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

Probit function technical support document

Date: 16 March 2023
Document id: 20230316-propylene oxide-INHOUDELIJK VASTGESTELD
Status: inhoudelijk vastgesteld (approved content)
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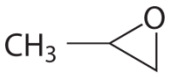
substance name	CAS number
Propylene oxide	**75-56-9**

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 "inhoudelijk vastgesteld" (approved content).

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 propylene oxide



1. Substance identification

CAS-number:	75-56-9
IUPAC name:	2-methyloxirane
Synonyms:	1,2-epoxypropane, methyloxirane, propene oxide, 1,2-propylene oxide
Molecular formula:	C_3H_6O
Molecular weight:	58.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	34°C (at 101.3 kPa)
Vapour pressure:	58.8 kPa (at 20°C)
Saturated vapor conc:	588000 ppm = 1401750 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.414 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.417 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H302-311-319-331-335-340-350

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

Acute effects: Much of the toxicologic evidence suggests that propylene oxide reacts at the site of entry. Therefore, inhalation of propylene oxide results in respiratory tract irritation, eventually leading to pulmonary oedema and death. Neurotoxic effects are also possible upon inhalation exposure to propylene oxide. General signs of toxicity after acute exposure to propylene oxide vapour included nasal discharge, lacrimation, salivation, gasping, lethargy and hypoactivity, weakness, and incoordination.

Long-term effects: Repeated exposures results in similar but generally reversible signs of toxicity.

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.

Data addressing inhalation toxicity of propylene oxide in humans were limited to one case report, general environmental work surveys, and molecular biomonitoring studies.

In AEGL (2010) the following is summarized: "Odor detection threshold values for propylene oxide ranged from 10 to 200 ppm (*24-483 mg/m^3*). The only case report of an occupational exposure was of a male worker accidentally exposed to a high concentration of propylene oxide for 10 to 15 min. Symptoms of exposure included eye and lung irritation, burning sensation in the chest, restlessness, headache, general weakness, diarrhea, and vomiting. The worker reportedly recovered. Other workplace exposure information was reported in environmental health surveys. Measured exposure concentrations of propylene oxide were as high as 1520 ppm (*3674 mg/m^3*) for 171 min with no reports of fatality. A strong odour and undefined irritation were noted at this concentration. In another report, 8-h TWAs measured over a 3-day sampling period indicated propylene oxide exposures ranging from 13.2 to 31.8 ppm (*32-77 mg/m^3*). Ambient air concentrations of propylene oxide ranged from none detected to 41.8 ppm (*101 mg/m^3*). The report noted no worker complaints.

[1] AEGL 2010

Molecular biomonitoring studies of workers exposed to low concentrations of propylene oxide have revealed a good correlation between haemoglobin adduction, decreased proficiency for DNA repair, and estimated exposure to propylene oxide. Cytogenetic studies have not found a significant correlation between in vivo propylene oxide exposure and micronuclei or chromosomal aberrations. Data on the potential carcinogenicity of propylene oxide in humans are limited and no definitive conclusions can be drawn."

The environmental health surveys were described in more details as follows and presented in the table below:

"In 1968, air sampling was conducted in the breathing zone of three workers during typical drumming operations of propylene oxide (CMA 1998). The sampling was conducted to evaluate the effectiveness of local exhaust ventilation in response to worker complaints of occasional eye irritation. Samples were taken starting 5 min after overhead heater fans were turned on (providing additional ventilation) or starting 5 min after the overhead heater fans were off (when worker complaints were typically noted). Air samples were collected in airtight Saran® bags and analyzed by vapor-phase chromatography."

and

"Exposures were 1,520 ppm (vol/vol) for 171 min, 1,310 ppm for 124 min, and 525 ppm for 121 min with the overhead heater fan turned off and 380 ppm for 177 min, 392 ppm for 135 min, and 460 ppm for 116 min with the overhead heater fan turned on (CMA 1998). The industrial hygienist was in the drumming booth during the monitoring periods and stated that "the odor was quite strong during the sampling; however, the irritation was not intolerable." Other observations noted by the hygienist included the following: "odor was quite obvious but not objectionable"; "pronounced odor, nonobjectionable"; and "general area in drumming room, about 10 feet from drumming station, odor was detectable but faint." No fatalities in the 30 potentially exposed workers (including the hygienist) occurred within 5 months of sampling, indicating that the measured exposures to propylene oxide were not fatal"

Summary Results of Personal Exposure Monitoring for Propylene Oxide During Typical Drumming Operations (AEGL, 2010)

Sample number	Description of Samples (taken in breathing zone of operators during drumming of propylene oxide)	Personnel Monitored	Sampling Duration (min)	TWA for Monitoring Period (ppm) *[mg/m^3]*
1	Sampling initiated 5 min after overhead heater fan turned on, heater fan on for duration of monitoring	Drumming operator 1	177	380 *[918]*
2	Sampling initiated 5 min after overhead heater fan turned off, heater fan off for duration of monitoring	Drumming operator 1	171	1520 *[3674]*
3	Sampling initiated 5 min after overhead heater fan turned off, heater fan off for duration of monitoring	Drumming operator 2	124	1310 *[3166]*
4	Sampling initiated 5 min after overhead heater fan turned off, heater fan off for duration of monitoring	Drumming operator 2	121	525 *[1269]*
5	Sampling initiated 5 min after overhead heater fan turned on,	Drumming operator 3	135	392

	heater fan on for duration of monitoring			*[947]*
6	Sampling initiated 5 min after overhead heater fan turned on, heater fan on for duration of monitoring	Drumming operator 3	116	460 *[1112]*

Abbreviation: TWA, time-weighted average.
Source: CMA 1998 (as cited in AEGL)

4. Animal acute toxicity data

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

1. AEGL final TSD and reference database for propylene oxide, 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 six studies were identified -with 11 datasets for four species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, six datasets were assigned status B1, two datasets were assigned status B2 and three 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 propylene oxide are displayed in Figure 1.

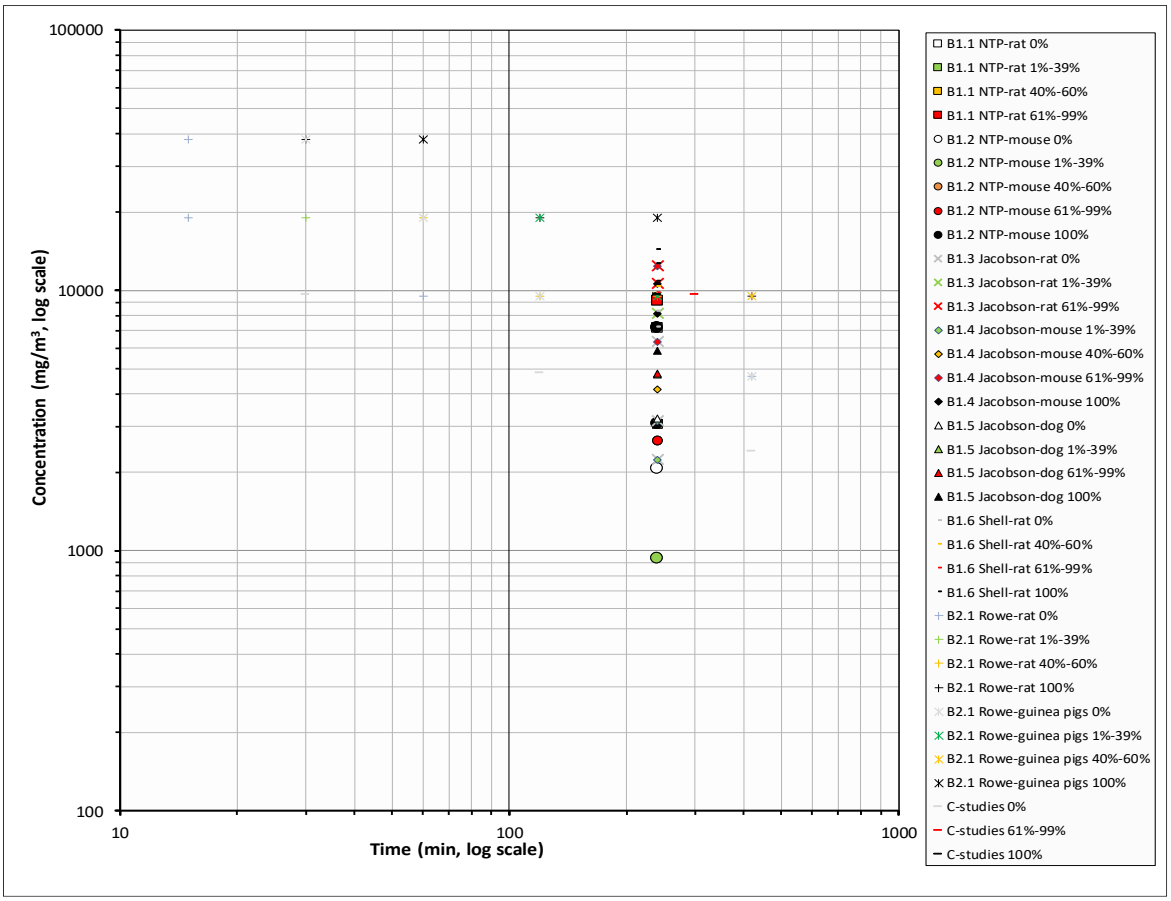


Figure 1 *All available acute lethality data for propylene oxide.*

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

All B studies were selected for derivation of the animal probit function for propylene oxide.

To enable intra-species pooling, LC_{50}-values of rat B1-studies were scaled using the n-value of 1.678 from rat-study B2.1 for extrapolation of rat data, and the average n-value of 1.629 (rat-study B2.1 and guinea pig-study B2.2) for extrapolation of mouse and dog data with the following formula (section 6):

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

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 = rat or average rat/guinea pig 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 1.

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	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}	8154 (1835 - 9749)	*28156*	N/A
B1.3	Rat	240-min LC_{50}	9464 (8384 - 10600)	*32679*	N/A
B1.6	Rat	240-min LC_{50}	10120 (9633 - 10580)	*34944*	N/A
B2.1	Rat	-42.7 + 3.87 ×lnC		29320 (22750 - 42710)	1.678 (1.262 – 2.093)
B1.2	Mouse	240-min LC_{50}	2634 (large variances disable estimating 95% confidence-limits)	*9441*	N/A
B1.4	Mouse	240-min LC_{50}	4130 (3283 - 5010)	*14802*	N/A
B1.5	Dog	240-min LC_{50}	4774 (large variances disable estimating 95% confidence-limits)	*17111*	N/A
B2.1	Guinea pig	-70.5 + 5.83×lnC		48670 (39660 - 63730)	1.580 (1.297 – 1.864)

The data of the B1 and B2 studies (rat, mouse, dog, guinea pig) are presented graphically below.

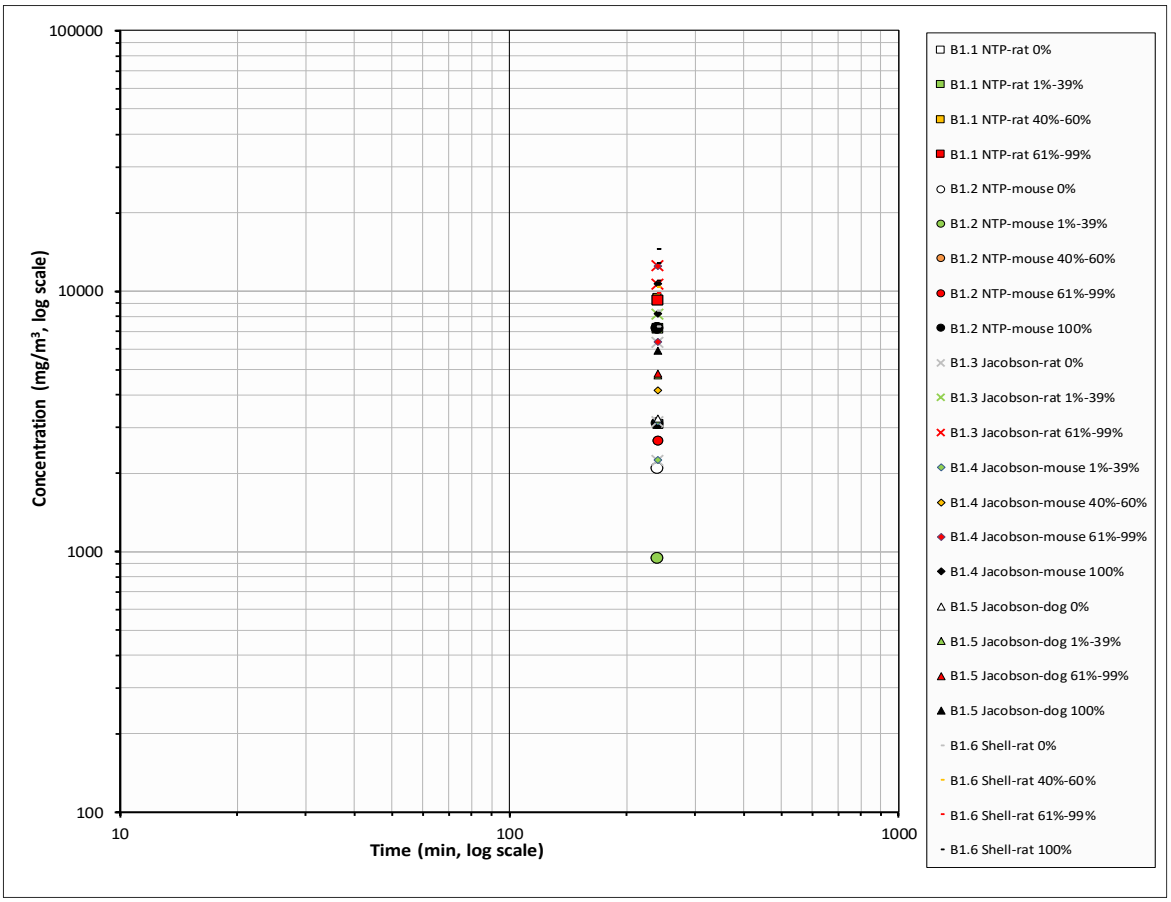


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of propylene oxide.*

Based on criteria outlined in the guideline, all B studies were selected for derivation of the animal probit function for propylene oxide. Rat studies B1.1, B1.3, B1.6, mouse studies B1.2 and B1.4 and dog study B1.5 were used to derive the LC_{50}. Studies B2.1 (rat) and B2.2 (guinea pig) were used to derive an n-value.
Figure 3 provides an overview of LC_{50} values and LC_{50}-time relationships for all studies in the final analysis. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 4.

The final data eligible for calculating the animal probit function contains 8 datasets from 4 studies and includes data from 4 animal species.

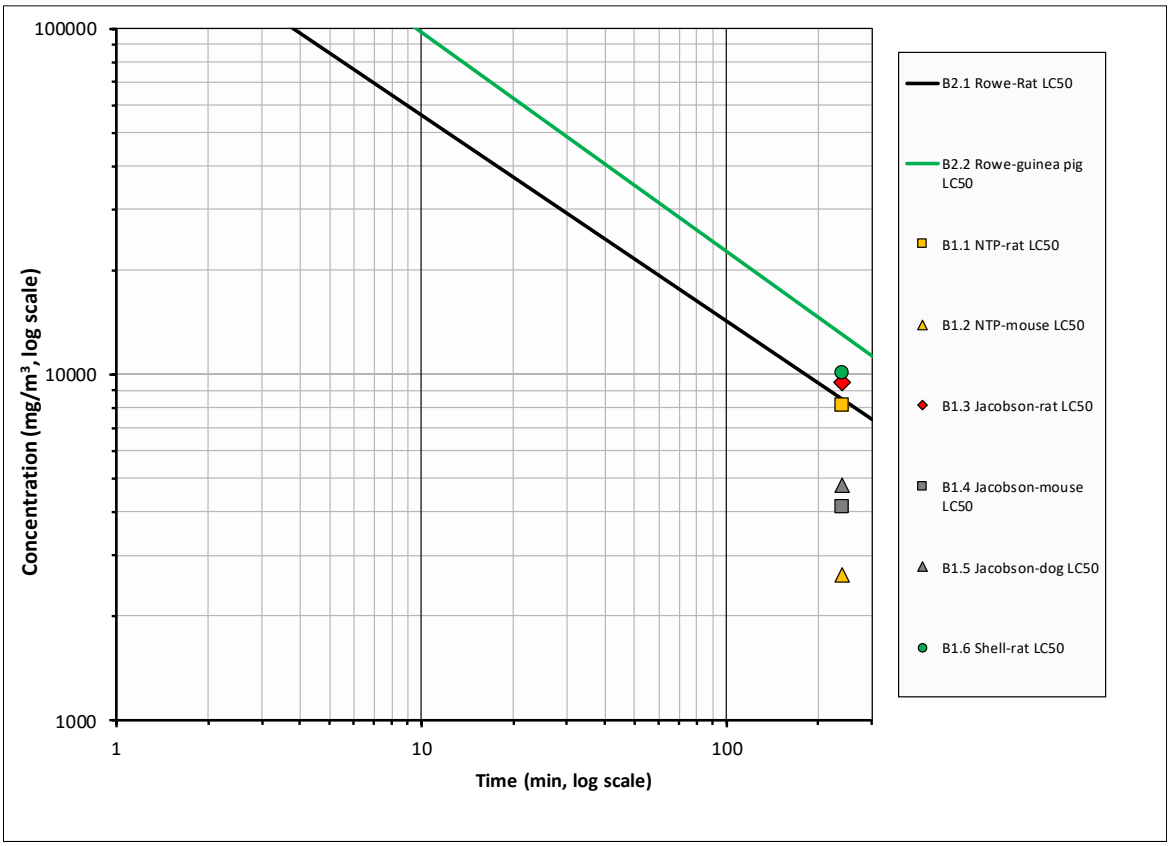


Figure 3 *LC_{50} values of B1 and B2 datasets for propylene oxide, over time where available.*

Table 2 *Data selected for the derivation of the animal probit function of propylene oxide (identical to table 1).*

Study ID	Species	Probit (C in mg/m³, t in min)	LC_{50} at tested exposure duration (mg/m³) 95% C.I.	LC_{50}, 30 minutes (mg/m³) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B1.1	Rat	240-min LC_{50}	8154 (1835 - 9749)	*28156*	N/A
B1.3	Rat	240-min LC_{50}	9464 (8384 - 10600)	*32679*	N/A
B1.6	Rat	240-min LC_{50}	10120 (9633 - 10580)	*34944*	N/A
B2.1	Rat	-42.7 + 3.87 ×lnC		29320 (22750 - 42710)	1.678 (1.262 – 2.093)
B1.2	Mouse	240-min LC_{50}	2634 (large variances disable estimating 95% confidence-limits)	*9441*	N/A
B1.4	Mouse	240-min LC_{50}	4130 (3283 - 5010)	*14802*	N/A

B1.5	Dog	240-min LC_{50}	4774 (large variances disable estimating 95% confidence-limits)	*17111*	N/A
B2.1	Guinea pig	-70.5 + 5.83×lnC		48670 (39660 - 63730)	1.580 (1.297 – 1.864)

The data of the selected datasets are presented graphically below.

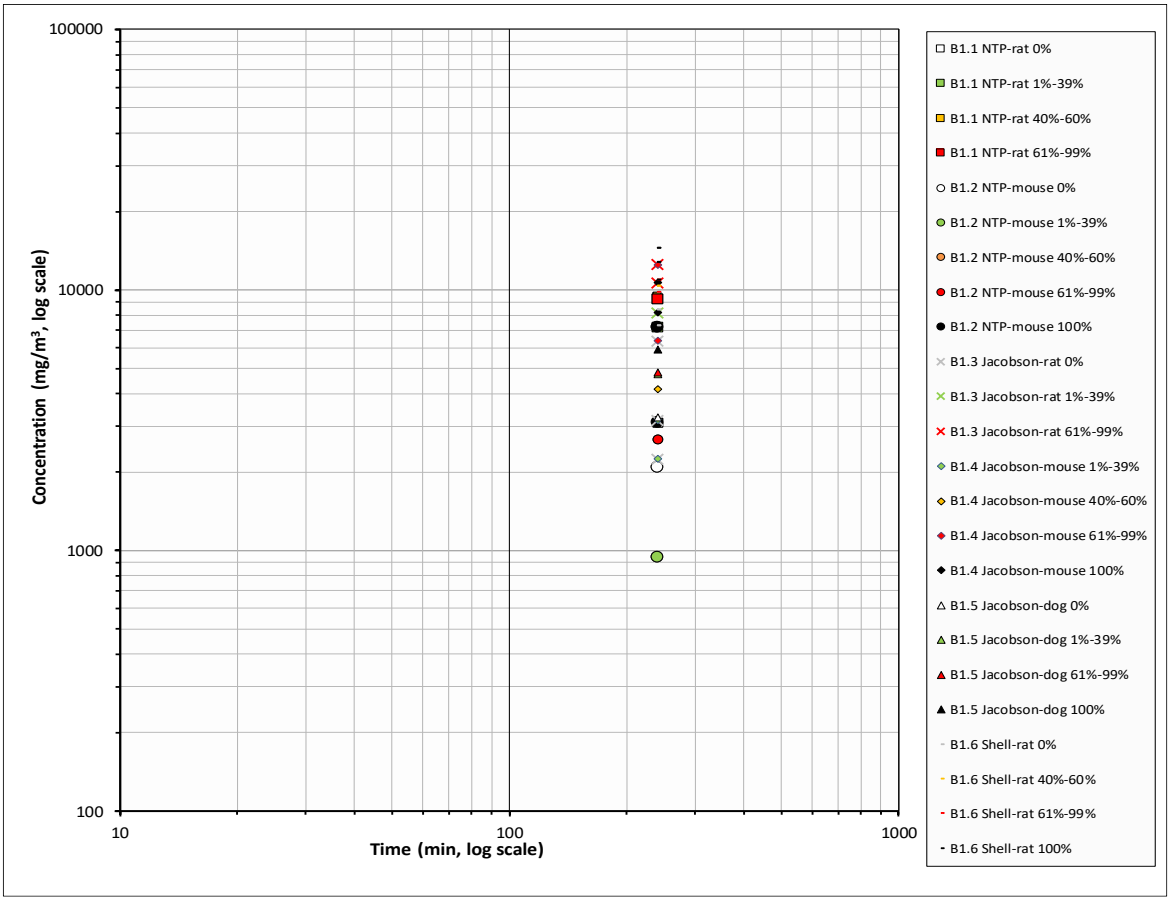


Figure 4 *Final data selected for derivation of the animal probit function of propylene oxide; identical to figure 2.*

6. Derivation of the human probit function

To derive the human probit function the results from rat studies B1.1, B1.3, B1.6 and mouse studies B1.2 and B1.4 and dog study B1.5 (and rat study B2.1 and guinea pig study B2.2 for derivation of the n-value) have been used to derive a point of departure as outlined above.

First, the arithmetic mean n-value was calculated from rat study B2.1 and guinea pig study B2.2. These values are almost identical.

The rat-specific n-value derived from study B2.1 was 1.678. The guinea pig-specific n-value derived from guinea pig study B2.2 was 1.580.

The arithmetic mean n-value across species is calculated to be 1.629.

Finally, the species-specific geometric mean LC_{50}-values were calculated from all available 240-min LC_{50} values of rat studies B1.1, B1.3, B1.6 and mouse studies B1.2 and B1.4, and the single LC_{50}-value taken from the dog study B1.5. Differences between species are observed, with mouse being the most sensitive species. The species-specific 240-min LC_{50}-value was 9270 mg/m^3 for the rat, 3330 mg/m^3 for the mouse, 4870 mg/m^3 for the dog. 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 240-minute geometric mean animal LC_{50} value of 5317 mg/m^3 and an arithmetic mean n-value of 1.629.

Differences between species are observed. The mouse is the most sensitive species with an overall 240-min LC_{50}-value of 3330 mg/m^3. Mice were followed by dogs (240-min LC_{50} of 4870 mg/m^3) and then rats (240-min LC_{50} of 9270 mg/m^3).
In addition to the rodent and dog data, the Probit Expert Panel made the following observations:

- Workplace exposure up to TWA concentration of 1520 ppm (*3674 mg/m^3*) for 171 min resulted in no fatalities (CMA (1998) as cited in AEGL (2010)). See section 3 for more details concerning these workplace exposures.
- Multiple repeated dose studies (focussing on potential neurophysiologic or neuropathologic effects, spermatogenic functions, sister chromatid exchanges or chromosome aberrations) in male Cynomolgus monkeys using exposure concentrations of 0, 100 and 300 ppm propylene oxide (*0, 242, 725 mg/m^3*) for 6h/day, 5 days/week, for 24 month resulted in no fatalities (Sprinz et al. (1982), Setzer et al. (1997), Lynch et al. (1983; as cited in AEGL), Lynch et al. (1984)). Also no adverse effects were shown in a study of Rowe et al. (1956) with rhesus monkeys with application of up to 154 exposures (7 h/day; 5 days/week) to 457 ppm (1104 mg/m^3).
  See appendix 1 for a detailed description of these repeated dose studies.

It is considered that monkeys may be a better model for lethality in humans than rodents. Based on these data and considerations, it was argued that the derivation of a probit function from the combined rat, mouse and dog data may overestimate the acute lethality of propylene oxide in non-human primates and hence also in humans. In addition, it is well known that mice have a relatively low enzymatic activity of epoxide hydrolase (EH) compared to rats and humans, and that therefore the mouse can be regarded as being a more sensitive species than man (Lorentz et al., 1984).

Using an overall assessment factor of 3 would provide a lethality value, i.e. a 60-min $LC_{0.1}$ of 884 mg/m^3, which is in conflict with the human and monkey data. Therefore, the assessment factor for animal to human extrapolation was reduced to 1 and an overall assessment factor of 1 was considered sufficient. This was further supported

by the consideration that the mechanism of toxicity, i.e. irritation, is a point-of-contact effect and is not expected to vary greatly among species.

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:	1	Based on the available data in workers and monkeys, an assessment factor of 1 was considered appropriate.
Nominal concentration	1	Analytically determined concentrations in studies B1.1, B1.2, B1.3, B1.4, B1.5 and B1.6
Adequacy of database:	1	Reasonable database with 3 rat B1 studies, 2 mouse B1 studies and 1 dog B1 study and supporting B2 studies in rat and guinea pig.

The estimated human equivalent 240-minute LC_{50} value is 5317 / 1 = **5317 mg/m³**.

The experimentally determined n-value was **1.629** (average from rat and guinea pig). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.23**.

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): $5 = a + 1.23 \times \ln (5317^{1.63} \times 240)$ resulting in the a-value of **-18.89**.

$Pr = -18.9 + 1.23 \times \ln (C^{1.63} \times t)$ with C in mg/m³ and t in min.

The derived human probit function has a scientifically acceptable basis. The probit function is based on 6 studies in the rat, mouse and dog with B1 quality and 2 studies in rat and guinea pig with B2 quality, including 266 rats, 121 mice, 12 dogs, and 55 guinea pigs, exposure durations ranging from 15-420 minutes, and exposure concentrations up to 38000 mg/m³.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 2656 mg/m³ and the calculated human 60 min LC_1 (Pr = 2.67) is 3883 mg/m³.

Table 4 *LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m³)	60 min (mg/m³)
0.1% lethality, this probit	4064	2656
1% lethality, this probit	5942	3883
AEGL-3[2] (2010, final)	3142	2103
ERPG-3[2] (2018)	-	1800
LBW (2021)	3200	2100

[2] AEGL and ERPG values were converted from ppm to mg/m³ with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m³ can deviate slightly from those reported in the AEGL and ERPG TSDs.

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

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: ***NTP, 1985***

Substance: propylene oxide
Species, strain, sex: rat, F344/N, male and female
Number/sex/conc. group: 5
Age and weight: not specified, animals assigned to groups so that average weights were approximately equal
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	No GLP statement provided
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	No information
Use of vehicle (other than air)	No
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	Propylene oxide was vaporized at room temperature, diluted with air, and introduced into the chambers.
Number of air changes per hour	No information
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information
Actual concentration measurement	Propylene oxide chamber air concentrations were measured 8 to 12 times per exposure period with a gas chromatograph.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Rat	3087		240	0/5	0/5
Rat	7178		240	1/5	2/5
Rat	9170		240	4/5	4/5
Rat	9426		240	3/5	3/5

Probit function

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

$Pr = a + b \times lnC + d \times S$

with C for concentration in mg/m^3 and S for sex (0 = male, 1 = female).

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-30.0	3.87	0.190	-
Sexes combined	Rat	-29.7	3.85	-	-

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 (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
240	8360 (2884 - 12690)	7960 (1049 - 10210)	8154 (1835 - 9749)

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

A graphical overview of the data is not presented.

Study ID: B1.2

Author, year: ***NTP, 1985***

Substance: propylene oxide
Species, strain, sex: mouse, $B6C3F_1$, male and female
Number/sex/conc. group: 5
Age and weight: not specified, animals assigned to groups so that average weights were approximately equal
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	No GLP statement provided
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	No information
Use of vehicle (other than air)	No
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	Propylene oxide was vaporized at room temperature, diluted with air, and introduced into the chambers.
Number of air changes per hour	No information
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information
Actual concentration measurement	Propylene oxide chamber air concentrations were measured 8 to 12 times per exposure period with a gas chromatograph.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Mouse	935		240	0/5	1/5
Mouse	2076		240	0/5	0/5
Mouse	2664		240	2/5	4/5
Mouse	3087		240	2/5	5/5
Mouse	7178		240	5/5	5/5

Probit function

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

$Pr = a + b \times lnC + d \times S$

with C for concentration in mg/m^3, and S for sex (0 = male, 1 = female).

Probit function	Species	a	b	d	n-value
Sex as variable	Mouse	-14.0	2.33	1.16	-
Sexes combined	Mouse	-10.6	1.98	-	-

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 (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
240	3377 (2520 - 5170)	2052 (1366 - 2752)	2634 (large variances disable estimating 95% confidence-limits)

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

A graphical overview of the data is not presented.

Study ID: B1.3

Author, year: ***Jacobson et al., 1956***

Substance: propylene oxide
Species, strain, sex: rat, unknown strain, male
Number/sex/conc. group: 10
Age and weight: no information available
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 available
Use of vehicle (other than air)	Nitrogen
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution	No information available
Homogeneity of test atmosphere in breathing zone of animals	The vapour was dispersed by passing nitrogen at a fixed rate through the propylene oxide liquid, maintained at a temperature of 0ºC. Constant flow gassing chambers of 0.4 m^3 capacity were used.
Number of air changes per hour	No information available
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information available
Actual concentration measurement	Propylene oxide atmospheres were analysed using a colorimetric procedure. Atmospheres were sampled by drawing chamber air through a series of Vigreaux-type bubblers, the first containing $CaCl_2.2H_2O$ in HCl and the second containing water to trap any acid.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
rat	2240		240	0/10

rat	3150		240	0/10
rat	6360		240	0/10
rat	8170		240	3/10
rat	10640		240	7/10
rat	12450		240	9/10

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
	Rat	-39.8	4.88	-

Duration (min.)	LC50 (mg/m^3) 95%-C.I.; as calculated by TSD author	LC50 (mg/m^3) 95%-C.I.; as presented by Jacobson *et al*.
240	9464 (8384 - 10600)	9667 (8580 - 10803)

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

A graphical overview of the data is not presented.

Study ID: B1.4

Author, year: ***Jacobson et al., 1956***

Substance: propylene oxide
Species, strain, sex: mouse, unknown strain, male
Number/sex/conc. group: 10-11
Age and weight: no information available
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)	Nitrogen
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 vapour was dispersed by passing nitrogen at a fixed rate through the propylene oxide liquid, maintained at a temperature of 0ºC. Constant flow gassing chambers of 0.4 m^3 capacity were used.
Number of air changes per hour	No information available
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information available
Actual concentration measurement	Propylene oxide atmospheres were analysed using a colorimetric procedure. Atmospheres were sampled by drawing chamber air through a series of Vigreaux-type bubblers, the first containing $CaCl_2.2H_2O$ in HCl and the second containing water to trap any acid.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
mouse	2240		240	2/11

mouse	3150		240	1/10
mouse	4160		240	5/10
mouse	6360		240	9/10
mouse	8170		240	10/10
mouse	10640		240	10/10
mouse	12450		240	9/10

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
	Mouse	-11.7	2.00	-

Duration (min.)	LC50 (mg/m^3) 95%-C.I.; as calculated by TSD author	LC50 (mg/m^3) 95%-C.I.; as presented by Jacobson *et al*.
240	4130 (3283 - 5010)	4205 (3335 - 5124)

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

A graphical overview of the data is not presented.

Study ID: B1.5

Author, year: ***Jacobson et al., 1956***

Substance: propylene oxide
Species, strain, sex: dog, beagle, male
Number/sex/conc. group: 3
Age and weight: no information available
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 available
Use of vehicle (other than air)	Nitrogen
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution	No information available
Homogeneity of test atmosphere in breathing zone of animals	The vapour was dispersed by passing nitrogen at a fixed rate through the propylene oxide liquid, maintained at a temperature of 0ºC. Constant flow gassing chambers of 0.7 m^3 capacity were used.
Number of air changes per hour	No information available
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information available
Actual concentration measurement	Propylene oxide atmospheres were analysed using a colorimetric procedure. Atmospheres were sampled by drawing chamber air through a series of Vigreaux-type bubblers, the first containing $CaCl_2.2H_2O$ in HCl and the second containing water to trap any acid.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
dog	3230		240	0/3

dog	4750		240	1/3
dog	4810		240	2/3
dog	5880		240	3/3*

* two of three dogs in the 5880 mg/m^3 group were dead when they were removed from the chamber; the third dog probably would have died soon and was therefore killed immediately.

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
	Dog	-82.5	10.3	-

Duration (min.)	LC50 (mg/m^3) 95%-C.I.; as calculated by TSD author
240	4774 (large variances disable estimating 95% confidence-limits)

For B1-studies: No C × t probit function could be calculated from these data alone.

A graphical overview of the data is not presented.

Study ID: B1.6

Author, year: ***Shell (1977)***

Substance: propylene oxide
Species, strain, sex: rat, Wistar, male and female
Number/sex/conc. group: 4
Age and weight: 10-13 weeks/ body weight not specified
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)	No
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 atmospheres were generated dynamically by nearly saturating part of the total air flow to the test chambers with propylene oxide vapour. This was accomplished by passing a controlled air flow through a wick-type saturator maintained at 0ºC in an ice/water bath with air stirring. The air/vapour mixture from the saturator was then blended with a controlled flow of 'clean air' in a 2 litre mixing vessel. The generated atmosphere then passed from the mixing vessel into the test chambers. Animals were housed in cylindrical glass exposure chambers consisting of 10 cm ID industrial glass pipe sections (QVF) 46 cm in length fitted with 10 to 2.5 cm reduction pieces at each end. The animals were placed in the tubes on metal carriers fabricated from 3 mm stainless steel rod. The upper surface of the carrier was divided into five compartments so that each pipe section housed max five animals. The two test chambers were supplied from a common manifold made up of 2.5 cm ID glass pipe sections.
Number of air changes per hour	No information
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	No information.

Actual concentration measurement	The concentration of propylene oxide in the test atmospheres were determined using an infra-red gas analyser. By replacing the blower fitted to the instrument with a metal bellows pump, the test atmosphere could be drawn from the mixing chamber exit through the analyser and then returned to the exposure chamber inlet manifold. A recirculatory system employing the metal bellow pump was also used for calibration purposes. This involved adding known amounts of propylene oxide to the recirculating atmosphere by means of a microliter syringe.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	**B1** Well performed study, though some details on study characteristics missing. Limited to one exposure duration.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
rat	7251		240	0/4	0/4
rat	8339		240	0/4	0/4
rat	9789		240	0/4	3/4
rat	10345		240	2/4	2/4
rat	10877		240	3/4	4/4
rat	12713		240	4/4	4/4
rat	14429		240	4/4	4/4

Probit function

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

$Pr = a + b \times lnC + d \times S$

with C for concentration in mg/m^3, and S for sex (0 = male, 1 = female).

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-107.5	12.1	0.99	-
Sexes combined	Rat	-99.2	11.3	-	-

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 (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
240	10540 (9919 - 11230)	9717 (9070 - 10320)	10120 (9633 - 10580)

The study authors calculated 240 min-LC_{50} value of 10143 mg/m^3 (95% confidence interval: 9430 – 10619 mg/m^3).

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

A graphical overview of the data is not presented.

Study ID: B2.1

Author, year: ***Rowe et al., 1956***
Substance: propylene oxide
Species, strain, sex: rat, albino, female
Number/sex/conc. group: 5-15
Age and weight: not specified
Observation period: 14 days

Evaluation of study quality
The source, feeding, selection, and handling of the animals used in the vapour inhalation experiments and the apparatus and technique employed in carrying out this study of Rowe et al. (1956) were essentially the same as those previously described by Spencer et al. (1951).

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)	No
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 introducing a metered amount of propylene oxide liquid into a tube through which air entered the 160-L inhalation chamber. Heat was applied at the point of vaporization as needed to complete volatilization. The pumphouses were held at temperatures of 10 to 15ºC by refrigeration, because this procedure facilitate the pumping of liquid propylene oxide to the point of vaporization.
Number of air changes per hour	Air flow of about 15-30 L/min in a 160 L chamber; corresponding to approximately 5.6 to 11.3 air changes per hour.
Equilibration time (t95)	16-32 minutes

Start of exposure relative to equilibration	Information in the cited publication of Spencer et al. (1951) is unclear. However the exposure probably started after concentration build-up based on the following: "The rats were introduced in groups of 5 to 12 within a period of 15 seconds and were removed through the chamber door within a similar interval of time at the end of exposure. It was shown by a continuously recording analyser that the animals were introduced without appreciable alteration of the vapour concentration."

Actual concentration measurement	Samples of the chamber atmosphere were drawn at a constant rate of one liter per minute through a fritted glass absorber containing dilute sulfuric acid which was nearly saturated with magnesium bromide. The excess acid was titrated with standard sodium hydroxide solution using a methyl orange-xylene cyanole indicator, and the quantity propylene oxide equivalent to the amount of sulfuric acid consumed was calculated. The authors stated that "the concentrations determined by analysis varied between 64% and 110% of the calculated (i.e. nominal) concentrations. There were very few values found at the extremes of this percentage range. Analytical concentrations were corrected for 96.4% average efficiency of absorption of propylene oxide in the absorber used. It was computed that the analytical concentration was 87% of the theoretical concentration on the average for all concentrations employed. The range of the analysed concentrations is believed to result from the combined problems of maintaining, sampling, and analysing vapor concentrations of a material which is highly reactive and readily soluble." Actual and nominal concentrations were however not presented by the authors. Based on type of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the reported target concentrations are indicative for the actual (analytical) and nominal concentrations.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A

Assessment of Reliability	**B2** The study included many C × t combinations. However, only target concentrations were reported and therefore the study was not given the A-status. The following is additionally noted: - Based on the method of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the reported target concentrations are indicative for the actual (analytical) and nominal concentrations. - Further, the authors state that the analytical concentrations varied between 64% and 110% of the nominal concentration. It was computed that the analytical concentration was 87% of the theoretical concentration on the average for all concentrations employed. - Propylene oxide has a high vapour pressure. For a vapour, it is expected that the nominal concentration will be close to the actual concentration unless condensation has occurred. This is confirmed by calculations of the ratio of the highest target concentration vs. saturated vapour concentration (SVC), which is below 0.25 (i.e. 38.0 x10^3/1401750 = 0.027). Nevertheless, an A status could not be assigned since actual concentrations were not reported, consequently the study is assigned the B2-status.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Target	Adjusted		Female
				Dead/tested
rat	4.7 × 10^3	N/A	420	0/10
rat	9.5 × 10^3	N/A	60	0/5
rat	9.5 × 10^3	N/A	120	4/10
rat	9.5 × 10^3	N/A	240	4/10
rat	9.5 × 10^3	N/A	420	10/10
rat	19.0 × 10^3	N/A	15	0/10
rat	19.0 × 10^3	N/A	30	2/10

rat	19.0 × 10^3	N/A	60	5/10
rat	19.0 × 10^3	N/A	120	10/10
rat	38.0 × 10^3	N/A	15	0/15
rat	38.0 × 10^3	N/A	30	10/10

Probit function

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

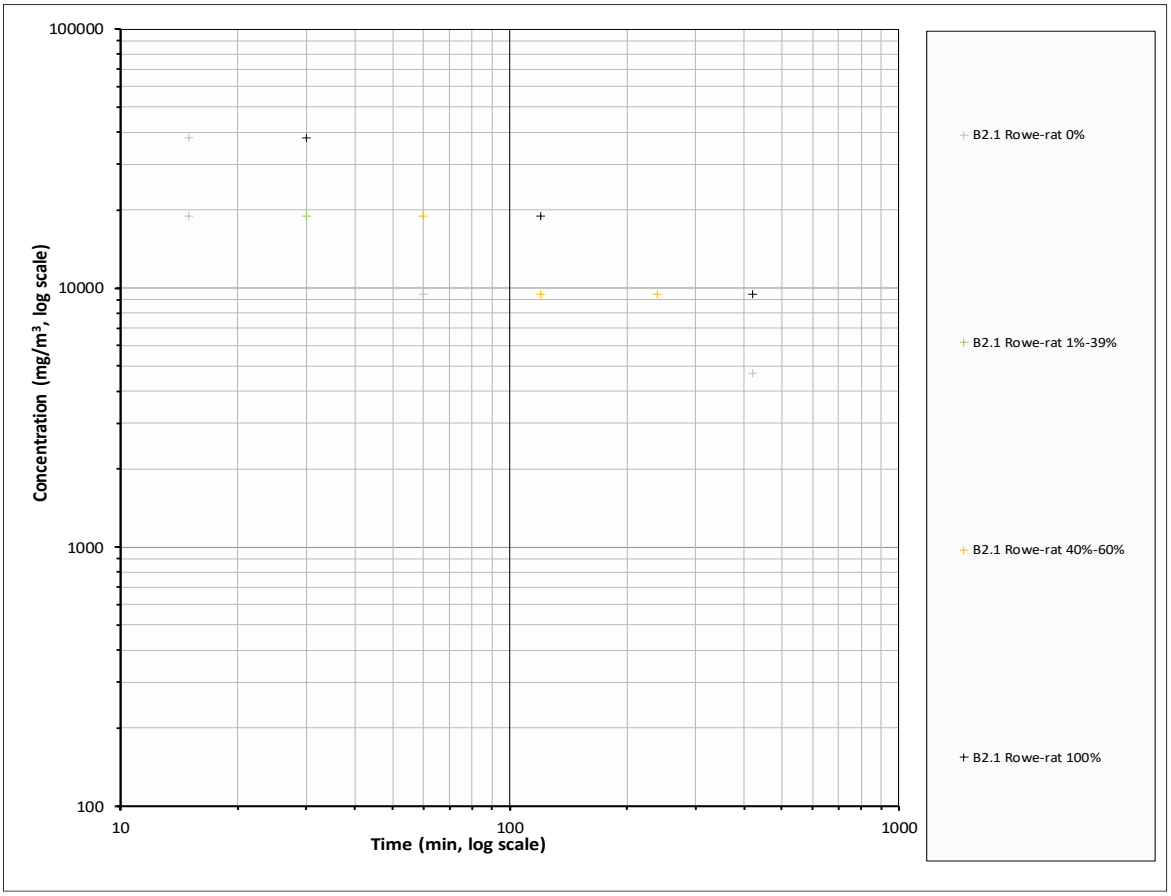
$Pr = a + b \times \ln C + c \times \ln t$

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

Probit function	Species	a	b	c	n-value
	Rat	-42.7	3.87	2.31	1.678 (1.262 – 2.093)

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Female
10	56430 (38180 - 102900)
30	29320 (22750 - 42710)
60	19400 (15660 - 25710)

A graphical overview of the data is presented below. Each concentration-time combination (with 5-15 female animals) represents one point in the plot.



Study ID: B2.2

Author, year: ***Rowe et al., 1956***

Substance: propylene oxide
Species, strain, sex: guinea pigs, unknown strain, female
Number/sex/conc. group: 5-10
Age and weight: not specified
Observation period: 14 days

Evaluation of study quality

The source, feeding, selection, and handling of the animals used in the vapour inhalation experiments and the apparatus and technique employed in carrying out this study of Rowe et al. (1956) were essentially the same as those previously described by Spencer et al. (1951).

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)	No
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 introducing a metered amount of propylene oxide liquid into a tube through which air entered the 160-L inhalation chamber. Heat was applied at the point of vaporization as needed to complete volatilization. The pumphouses were held at temperatures of 10 to 15 ºC by refrigeration, because this procedure facilitate the pumping of liquid propylene oxide to the point of vaporization.
Number of air changes per hour	Air flow of about 15-30 L/min in a 160 L chamber. Approximately 5.6 to 11.3 air changes per hour.
Equilibration time (t95)	16-32 minutes
Start of exposure relative to equilibration	Information in the cited publication of Spencer et al. (1951) is unclear. They state: "The rats were introduced in groups of 5 to 12 within a period of 15 seconds and were removed through the chamber door within a similar interval of time at the end of exposure. It was shown by a continuously recording analyser that the animals were introduced without appreciable alteration of the vapour concentration." It is however not clear whether this does apply to the other species including guinea pigs as well.

Actual concentration measurement	Samples of the chamber atmosphere were drawn at a constant rate of one liter per minute through a fritted glass absorber containing dilute sulfuric acid which was nearly saturated with magnesium bromide. The excess acid was titrated with standard sodium hydroxide solution using a methyl orange-xylene cyanole indicator, and the quantity propylene oxide equivalent to the amount of sulfuric acid consumed was calculated. The authors stated that "the concentrations determined by analysis varied between 64% and 110% of the calculated (i.e. nominal) concentrations. There were very few values found at the extremes of this percentage range. Analytical concentrations were corrected for 96.4% average efficiency of absorption of propylene oxide in the absorber used. It was computed that the analytical concentration was 87% of the theoretical concentration on the average for all concentrations employed. The range of the analysed concentrations is believed to result from the combined problems of maintaining, sampling, and analysing vapor concentrations of a material which is highly reactive and readily soluble." Based on type of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the reported target concentrations are indicative for the actual (analytical) and nominal concentrations.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A

Assessment of Reliability	***B2*** The study included many C × t combinations. However, only target concentrations were reported and therefore the study was not given the A-status. The following is additionally noted: - Based on the method of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the reported target concentrations are indicative for the actual (analytical) and nominal concentrations. - Further, the authors state that the analytical concentrations varied between 64% and 110% of the nominal concentration. It was computed that the analytical concentration was 87% of the theoretical concentration on the average for all concentrations employed. - Propylene oxide has a high vapour pressure. For a vapour, it is expected that the nominal concentration will be close to the actual concentration unless condensation has occurred. This is confirmed by calculations of the ratio of the highest target concentration vs. saturated vapour concentration (SVC), which is below 0.25 (i.e. 38.0 x10^3/1401750 = 0.027). Nevertheless, an A status could not be assigned since actual concentrations were not reported, consequently the study is assigned the B2-status.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Target	Adjusted		
				Dead/tested
Guinea pig	4.7 × 10^3	N/A	420	0/5
Guinea pig	9.5 × 10^3	N/A	120	0/5
Guinea pig	9.5 × 10^3	N/A	240	1/5
Guinea pig	9.5 × 10^3	N/A	420	2/5
Guinea pig	19.0 × 10^3	N/A	60	0/10
Guinea pig	19.0 × 10^3	N/A	120	1/5
Guinea pig	19.0 × 10^3	N/A	240	10/10

Guinea pig	38.0 × 10^3	N/A	30	0/5
Guinea pig	38.0 × 10^3	N/A	60	5/5

Probit function

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

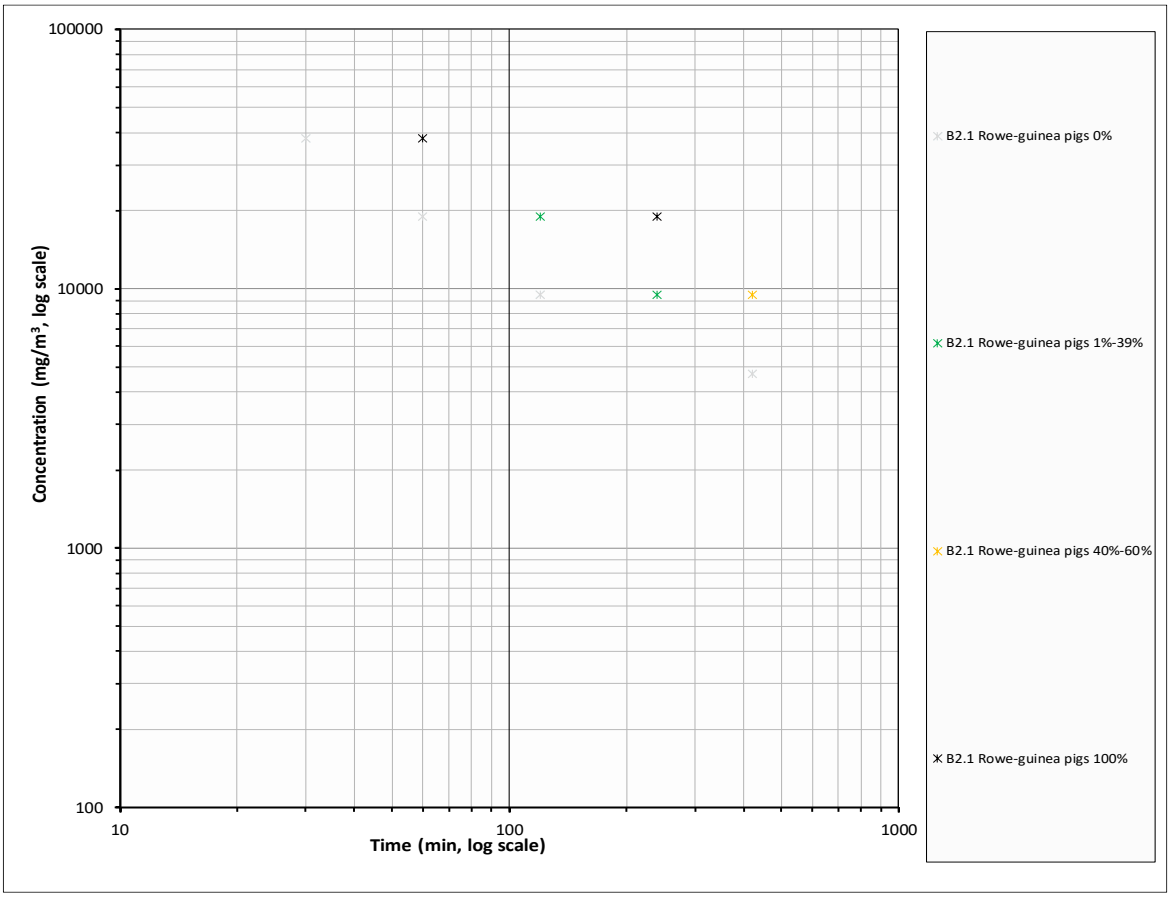
$Pr = a + b \times lnC + c \times lnt$

with C for concentration in mg/m^3, t for time in minutes and S for sex (0 = female, 1 = male).

Probit function	Species	a	b	c	n-value
	Guinea pig	-70.5	5.83	3.69	1.580 (1.297 – 1.864)

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Female
10	97530 (70920 - 149600)
30	48670 (39660 - 63730)
60	31390 (27190 - 37620)

A graphical overview of the data is presented below. Each concentration-time combination (with 5-10 female animals) represents one point in the plot.



Study ID: C studies

Rowe et al. (1956) also exposed groups of five female albino rats to propylene oxide at target concentrations of 4,000 ppm (9667 mg/m^3) for 30 min, 2,000 ppm (4834 mg/m^3) for 2 h, or 1,000 ppm (2417 mg/m^3) for 7 h. A short post-exposure observation period was applied. Twenty-four hours after exposure, animals were killed, organs were weighed, and gross and microscopic evaluation of the tissues was performed. No treatment-related effects were observed.

Smyth and Carpenter (1948; also described in Smyth et al., 1969; method described in Smyth et al., 1962) exposed Sherman rats to propylene oxide for four hours by inhalation. Limited details on study characteristics are available. Concentrations were not analytically verified but estimated. Exposure to a target concentration of 4000 ppm (9667 mg/m^3) for 4 hours resulted in mortality rate of 6/6.

Weil *et al.* (1963) exposed rats to propylene oxide for four hours by inhalation. Limited details on study characteristics are available. Concentrations recorded were target and not analytically verified. Exposure to a target concentration of 4000 ppm (9667 mg/m^3) for 4 hours resulted in mortality rate of 4/6. Exposure to a saturated vapour concentration resulted in death of 6/6 animals within 5 minutes.

Study ID: relevant repeated dose studies

Sprinz et al. (1982) repeatedly exposed male cynomolgus monkeys (n=2/exposure group) to 0, 100 and 300 ppm propylene oxide (*0, 242, 725 mg/m^3*) for 6h/day, 5 days/week, for 24 months. The study focussed on the potential neuropathologic effects. Animals were tested bimonthly for alterations of nerve conduction velocities as well as changes in other organ systems. The only observable differences noted between treated and control monkeys were signs of axonal dystrophy in the medulla oblongata of the brain.

Setzer et al. (1997) repeatedly exposed cynomolgus monkeys (n=12/exposure group) to propylene oxide vapour at 0, 100, or 300 ppm (*0, 242, 725 mg/m^3*) for 7 h/day, 5 days/week, for 24 months. Body weights, electroencephalograms, and motor nerve conduction velocities of the sciatic and ulnar nerves were assessed six times throughout the exposure period. They found no neurophysiologic or neuropathologic changes.

Lynch et al. (1983; as cited in AEGL) evaluated spermatogenic functions in male cynomolgus monkeys after exposure to propylene at 0, 100, or 300 ppm for 7 h/day, 5 days/week, for 24 months. Exposed monkeys had statistically significant decreases in sperm count and sperm motility and an increase in drive range.
However, no increases were noted in sperm head abnormalities.

Lynch et al. (1984) repeatedly exposed male cynomolgus monkeys (n=12/exposure group) to 0, 100 and 300 ppm propylene oxide (*0, 242, 725 mg/m^3*) for 7h/day, 5 days/week, for 24 months. The study focussed on the ability of long-term exposure to induce sister-chromatid exchanges (SCEs) and chromosome aberrations in peripheral lymphocytes of monkeys. No adverse genotoxic effects were found.

Rowe et al. (1956) exposed one female rhesus monkey 154 times to 457 ppm (*1104 mg/m^3*), two female rhesus monkeys 154 times to 195 ppm (*471 mg/m^3*), and two female rhesus monkeys 154 times to 102 ppm (*247 mg/m^3*) for 7 h/day, 5 days/week. No adverse effects were shown (Rowe et al. 1956).

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