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
Allyl alcohol	**107-18-6**

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.

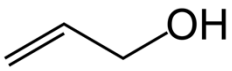
This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have 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 Allyl alcohol

1. Substance identification



CAS-number:	107-18-6
IUPAC name:	Prop-2-en-1-ol
Synonyms:	2-propen-1-ol, propenyl alcohol, vinyl carbinol
Molecular formula:	C_3H_6O
Molecular weight:	58.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	97°C (at 101.3 kPa)
Vapour pressure:	2.4 kPa (at 20°C)
Saturated vapor conc:	24,000 ppm = 58 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.413 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.42 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H:331, 311, 301, 319, 335, 315

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

Acute effects: The main target organs and tissues for inhalation exposure to allyl alcohol are the respiratory tract, the liver, kidneys and gastrointestinal tract. Allyl alcohol is a potent sensory irritant and can lead to corneal and skin burns upon contact. Blurred vision may occur at high exposures. Local toxic effects include lacrimation, pulmonary congestion and oedema , inflammation, and haemorrhages leading to abdominal pain and laboured breathing. Systemic effects include degenerative effects in the liver, kidney cells in the convoluted tubules, myocardium, ganglion cells of the spinal cord, and retina.
Lethality results from pulmonary congestion leading to edema and compensatory emphysema.
Long-term effects: Chronic exposure produces similar effects as observed after acute exposure.

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.

Human volunteer studies have been performed with allyl alcohol exposure. The highest reported concentration was 5 ppm (12.1 mg/m^3) for 5 minutes where all subjects (n = 5) reported moderate to severe eye and nose irritation (AEGL, 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 allyl alcohol, 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

[1] AEGL (2014).

- 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 6 studies were identified -with 10 datasets for 5 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, one datasets was assigned status B and 9 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of 3 studies were identified in which sensory irritation was studied. In these studies the following RD_{50} values were observed:

Table 1 *Sensory irritation data for allyl alcohol*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
male Ssc:CF-1 mice	9.4^P 11.6 (mean over last 10 min.)	30	Nielsen et al., 1984
male ICR mice	6.1^U	30	James et al., 1987
Mice	3.9^U	unknown	Muller and Greff, 1984

P: a plateau was reached. U: unknown whether a plateau has been reached.

5. Probit functions from individual studies

All available acute lethality data on allyl alcohol are displayed in figure 1.

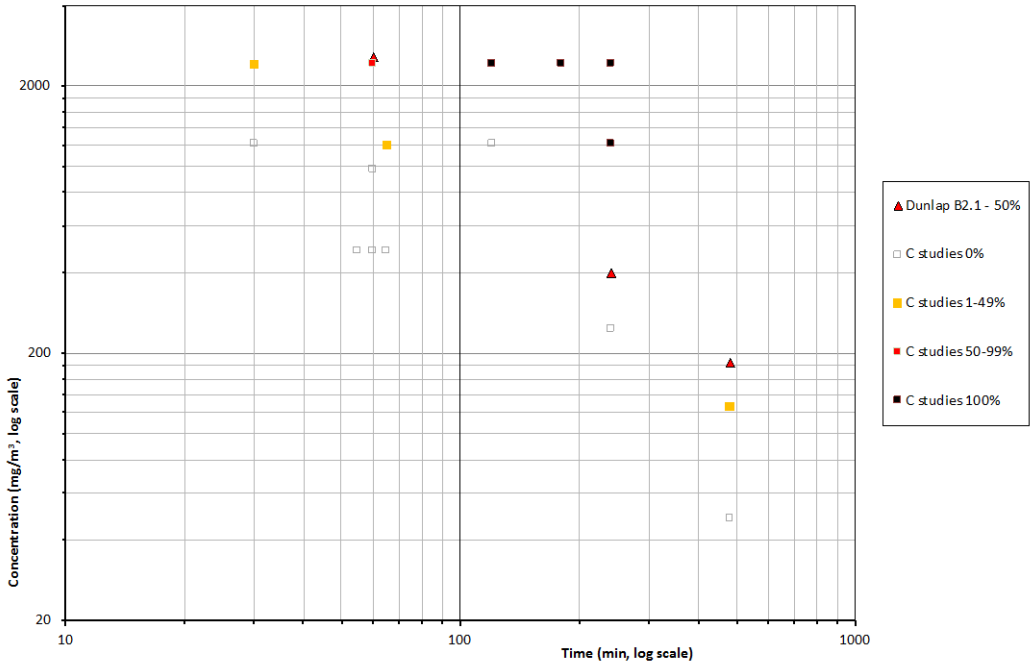


Figure 1 *All available acute lethality data for allyl alcohol.*

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

The probit function was derived using data from the B2.1 study listed in the table below, because studies with A or B1 quality were not identified.

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

Table 2 *Data selected for initial analysis of the animal probit function of allyl alcohol.*

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.
B2.1	Rat	60-min LC_{50} 240-min LC_{50} 480-min LC_{50}	2565 399 184	*6238* *5738* *6435*	0.78

The data of the B2.1 study with rats are presented graphically below.

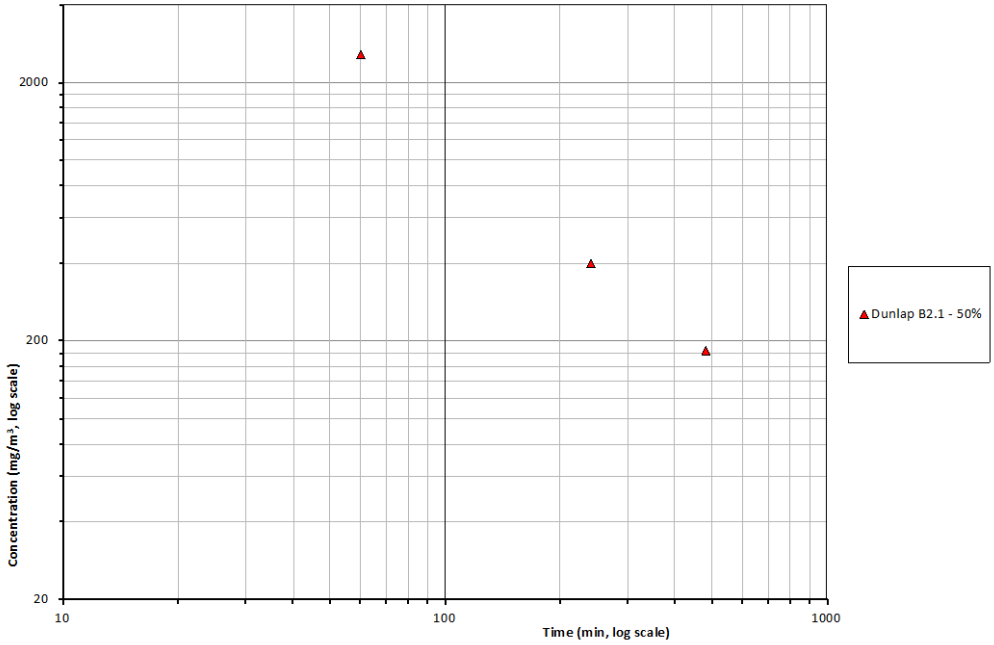


Figure 1 *Data selected for the initial analysis for the derivation of the animal probit function of allyl alcohol*

Based on criteria outlined in the guidance and the fact that the Dunlap et al study (B2.1) is the only eligible study for probit function derivation, the data from this study were selected for the final dataset for the derivation of the animal probit function. The study report contained sufficient information on the study design, however did not provide the actual concentration data used and corresponding lethality ratios, only LC_{50} values were reported. The data that were selected for final analysis of the animal probit function are presented in Table 3 and Figure 3.

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

Table 3 *Data selected for the derivation of the animal probit function of allyl alcohol (identical to table 2).*

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.
B2.1	Rat	60-min LC_{50} 240-min LC_{50} 480-min LC_{50}	2565 399 184	*6238* *5738* *6435*	0.78

The data of the selected datasets are presented graphically below.

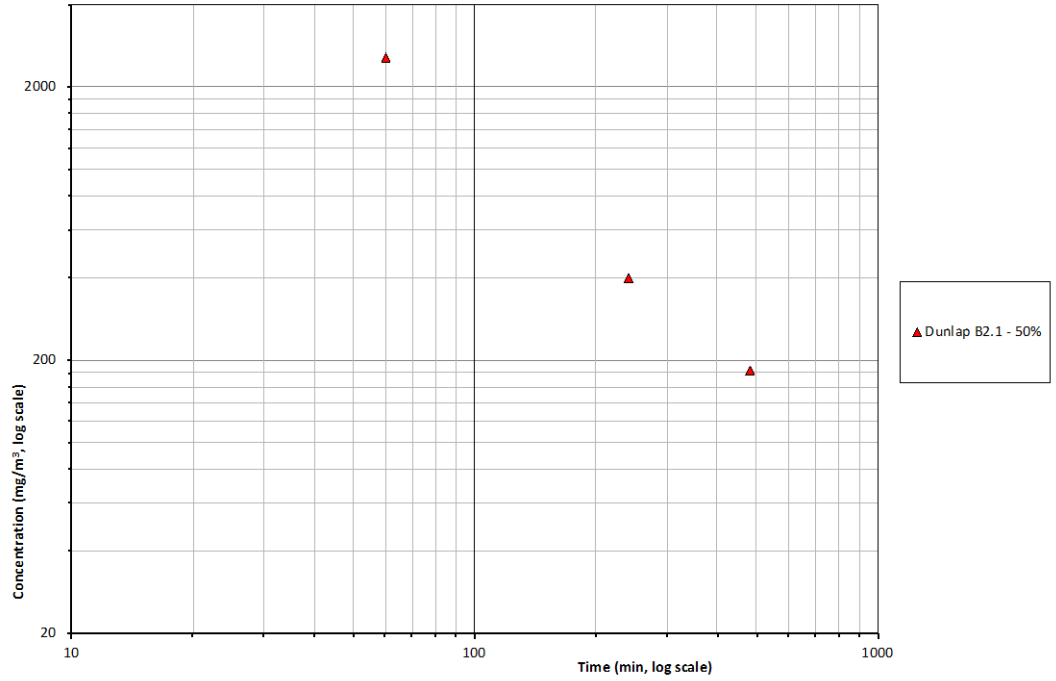


Figure 2 *Final data selected for derivation of the animal probit function of allyl alcohol (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from Dunlap et al., 1958 (B2.1) have been used to derive a point of departure as outlined above. Since no other information is qualified to be used for probit function derivation, the data were used with the notion of the poor database adequacy for which an assessment factor of 2 was applied according to the criteria set out in the guideline.

The n-value was calculated to be 0.782 (see appendix 1 for study description and derivation of the n-value based on the three LC_{50} values).

The 60-min LC_{50} value from Dunlap et al. was selected as point of departure as this duration is closest to the desired 30 to 60 minute time frame as outlined in the methodology (Ruijten et al., 2015).

Since the authors remarked that actual concentrations were 15-25% below the reported nominal concentrations, the probit panel decided to adjust (reduce) the reported concentrations by 20% before application in the calculations. The 60-min LC_{50} value for the probit derivation was calculated as 2565 × 0.8 = 2052 mg/m^3.

The Point of Departure for the human probit function is a 60-minute animal LC_{50} value of 2052 mg/m^3 and an n-value of 0.78.

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

Table 4 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	Default value. In addition, sensory irritation as defined by the RD_{50} value is well below the calculated LC_{50} values, indicating an additional protection mechanism in the test species compared to humans.
Nominal concentration	1	Nominal concentrations were reported. Author reported that actual concentrations were 15-25% lower than nominal concentrations, so the reported concentrations were reduced by 20%.
Adequacy of database:	2	Only one B2 study, for which only the LC_{50} values were reported is available. A few C studies are available that do seem to support the B2 study.

The estimated human equivalent 60-minute LC_{50} value is 2052 / 6 = **342 mg/m^3**.

The experimentally determined n-value was **0.782** (B2.1). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **2.56**.

The human probit function is then calculated on the human equivalent 60 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): 5 = a + 2.56 × ln ($342^{0.78}$× 60) resulting in the a-value of **-17.14**.

$Pr = -17.1 + 2.56 \times \ln (C^{0.78} \times t)$ 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 in the rat with B2 quality, for which only LC_{50} values were reported.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 71 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 103 mg/m^3.

Table 5 *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	172	71
1% lethality, this probit	251	103
AEGL-3[2] (2014, final)	65	31
ERPG-3		N/A
LBW (2016)	61	48

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

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

Appendix 1 Animal experimental research

Study ID: B2.1

Author, year: ***Dunlap et al. 1958***
Substance: allyl alcohol
Species, strain, sex: Long-Evans male rats
Number/sex/conc. group: 6/group
Age and weight: 100 to 200 gram, age unknown
Observation period: at least 10 days

o**Evaluation of study quality**

Criteria	***Comment***
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*stable*
Use of vehicle (other than air)	
Whole body / nose-only (incl. head/nose-only) exposure	*whole body*
Type of restrainer	*N/A*
Pressure distribution	*no information*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by delivering allyl alcohol from a 10 mL syringe into the cylindrical glass chamber (19.5 L) through an evaporator through which air was forced.*
Number of air changes per hour	*Air flow was 8.6 to 12.9 L/min, resulting in 26.5 to 39.7 air changes per hour.*
Equilibration time (t95)	*4.53 to 6.8 minutes*
Start of exposure relative to equilibration	*The vapour was allowed to equilibrate to (theoretically) 95-99% of the desired concentration*
Actual concentration measurement	*Vapour concentrations were analysed by drawing a sample of air through distilled water, adding bromine in acetic acid in the presence of mercapturic acetate as a catalyst, reducing the excess bromine with iodide, and then titrating the iodine with thiosulfate. Analysis of allyl alcohol vapour in the chamber revealed that concentrations ranged from 15 to 25% less than nominal. However, actual concentrations were not reported. The nominal concentrations used ranged from 97 to 5566 mg/m^3.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*

Assessment of Reliability	***B2*** *Multiple concentration levels and durations were tested. Data of the concentration groups were not reported. The LC_{50} values and confidence intervals for three exposure durations were reported.*

Remark: the paper is in poor condition, hampering part of the publication's legibility. For this reason, the confidence intervals of the LC_{50} values could not be reported in this TSD.

Since the authors remarked that actual concentrations were 15-25% below the reported nominal concentrations, the probit panel decided to adjust (reduce) the reported concentrations by 20% before application in the calculations.

Results

The study authors calculated the LC_{50} values for each of the exposure durations.

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Reported	Adjusted		
Rat	2565	2052	60	LC_{50}
	399	319	240	LC_{50}
	184	147	480	LC_{50}

Based on these results an n-value can be calculated according to the equation stated below (AEGL SOP). An n-value of 0.782 was derived.

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

Study ID: C studies

In the McCord 1932 study several species were exposed to allyl alcohol for 7 hrs a day, 7 days a week until the study was terminated at approximately 30 days (longest reported study duration). One monkey, seven rabbits and 16 rats were included in the study. One monkey (sex not given) exposed to 1000 ppm (2420 mg/m^3) allyl alcohol died after a single 4-hour exposure.
Six rats (strain and sex not given) exposed to 1000 ppm (2420 mg/m^3) allyl alcohol died after a single 3-hour exposure in an intended 7-hour exposure. Four rats exposed to 200 ppm (484 mg/m^3) allyl alcohol for 7 hours/day died on the first or second day of exposure. Four of five rats exposed to 50 ppm (121 mg/m^3) allyl alcohol for 7 hours/day died after approximately 30 days of exposure.
Two rabbits (strain and sex not given) were exposed to 1000 ppm (2420 mg/m^3) allyl alcohol. One died after 3.5 hours exposure and the other died after 4.25 hours. Three rabbits were exposed to 200 ppm (484 mg/m^3) allyl alcohol for 7 hours/day. One rabbit convulsed and died after three days exposure, a second rabbit died after six days of exposure, and the third died after 18 days of exposure. Two rabbits were exposed to 50 ppm (121 mg/m^3) allyl alcohol for 7 hours/day. One rabbit died after 14 exposures, and the second was killed after 28 exposures.

Six Sherman rats (sex not specified) were exposed to 1000 ppm (2420 mg/m^3) allyl alcohol vapour for 1 hour (no details on exposure conditions provided) and observed for 14 days for mortality (Smyth and Carpenter, 1948). Four of the six exposed rats died. The exposure concentration was not confirmed by analytical methods.

Union Carbide and Carbon Corporation (1951) exposed mice (10/group), rats (6) and rabbits (4) to three (probably target) concentrations for 30, 60, 120, or 240 minutes. No information about controls, method of exposure, strain or sex of rats, analytic verification of concentrations, or period of observation was provided. Results are shown in the table below. No further information on study design or conduct is available.

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality
Rat	484	60	0/10
	2420	30	1/6
	2420	60	4/6
	2420	120	6/6
Mouse	484	60	0/10
	1210	30	0/10
	1210	60	4/10
	2420	60	6/10
	2420	120	8/10
	2420	240	10/10
Rabbit	484	60	0/10
	1210	120	0/4
	1210	240	4/4

Four guinea pigs were individually exposed in a bell jar, with allyl alcohol present in a petri dish below the jar (Adams 1958). The exact exposure concentrations were unknown and exposure durations ranged from 15 to 55 minutes. One exposed guinea pig was removed after 30 minutes of exposure; marked lacrimation and exudation of serous fluid from the nose and mouth was noted as well as pronounced

exophthalmos. The guinea pig died 50 minutes post exposure from respiratory failure. A second guinea pig was exposed in the bell jar until death, which occurred at 55 minutes of exposure. Clinical signs included exophthalmos, lacrimation, and oral and nasal serous fluid exudate. A third guinea pig was exposed to allyl alcohol for 20 minutes and died of respiratory failure 5 hours post exposure showing the same clinical signs. A fourth guinea pig was exposed for 15 minutes and developed the same clinical signs as the others, but recovered and was still alive 6 days post exposure.

Groups of five Crl:CD(SD) rats/sex were exposed by whole body inhalation to allyl alcohol vapour at measured concentrations of ranging from 0 to 403 ppm (975 mg/m^3) for 1 hour; from 0 to 102 ppm (247 mg/m^3) for 4 hours; or from 0 to 52 ppm (126 mg/m^3) for 8 hours (Kirkpatrick, 2008 (listed as unnamed report on ECHA public dissemination website)). All animals survived except for one male exposed to 52 ppm (126 mg/m^3) for 8 hours that died the day after exposure. The results of this study do not allow a derivation of a LC_{50} value or derivation of a probit function.

Appendix 2 Reference list

Adams, E.M. 1958. The toxicity of allyl alcohol: An unpublished report of the Dow Chemical Company. Biochemical Research Laboratory, The Dow Chemical Company, Midland, MI, 48642 (cited in AEGL).

AEGL, 2014. National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 16. Washington, DC. The National Academies Press, 2014.

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

Dunlap, M.K., Kodama, J.K., Wellington, J.S., Anderson, H.H., and Hine, C.H. 1958. The toxicity of allyl alcohol. A.M.A. Arch. Ind. Health 18: 303-311.

James, J.T., Buettner, L.C., and Hsu, S.S. 1987. Sensory irritation of methylisocyanate vapor. J. Appl. Toxicol. 7: 147-148.

Kirkpatrick, D.T. 2008. Acute inhalation toxicity study of allyl alcohol in albino rats (with 1-, 4-, and 8-hour exposure durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH. Sponsored by Lyondell Chemical Company, Houston, TX. (cited in AEGL).

McCord, C.P. 1932. The toxicity of allyl alcohol. J. Am. Med. Assoc. 98: 2269.

Muller, J., and Greff, G. 1984. Recherche de relations entre toxicité de molécules d'intérêt industrial et propriétés physico-chimiques: test d'irritation des voies aériennes supérieures appliqué à quattre familles chimiques. Food Chem. Toxicol. 8: 661.

Nielsen, G.D., Bakbo, J.C., and Holst, E. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. et Toxicol. 54: 292-298.

RIVM 2016. Interventiewaarden gevaarlijke stoffen. http://www.rivm.nl/rvs/Normen/Rampen_en_incidenten/Interventiewaarden.

Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard *et al*. Methods for the derivation of probit functions to predict acute lethality following inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.

Smyth, H.F., and Carpenter, C.P. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30: 63-68. (cited in AEGL).

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem to USEPA regarding a letter about toxicity studies with allyl alcohol with cover letter dated 10/15/92. Union Carbide and Carbon Corporation, New York, N.Y. Doc. # 88-920009857.