this saturated air stream with a main air stream. The concentration of the acrylonitrile was varied by adjusting the volume of air passing through the bubbler. Air was mixed by an electric fan.*
Number of air changes per hour	*Air flow through the exposure chamber was 260 L/min (±2%). Chamber volume not stated.*
Equilibration time (t95)	*Cannot be derived.*
Start of exposure relative to equilibration	*It was stated by the study authors that "a 20-min interval was allowed in order to bring the chamber to the desired concentration. In past experience, this was interval was found ample to provide an atmosphere of the desired concentration inside the chamber. By this procedure the animals were introduced into and withdrawn from a constant known concentration so that the known exposure was begun and terminated at a definite time".*

Actual concentration measurement	*Analytical concentrations were not given. The concentration of acrylonitril in the chamber was determined by the change in weight of the acrylonitrile in the bubbler, air flows and start/stop times. Concentrations listed in the results table are target concentrations. The concentration in the chamber was stated by the authors to be constant and accurate to within the limits of ± 2%.* *The authors referred to a study by Dudley and Millar (1937) where the dose regime was clarified, showing high correlations between nominal and analytical concentrations measured in the chamber of hydrogen selenide.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***B2*** *The study was not given the A status because the observation period after exposure is unclear and actual analytical concentrations were not given.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		combined	remark
Rat	5300	N/A	30	0/16	
	3230		30	0/16	
	2750		30	0/16	
	1440		30	0/16	
	5300		60	13/16	
	3230		60	4/16	
	2750		60	0/16	
	1440		60	0/16	
	2730		120	16/16	
	1290		120	1/16	
	660		120	0/16	
	1380		240	16/16	
	680		240	5/16	
	280		240	0/16	
	690		480	15/16	
	590		480	7/16	
	460		480	1/16	
	290		480	0/16	
	200		480	0/16	

Rat, 4hr	1380		240	16/16	possibly reported twice
	680		240	5/16	possibly reported twice
	280		240	0/16	possibly reported twice
	210		240	0/16	

Probit function

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

$Pr = a + b \times lnC + c \times lnt$

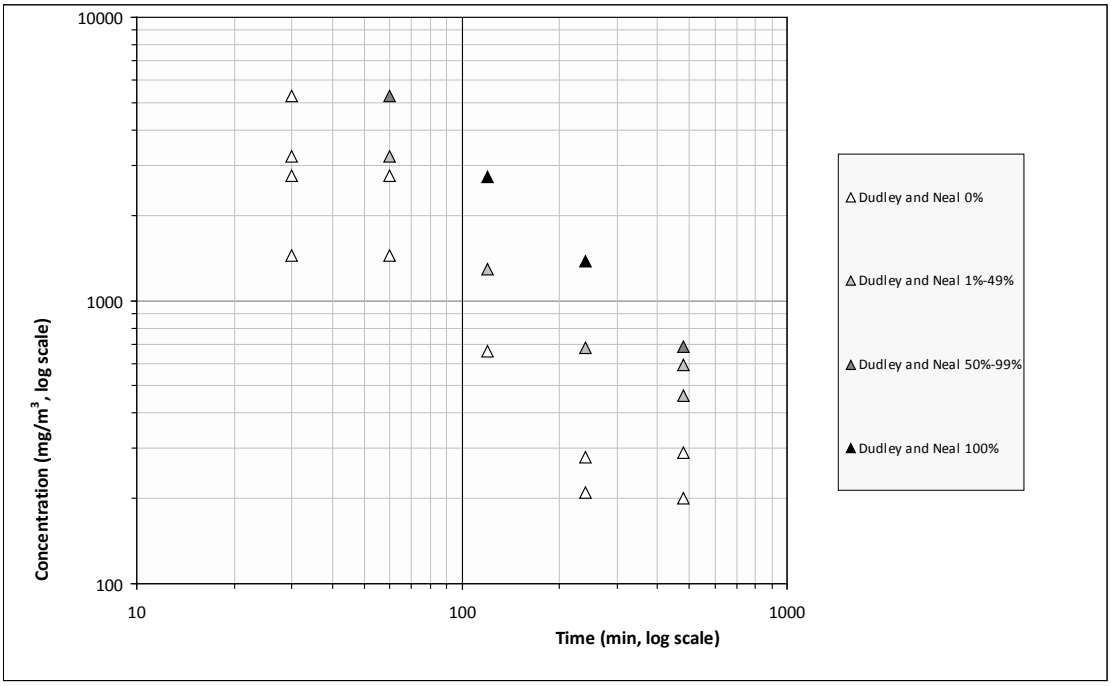
with C for concentration in mg/m^3, t for time in minutes.

Probit function	*Species*	*a*	*b*	*C*	*n-value*
Sexes combined	*Rat*	*-43.5*	*3.96*	*3.83*	*1.03 (0.92 - 1.15)*
Sexes combined, incl. possibly double reported data	*Rat*	*-40.1*	*3.67*	*3.62*	*1.01 (0.90 – 1.12)*

Because it is uncertain whether or not the 4-hr data was reported twice and the probit analyses show no significant differences, the lethality values below are based on the dataset without the possibly double reported data.

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.*
10	22190 (16380-32540)
30	7670 (6270-9874)
60	3924 (3395-4689)

A graphical overview of the data is presented below. Each concentration-time combination (with 16 animals) represents one point in the plot.


10000
1000
100
10
100
1000
Concentration (mg/m3 , log scale)
Time (min, log scale)
Dudley and Neal 0%
Dudley and Neal 1%-49%
Dudley and Neal 50%-99%
Dudley and Neal 100%

Study ID: B2.2

Author, year: Appel et al., 1981

Substance: acrylonitril
Species, strain, sex: male Wistar rats
Number/sex/concentration group: 3 or 6/group
Age and weight: age unknown, weights ranged from 200-300 g.
Observation period: not stated

Evaluation of study quality

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*No statement of compliance with OECD guideline 403 provided*
Stability of test compound in test atmosphere	*stable*
Use of vehicle (other than air)	*synthetic 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	*Air stream entering a halothane vaporator containing acrylonitril. This air stream leaving the vaporator is mixed with a diluting air flow.*
Number of air changes per hour	*Air changes not stated.*
Equilibration time (t95)	*Insufficient information to calculate*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*The gas mixture samples were drawn from the closed system and injected in the gas chromatograph.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***B2,*** *little information was provided about the experimental design.*

Results

Species	Concentration (analytical, mg/m^3)	Concentration (analytical, mg/m^3) adjusted	Exposure duration (min)	Lethality	
				Male	
Rat	1437	N/A	180	1/3	
	2100		120	1/3	
	2431		120	3/3	
	3536		30	0/3	
	5304		10	0/3	
	5746		30	1/3	

	6630		30	6/6	

Probit function

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

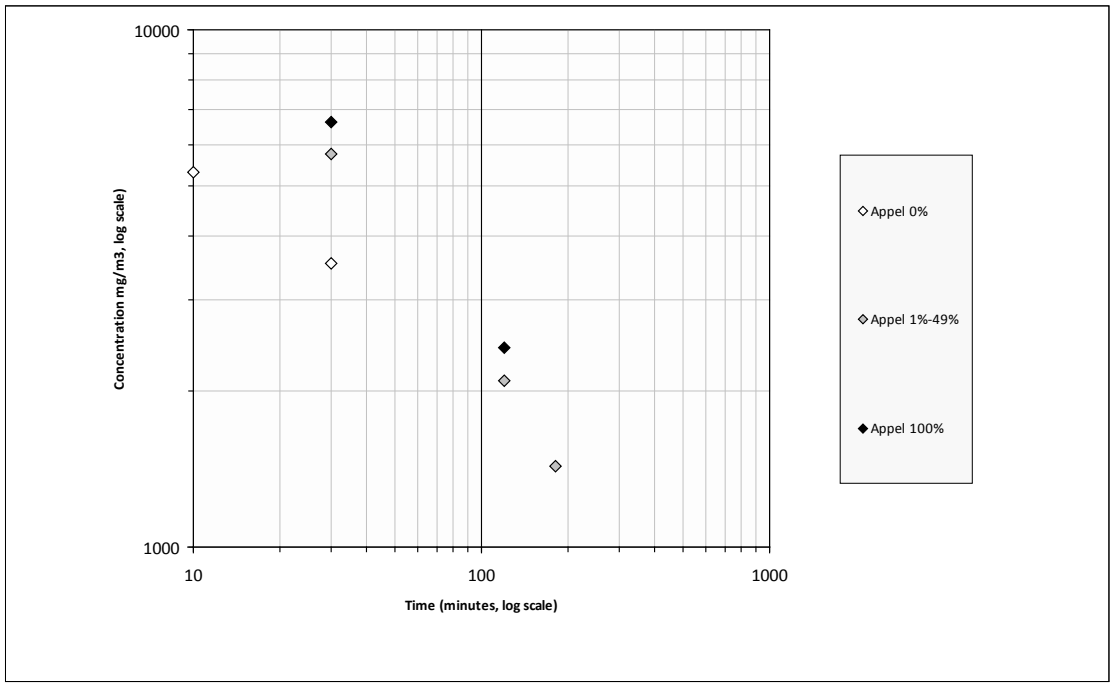
$Pr = a + b \times \ln C + c \times \ln t$

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

Probit function	*Species*	*a*	*b*	*c*	*n-value*
	Rat	*-144*	*13.3*	*9.91*	*1.34 (1.21 - 1.47)*

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.*
10	13290 (9494-15330)
30	5858 (4836-6330)
60	3494 (3099-3693)

A graphical overview of the data is presented below. Each concentration-time combination (3-6 animals) represents one point in the plot.



Study ID: C

Author, year: Dudley and Neal, 1942

Substance: acrylonitril
Species, strain, sex: Albino Osborne-Mendel rats, guinea pigs, albino rabbits, cats, dogs, rhesus monkeys
Number/sex/concentration group: 16/group (rats), 8 or 16/group (guinea pigs), 2 or 3/group (rabbits), 2 or 4/groups (cats), 2 or 3/group (dogs), 2 or 4/group (rhesus monkeys)
Age and weight: all adults. Average weights: 295 g (rats), 695 g (guinea pigs), 4530 g (rabbits), 3620 g (cats). Weights of dogs ranged from 5 to 12 kg and rhesus monkeys ranged from 4.2 to 4.8 kg.
Observation period: Unclear, dogs exposed in the same study were observed up to 15 days after exposure.

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)	*N/A*
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	*Test atmosphere was generated by bubbling air through test substance (with a boiling point of 76-77°C) and mixing this saturated air stream with a main air stream. The concentration of the acrylonitril was varied by adjusting the volume of air passing through the bubbler. Air was mixed by an electric fan.*
Number of air changes per hour	*Air flow through the exposure chamber was 260 L/min (±2%). Chamber volume unknown*
Equilibration time (t95)	*Cannot be derived.*
Start of exposure relative to equilibration	*It was stated by the study authors that "a 20-min interval was allowed in order to bring the chamber to the desired concentration. In past experience, this was interval was found ample to provide an atmosphere of the desired concentration inside the chamber. By this procedure the animals were introduced into and withdrawn from a constant known concentration so that the known exposure was begun and terminated at a definite time".*

Actual concentration measurement	*Concentrations were not analytically determined. The concentration of acrylonitrile in the chamber was determined by the change in weight of the acrylonitrile in the bubbler, air flows and start/stop times. Concentrations listed in the results table are target concentrations. The concentration in the chamber was stated by the authors to be constant and accurate to within the limits of ± 2%.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***C,*** *Despite the fact that the rat-study with several C x t combinations was given the B2 qualification (also because of the C x t combinations), the results for the individual species included in this reference with only one exposure duration, an unclear observation period and lack of actual concentrations analyses, and in some cases only zero or 100% mortality led to the qualification C-study.*

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality
Rats[3]	1380	240	16/16
	680	240	5/16
	280	240	0/16
	210	240	0/16
Guinea pigs	2520	240	8/8
	1250	240	5/8
	580	240	0/8
	210	240	0/16
Rabbits	1260	240	2/2
	560	240	2/2
	290	240	0/2
	210	240	0/3
Cats	1300	240	2/2
	600	240	0/2
	210	240	0/4

[3] Data also reported in results table under study B2.1

Dogs	360	240	2/2
	240	240	2/3
	213	240	0/3
	140	240	1/2
	63	240	0/3
Rhesus monkey	198	240	0/2
	140	240	0/4

Study ID: other C study

In a lethality study conducted at Haskell Laboratory (du Pont, 1968), groups of adult male ChR-CD rats (248-268 g) were exposed to acrylonitrile for 4 hours. The test chamber atmosphere was analyzed at least every half hour by gas chromatography. Test animals were observed for 14 days. During exposure the rats exhibited irregular respiration, hyperemia, lacrimation, tremors, convulsions. Deaths occurring during exposure occurred within 2-4 hours after the start of the exposure. Deaths occurring after exposure occurred between 7 minutes and 18 hours. A 4-hr LC_{50} of 333 ppm (275-405 ppm 95% confidence interval) (736 (608-895) mg/m^3) was reported. Rats surviving the exposure exhibited mild to severe, dose-related weight loss the first day of observation followed by normal weight gain.

Appendix 2 Reference list

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