



Probit function technical support document

Date: 19 July 2018  
Comments before: 1 September 2018  
Document id: 20180719-methyl isocyanate-PROPOSED  
Status: proposed  
Author: L. Geraets (RIVM)  
E-mail response to: [safeti-nl@rivm.nl](mailto:safeti-nl@rivm.nl)

substance name	CAS number
<b>Methyl isocyanate</b>	<b>624-83-9</b>

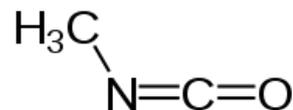
This draft document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute for Public Health and the Environment (RIVM) and has been assigned the status "proposed". The scientific expert panel on probit functions has approved this document for public discussion and comments. Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the email address mentioned above.

If the proposed probit function is approved by the expert panel on scientific grounds, after review and revisions following of public comments, the status of the document and probit function will be raised to "interim".

Subsequently, the Ministry of Infrastructure and the Environment will decide whether the probit function will be formally implemented. The decision on actual implementation will primarily be based on the results of a consequence analysis.

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](http://www.rivm.nl/en/Topics/P/Probit_functions).

1 **Technical support document Methyl isocyanate**

2

3 **1. Substance identification**

4	CAS-number:	624-83-9
5	IUPAC name:	Isocyanatomethane
6	Synonyms:	Methyl carbamylamines; MIC
7	Molecular formula:	C <sub>2</sub> H <sub>3</sub> NO
8	Molecular weight:	57.1 g/mol
9	Physical state:	liquid (at 20°C and 101.3 kPa)
10	Boiling point:	38°C (at 101.3 kPa)
11	Vapour pressure:	46.4 kPa (at 20°C)
12	Saturated vapour conc:	464,000 ppm = 1,102 g/m <sup>3</sup> (at 20°C)
13	Conversion factor:	1 mg/m <sup>3</sup> = 0.421 ppm (at 20°C and 101.3 kPa)
14		1 ppm = 2.375 mg/m <sup>3</sup> (at 20°C and 101.3 kPa)
15	Labelling:	H301-311-315-317-318-330-334-335-361d

16

17

18 **2. Mechanism of action and toxicological effects following acute exposure<sup>1</sup>**

19 **Acute effects:** The main target organs and tissues for inhalation exposure to methyl  
20 isocyanate are the respiratory tract and the ocular system. Methyl isocyanate causes  
21 severe irritation to the respiratory tract and has potent lachrymal properties. The  
22 mechanism of action for the pulmonary, skin, and ocular toxicity is irritation, but the  
23 mechanism of action for the systemic effects is unknown. Death due to methyl  
24 isocyanate exposure is attributed to pulmonary edema.

25 Methyl isocyanate has a harmonized classification for respiratory sensitisation in EU.  
26 However, it is noted that after the Bhopal, India, accident (see section 3), no cases of  
27 respiratory sensitisation were observed.

28 After the Bhopal accident, an unusually high percentage of survivors had disorders of  
29 the reproductive system, including leukorrhoea, pelvic inflammatory disease, excessive  
30 menstrual bleeding, and suppression of lactation. Other adverse effects included  
31 increases in the number of stillbirths, spontaneous abortions, and increased infant  
32 mortality. Animal studies have reported increased incidence of fetal deaths and  
33 decreased fertility, live litter size, fetal body weight, and neonatal survival following  
34 inhalation exposure to methyl isocyanate during pregnancy.

35 **Long-term effects:** Long-term pulmonary and ocular sequelae have been  
36 documented in survivors of the Bhopal incident.

37

38

39

40 **3. Human toxicity data**

41 In 1984, an estimated 30 tons of methyl isocyanate gas were released over Bhopal,  
42 India, from a carbamate factory when water entered the storage tank. The official  
43 death toll was 2,250 individuals, with another 50,000 incapacitated and about  
44 100,000 treated in area hospitals. In general, deaths were not instantaneous but  
45 occurred in phases over the next few days following the release. Only a few deaths  
46 were recorded within the first few hours; a second phase occurred between 8 and  
47 12h, and the greatest number of deaths occurred between 24 and 72h after the  
48 methyl isocyanate release. The most frequently reported symptoms were burning  
49 and/or watering of the eyes, coughing, respiratory distress, pulmonary congestion,  
50 nausea, vomiting, muscle weakness, and CNS involvement secondary to hypoxia. The

---

<sup>1</sup> AEGL (2003)

1 frequency of reports of cough as an initial symptom most closely followed the  
 2 distribution of deaths in the exposed population, deaths resulting from pulmonary  
 3 edema or cardiac arrest following pulmonary edema. Between areas in which deaths  
 4 occurred and areas where only symptoms were reported, distance to the factory was  
 5 a contributing factor, but the duration of exposure (up to 4h) did not appear to vary.  
 6 Although most survivors improved within 2 weeks, many had restrictive respiratory  
 7 function with radiographic changes suggestive of interstitial deposits (AEGL, 2003).

8  
 9 In addition, AEGL (2003) describes three human volunteer studies:

- 10 - Four subjects were each exposed for 1-5 min to MIC at 0.4, 2, 4, or 21 ppm  
 11 (*0.95, 4.75, 9.5, 49.9 mg/m<sup>3</sup>*) (Kimmerle and Eben 1964). At 0.4 ppm, no odor  
 12 was detected and no irritation was reported by any of the volunteers. Minor but  
 13 distinct irritation of mucous membranes (particularly lacrimation) was noted  
 14 without odor at 2 ppm. Ocular irritation became more pronounced at 4 ppm.  
 15 Exposure to 21 ppm was intolerable for even a moment.
- 16 - Eight volunteers were exposed to MIC at an analyzed concentration of 1.75 ppm  
 17 (*4.2 mg/m<sup>3</sup>*) for 1 min (Mellon Institute 1970). All individuals reported eye  
 18 irritation, seven had tearing, and three reported nose and throat irritation.  
 19 Complaints of these effects ceased within 10 min, except that one woman  
 20 reported a sensation of "something in her eye" for 45 min. Six of the same  
 21 individuals were subsequently exposed to MIC at 0.5 ppm for 10 min. All reported  
 22 eye irritation, five had tearing, four had nose irritation, and two reported throat  
 23 irritation. One person detected an odor after 3 min. Additional experimental  
 24 details were not available.
- 25 - In a slightly larger study, seven male volunteers were exposed to nominal  
 26 concentrations at 0.3, 1.0, 2.5, or 5.0 ppm (*0.71, 2.375, 5.9, 11.9 mg/m<sup>3</sup>*) for 1  
 27 min or 1 ppm for 10 min (Mellon Institute 1963a). No effects were reported for  
 28 0.3 or 1.0 ppm for 1 min. Exposure at 2.5 and 5.0 ppm resulted in eye irritation in  
 29 4/7 and 7/7, nose irritation in 2/7 and 2/7, and tearing in 1/7 and 7/7,  
 30 respectively. Throat irritation was also reported by one individual, and 3/7 could  
 31 detect an odor during exposure at 5.0 ppm. During the 10-min exposure at 1  
 32 ppm, eye irritation and tears were reported in 7/7 individuals by 4 and 5 min,  
 33 respectively, and nose and throat irritation were reported by 3/7 after 9 min of  
 34 exposure; no odor was detected.

#### 37 **4. Animal acute toxicity data**

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

- 40 1. AEGL final TSD, ERPG document and EU RAR and reference database for methyl  
 41 isocyanate, covering references before and including 1995.
- 42 2. An additional search covering publications from 1980 onwards was performed in  
 43 HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA, RTECS, IRIS and ToxNet with  
 44 the following search terms:
  - 45 • Substance name and synonyms
  - 46 • CAS number
  - 47 • lethal\*
  - 48 • mortal\*
  - 49 • fatal\*
  - 50 • LC<sub>50</sub>, LC
  - 51 • probit
- 52 3. Unpublished data were sought through networks of toxicological scientists.

53  
 54 Animal lethal toxicity data focused on acute exposure are described in Appendix 1. A  
 55 total of 20 studies were identified -with 29 datasets for four species- with data on  
 56 lethality following acute inhalation exposure. No datasets were assigned status A for

1 deriving the human probit function, 9 datasets were assigned status B and 20 were  
2 assessed to be unfit (status C) for human probit function derivation.

3

#### 4 **Sensory irritation**

5 Two studies were identified in which sensory irritation was studied. In these studies  
6 the following RD<sub>50</sub> values were observed:

7

8 **Table 1** *Sensory irritation data for methyl isocyanate*

Species/strain	RD <sub>50</sub> (mg/m <sup>3</sup> )	Exposure duration (min)	Author/year
Mouse, Swiss-Webster	3.1 <sup>P</sup>	90	Ferguson et al., 1986; Alarie et al., 1987
Mouse, ICR	6.9 <sup>P</sup>	30	James et al., 1987

9 P: a plateau was reached

10

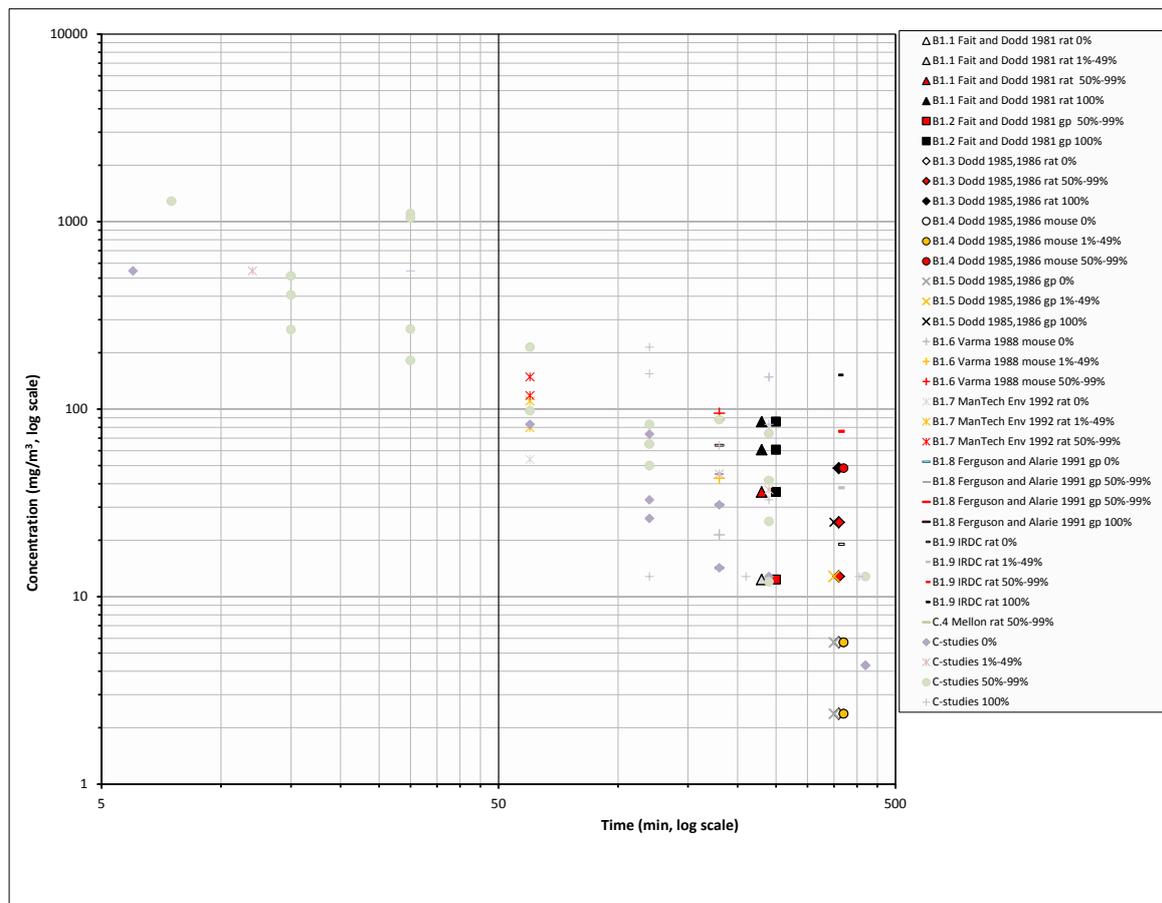
11

### 12 **5. Probit functions from individual studies**

13

14

1 All available acute lethality data on methyl isocyanate are displayed in Figure 1.  
 2  
 3



4  
 5 **Figure 1** All available acute lethality data for methyl isocyanate.  
 6

7  
 8 The data that were selected for initial analysis of the animal probit function are  
 9 presented in Table 2 and Figure 2.

10  
 11 It was not possible to derive a probit function for methyl isocyanate based on studies  
 12 with A quality as these were not available. Therefore, the probit function was derived  
 13 using data from the studies with B1 quality, none of which enabled to produce a  
 14 concentration-time-lethality relationship.

15  
 16 All B1 studies were selected for derivation of the animal probit function for methyl  
 17 isocyanate.

18  
 19 Although the Mellon 1970 study was classified as a C-study the n-value of 1.01 found  
 20 in that study was preferred over the default value (n=2) to scale the LC<sub>50</sub> values of  
 21 the B1-studies. This was also supported by species-specific n-values when LC<sub>50</sub> values  
 22 of the various B1-studies were pooled. This resulted in n-values of 1.24 (rat), 0.54  
 23 (guinea pig), and 1.04 (mouse) (analyses not shown). To enable intra-species  
 24 pooling, LC<sub>50</sub>-values of B1-studies were scaled using the species specific (overall) n-  
 25 value of 1.01 (study C.4; Mellon 1970) with the following formula (section 6):  
 26  
 27  
 28

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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12

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  
 $n$  = species specific (overall) n-value

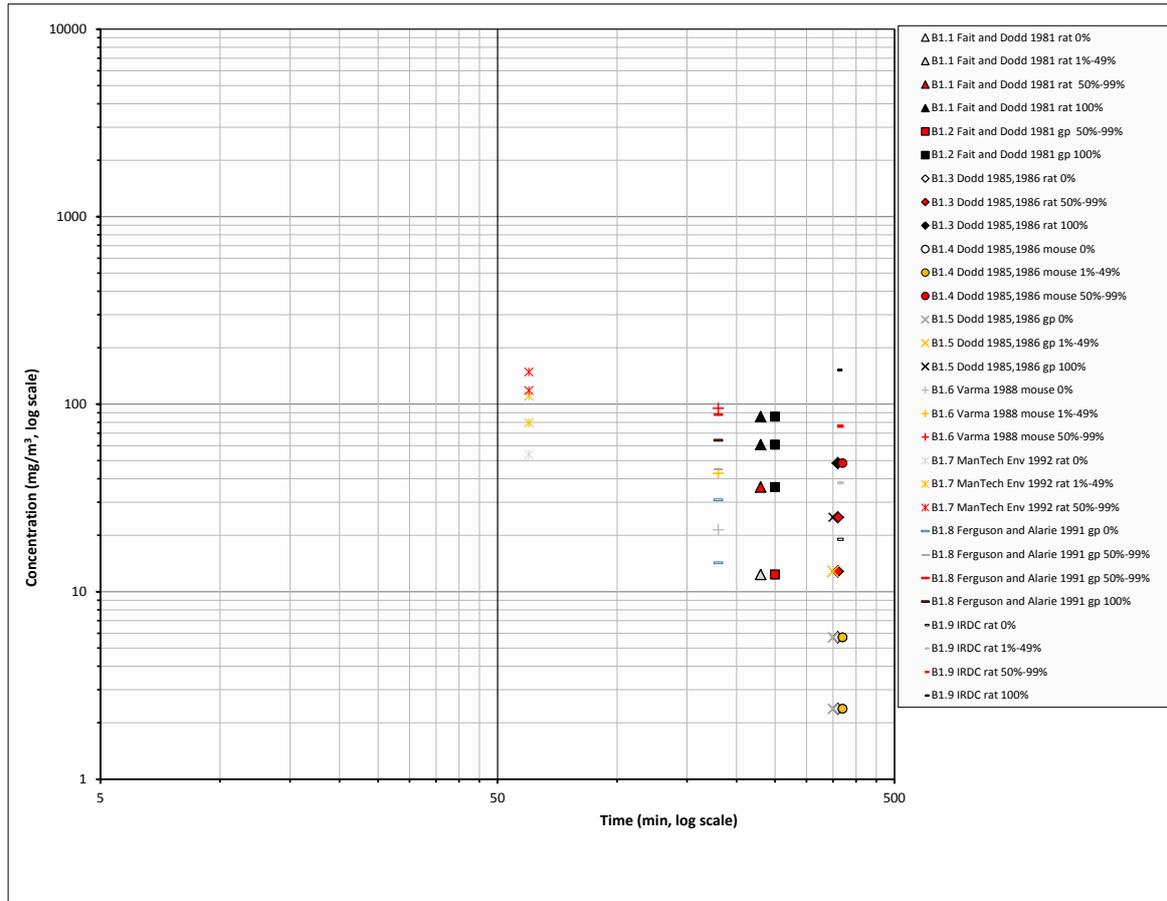
Probit functions have been calculated and reported in Appendix 1 for each of the reported studies. The results of the calculations are presented in Table 2.

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

Study ID	Species	Probit (C in mg/m <sup>3</sup> , t in min)	LC50 at tested exposure duration (mg/m <sup>3</sup> ) 95% C.I.	<u>LC50, 60 minutes (mg/m<sup>3</sup>) 95% C.I. (underline italic for scaled values)</u>	n-value 95% C.I.
B1.1	Rat	240-min LC50	25.9 (17.5-34.2)	<u>102</u>	N/A
B1.3	Rat	360-min LC50	14.3 (10.6-18.6)	<u>84</u>	N/A
B1.7	Rat	60-min LC50	109 (98-120)	109	N/A
B1.9	Rat	360-min LC50	51.0 (24.3-80.3)	<u>301</u>	N/A
B1.2	Guinea pig	240-min LC50	9.42 (0.812-16.43)	<u>37</u>	N/A
B1.5	Guinea pig	360-min LC50	13.1 (C.I. could not be calculated)	<u>77</u>	N/A
B1.8	Guinea pig	180-min LC50	54.4 (43.4-67.8)	<u>161</u>	N/A
B1.4	Mouse	360-min LC50	29.6 (22.3-42.1)	<u>175</u>	N/A
B1.6	Mouse	180-min LC50	57.5 (38.6-73.2)	<u>171</u>	N/A

13  
14  
15  
16

The data of the rat studies B1.1, B1.3, B1.7 and B1.9, guinea pig studies B1.2, B1.5 and B1.8 and mouse studies B1.4 and B1.6 are presented graphically below.



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

Based on criteria outlined in the guideline the data from rat study B1.7 (ManTech Environmental, 1992) were selected for the final dataset for the derivation of the animal probit function.

According to the methodology, studies with an exposure duration closer to the target of 30-60 min are preferred. For the species rat, four B1-studies were available, i.e. studies B1.1, B1.3, B1.7 and B1.9 with an exposure duration of 240 min, 360 min, 60 min and 360 min, respectively. For the species mouse, two B1-studies were available, i.e. studies B1.4 and B1.6 with an exposure duration of 360 min and 180 min, respectively. For the species guinea pig, three B1-studies were available, i.e. studies B1.2, B1.5 and B1.8 with an exposure duration of 240 min, 360 min and 180 min, respectively.

An extrapolation from an exposure duration of 180 min, 240 min or 360 min to a 30-60 min value is believed to be too uncertain, even more so as the n-value was based on a study with C-quality.

Therefore, preference was given to rat study B1.7.

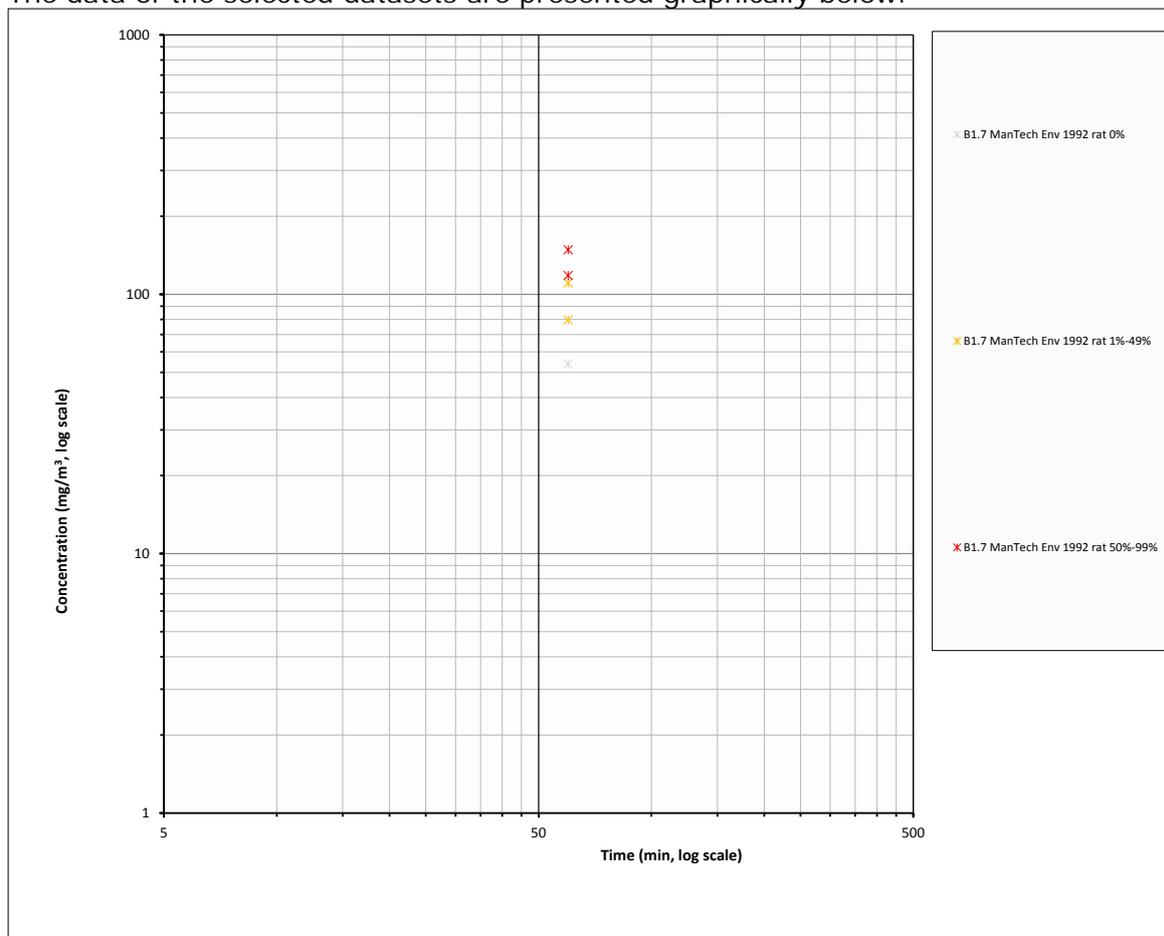
The data that were selected for final analysis of the animal probit function are presented in Table 3 and Figure 3.

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

1 **Table 3** Data selected for the derivation of the animal probit function of methyl  
 2 isocyanate.

Study ID	Species	Probit (C in mg/m <sup>3</sup> , t in min)	LC <sub>50</sub> at tested exposure duration (mg/m <sup>3</sup> ) 95% C.I.	n-value 95% C.I.
B1.7	Rat	60-min LC <sub>50</sub>	109 (98-120)	N/A

3  
 4  
 5 The data of the selected datasets are presented graphically below.



6  
 7 **Figure 3** Final data selected for derivation of the animal probit function of methyl  
 8 isocyanate.  
 9  
 10  
 11

## 6. Derivation of the human probit function

To derive the human probit function the results from rat study B1.7 have been used to derive a point of departure as outlined above.

The Point of Departure for the human probit function is a 60-minute animal LC<sub>50</sub> value of 109 mg/m<sup>3</sup> and a species specific (overall) n-value of 1.01 (study C.4; Mellon 1970). The value for n was derived from a C-quality study. The Mellon (1970) was given the C quality status in view of a poor documentation of the study and a lack of reliable quantitative data; however this does not affect the derivation of the n-value. Because the n-value was based on animal data and supported by findings from pooled analyses of B1-studies, this chemical-specific n-value was preferred over a default value of 2.

The human equivalent LC<sub>50</sub> 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
Nominal concentration	1	Analytical concentrations available
Adequacy of database:	1	In total nine B1-studies available.

The estimated human equivalent 60-minute LC<sub>50</sub> value is  $109 / 3 = 36 \text{ mg/m}^3$ .

The experimentally determined n-value was **1.01** (study C.4). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as  $2 / n = 1.98$ .

The human probit function is then calculated on the human equivalent 60 min LC<sub>50</sub> using the above parameters to solve the following equation to obtain the a-value (the intercept):  $5 = a + 1.98 \times \ln(36^{1.01} \times 60)$  resulting in the a-value of **-10.29**.

**Pr = -10.3 + 1.98 × ln (C<sup>1.01</sup> × t) with C in mg/m<sup>3</sup> and t in min.**

The derived human probit function has a scientifically acceptable basis. The probit function is based on one study in the rat with B1 quality and a study with C quality for the n-value.

The calculated human 60 min LC<sub>0.1</sub> (Pr = 1.91) calculated with this probit equation is 8 mg/m<sup>3</sup> and the calculated human 60 min LC<sub>1</sub> (Pr = 2.67) is 11 mg/m<sup>3</sup>.

**Table 5** LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.

Estimated level	30 min (mg/m <sup>3</sup> )	60 min (mg/m <sup>3</sup> )
0.1% lethality, this probit	15	8

1% lethality, this probit	23	11
AEGL-3 <sup>2</sup> (2003, final)	0.95	0.48
ERPG-3 <sup>2</sup> (2005)	-	3.6
LBW (2016)	6.6	3.3

1  
2  
3  
4  
5  
6

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are one order of magnitude higher than AEGL and approximately two times higher than the Dutch Intervention Values.

---

<sup>2</sup> AEGL and ERPG values were converted from ppm to mg/m<sup>3</sup> with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m<sup>3</sup> can deviate slightly from those reported in the AEGL and ERPG TSDs.

## Appendix 1 Animal experimental research

### Study ID: B1.1

**Author, year:** *Fait and Dodd (1981) \**  
**Substance:** methyl isocyanate  
**Species, strain, sex:** Rat, Fischer 344, male+female  
**Number/sex/conc. group:** 6  
**Age and weight:** 7-8 weeks old at start of exposure, weight at start of exposure not specified  
**Observation period:** 14 days

\* it is noted that the data of Fait and Dodd (1981) have also been presented by Dodd et al. (1985,1986)

### Evaluation of study quality

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>stable</i>
Use of vehicle (other than air)	<i>Nitrogen</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>MIC was stored in a stainless-steel cylinder equipped with a pressure-relief valve, and several metering valves. A filling tube extended close to the bottom of the cylinder. A nitrogen gas supply (20 psig) was attached to the filling tube. When nitrogen was introduced into the cylinder, it was saturated with MIC and the resultant N<sub>2</sub>-MIC mixture was regulated at approximately 5 psig, and was needle-valve controlled (measured with a rotameter). The N<sub>2</sub>-MIC vapour was further diluted with filtered room air and drawn through the chambers.</i>
Number of air changes per hour	<i>An airflow of approximately 1100 L/min and a 4350 L inhalation chamber: ca. 15 air changes/hour</i>
Equilibration time (t95)	<i>11.9 min</i>
Start of exposure relative to equilibration	<i>No information</i>
Actual concentration measurement	<i>Chamber atmosphere was sampled approximately once per hour. Each sample was taken from a single port located in the center of the chamber. Analysis was done by a gas chromatograph equipped with a flame ionization detector.</i>

Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	<b>B</b> <i>Well-performed study. Limited to one exposure duration.</i>

1  
2**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Rat	12.4	N/A	240	0/6	1/6
Rat	36.1	N/A	240	5/6	4/6
Rat	60.8	N/A	240	6/6	5/6
Rat	85.7	N/A	240	6/6	6/6

3  
4  
5  
6  
7  
8  
9**Probit function**

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

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

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

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-0.940	1.87	-0.259	N/A
Sexes combined	Rat	-1.06	1.86		N/A

10

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male *	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Female *	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Combined
240	23.9 (14.3-36.2)	27.5 (16.6-40.7)	25.9 (17.5-34.2)

11 \* Fait and Dodd (1981) derived 4h LC<sub>50</sub> values of 26.4 (17.8-39.2) mg/m<sup>3</sup> and 26.1 (14.5-  
12 47.3) mg/m<sup>3</sup> for males and females, respectively.

13  
14  
15  
16  
17  
18  
19

The 4-hour LC<sub>50</sub> 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 4-hour data from both sexes were pooled and analysed to derive the animal probit function.

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

1 **Study ID: B1.2**

2

3 **Author, year:** *Fait and Dodd (1981) \**

4 Substance: methyl isocyanate

5 Species, strain, sex: Guinea pigs, Hartley albino, male and female

6 Number/sex/conc. group: 6

7 Age and weight: 4-5 weeks of age at start of exposure; weight at start of

8 exposure not specified

9 Observation period: 14 days

10

11 \* it is noted that the data of Fait and Dodd (1981) have also been presented by Dodd et al. (1985,1986)

12 **Evaluation of study quality**

13

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>stable</i>
Use of vehicle (other than air)	<i>Nitrogen</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>MIC was stored in a stainless-steel cylinder equipped with a pressure-relief valve, and several metering valves. A filling tube extended close to the bottom of the cylinder. A nitrogen gas supply (20 psig) was attached to the filling tube. When nitrogen was introduced into the cylinder, it was saturated with MIC and the resultant N<sub>2</sub>-MIC mixture was regulated at approximately 5 psig, and was needle-valve controlled (measured with a rotameter). The N<sub>2</sub>-MIC vapour was further diluted with filtered room air and drawn through the chambers.</i>
Number of air changes per hour	<i>An airflow of approximately 1100 L/min and a 4350 L inhalation chamber: ca. 15 air changes/hour</i>
Equilibration time (t95)	<i>11.9 min</i>
Start of exposure relative to equilibration	<i>No information</i>
Actual concentration measurement	<i>Chamber atmosphere was sampled approximately once per hour. Each sample was taken from a single port located in the center of the chamber. Analysis was done by a gas chromatograph equipped with a flame ionization detector.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>

Assessment of Reliability	<b>B</b> <i>Well-performed study. Limited to one exposure duration.</i>
---------------------------	--

1  
2  
3**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Guinea pig	12.4	N/A	240	4/6	3/6
Guinea pig	36.1	N/A	240	6/6	6/6
Guinea pig	60.8	N/A	240	6/6	5/6
Guinea pig	85.7	N/A	240	6/6	6/6

4  
5**Probit function**

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

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

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

6  
7  
8  
9  
10  
11

Probit function	Species	a	b	d	n-value
Sex as variable	Guinea pig	2.79	1.12	-0.647	N/A
Sexes combined	Guinea pig	2.64	1.05		N/A

12

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male *	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Female *	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Combined
240	7.13 (0.420-15.84)	12.69 (1.649-23.67)	9.42 (0.812-16.43)

13  
14  
15  
16  
17  
18  
19  
20  
21

\* Fait and Dodd (1981) reported 4h LC<sub>50</sub> values of < 12.4 mg/m<sup>3</sup> (males and females combined).

The LC<sub>50</sub> 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.

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

1 **Study ID: B1.3**

2  
 3 **Author, year:** *Dodd et al. (1985, 1986) \**  
 4 Substance: Methyl isocyanate  
 5 Species, strain, sex: rat, Fischer 344, male and female  
 6 Number/sex/conc. group: 6  
 7 Age and weight: 10-11 weeks (6-h experiment); weight not specified  
 8 Observation period: 14 days

9  
 10 \* It is noted that Dodd et al (1985, 1986) also presented 4-hour exposure data for rat and guinea pig,  
 11 however these were similar to the data of Fait and Dodd (1981, studies B1.1/B1.2). Therefore, only the 6-  
 12 hour data is presented below.  
 13 Further, it is noted that the 6-hour data of Dodd et al. (1985,1986) have also been presented by Fowler  
 14 and Dodd (1987).

15  
16 **Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>Nitrogen</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>

Homogeneity of test atmosphere in breathing zone of animals	<i>MIC was stored in a stainless-steel cylinder equipped with a pressure-relief valve, a pressure gauge, and several metering valves. A filling tube extends from the bottom of the cylinder to the union with the metering valves. A nitrogen gas supply (20 psig) was attached to the filling tube. When nitrogen was introduced into the cylinder, it was saturated with MIC and the resultant N<sub>2</sub>-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The N<sub>2</sub>-MIC mixture was metered into a stainless-steel manifold line leading to the chambers. The valves, fittings, pipings, and manifold connected to the storage cylinder were thermally controlled due to the latent heat of vaporization. The N<sub>2</sub>-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the N<sub>2</sub>-MIC mixture occurred. The concentration of MIC in the cylinder head space was lowered by cooling the storage cylinder. After each exposure, the chamber manifold line was flushed with nitrogen. This was accomplished by replacing the two metering valves located at the top of the storage cylinder with two-way ball valves and attaching a tube between the ball valves.</i>
Number of air changes per hour	<i>An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour</i>
Equilibration time (t <sub>95</sub> )	<i>13.05 min</i>
Start of exposure relative to equilibration	<i>Not specified</i>
Actual concentration measurement	<i>Chamber air was sampled one to five times an hour with an automatic gas sampling system. Samples were drawn with a vacuum pump from a sampling line located in the centre of the chamber. Analysis was performed with a gas chromatograph equipped with a nitrogen-phosphorus detector.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>B1</b> <i>Well performed study; limited to one exposure duration.</i>

1  
2**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality*
	Measured	Adjusted		
				Dead/tested
Rat	2.4	N/A	360	0/12
Rat	5.7	N/A	360	0/12
Rat	13	N/A	360	6/12
Rat	25	N/A	360	10/12
Rat	48	N/A	360	12/12

3 \* Dodd et al. (1985, 1986) presented the 6-hour lethality data on a combined male and female analysis  
4 only

5  
6  
7**Probit function**

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

$$10 \text{ Pr} = a + b \times \ln C$$

11 with C for concentration in mg/m<sup>3</sup>.

12

Probit function	Species	a	b	n-value
Sexes combined	Rat	-0.702	2.15	N/A

13

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Combined *
360	14.3 (10.6-18.6)

14 \* Dodd et al (1985,1986) derived a 6h LC<sub>50</sub> value of 14.5 (10.9-19.5) mg/m<sup>3</sup>.

15

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

17

1 **Study ID: B1.4**

2

3 **Author, year:** *Dodd et al. (1985, 1986) \**

4 Substance: Methyl isocyanate

5 Species, strain, sex: mouse, B6C3F1, male and female

6 Number/sex/conc. group: 6

7 Age and weight: 10-11 weeks; weight not specified

8 Observation period: 14 days

9

10 \* it is noted that the 6-hour data of Dodd et al. (1985,1986) have also been presented by Fowler and Dodd  
11 (1987)

12

13

**Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>Nitrogen</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>

Homogeneity of test atmosphere in breathing zone of animals	<i>MIC was stored in a stainless-steel cylinder equipped with a pressure-relief valve, a pressure gauge, and several metering valves. A filling tube extends from the bottom of the cylinder to the union with the metering valves. A nitrogen gas supply (20 psig) was attached to the filling tube. When nitrogen was introduced into the cylinder, it was saturated with MIC and the resultant N<sub>2</sub>-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The N<sub>2</sub>-MIC mixture was metered into a stainless-steel manifold line leading to the chambers. The valves, fittings, pipings, and manifold connected to the storage cylinder were thermally controlled due to the latent heat of vaporization. The N<sub>2</sub>-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the N<sub>2</sub>-MIC mixture occurred. The concentration of MIC in the cylinder head space was lowered by cooling the storage cylinder. After each exposure, the chamber manifold line was flushed with nitrogen. This was accomplished by replacing the two metering valves located at the top of the storage cylinder with two-way ball valves and attaching a tube between the ball valves.</i>
Number of air changes per hour	<i>An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour</i>
Equilibration time (t95)	<i>13.05 min</i>
Start of exposure relative to equilibration	<i>Not specified</i>
Actual concentration measurement	<i>Chamber air was sampled one to five times an hour with an automatic gas sampling system. Samples were drawn with a vacuum pump from a sampling line located in the centre of the chamber. Analysis was performed with a gas chromatograph equipped with either a nitrogen-phosphorus detector.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>B1</b> <i>Well performed study. Limited to one exposure duration.</i>

1  
2**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality*
	Measured	Adjusted		
				Dead/tested
Mouse	2.4	N/A	360	0/12
Mouse	5.7	N/A	360	0/12
Mouse	13	N/A	360	1/12
Mouse	25	N/A	360	4/12
Mouse	48	N/A	360	10/12

3 \* Dodd et al. (1985, 1986) presented the lethality data on a combined male and female analysis only

4  
5**Probit function**6 The probit function and associated LC-values have been calculated using the  
7 DoseResp program (Wil ten Berge, 2016) as

8 
$$Pr = a + b \times \ln C$$

9 with C for concentration in mg/m<sup>3</sup>.10  
11

Probit function	Species	a	b	n-value
Sexes combined	Mouse	-1.18	1.82	N/A

12

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Combined *
360	29.6 (22.3-42.1)

13 \* Dodd et al (1985,1986) derived a 6h LC<sub>50</sub> value of 29.0 (20.0-41.6) mg/m<sup>3</sup>.

14

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

1 **Study ID: B1.5**

2  
 3 **Author, year:** *Dodd et al. (1985, 1986) \**  
 4 Substance: Methyl isocyanate  
 5 Species, strain, sex: guinea pig, Hartley albino, male and female  
 6 Number/sex/conc. group: 6  
 7 Age and weight: 10 weeks (6-h experiment); weight not specified  
 8 Observation period: 14 days

9  
 10 \* It is noted that Dodd et al (1985, 1986) also presented 4-hour exposure data for rat and guinea pig,  
 11 however these were similar to the data of Fait and Dodd (1981, studies B1.1/B1.2). Therefore, only the 6-  
 12 hour data is presented below.  
 13 Further, it is noted that the 6-hour data of Dodd et al. (1985,1986) have also been presented by Fowler  
 14 and Dodd (1987).

15  
16 **Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>Nitrogen</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>

Homogeneity of test atmosphere in breathing zone of animals	<i>MIC was stored in a stainless-steel cylinder equipped with a pressure-relief valve, a pressure gauge, and several metering valves. A filling tube extends from the bottom of the cylinder to the union with the metering valves. A nitrogen gas supply (20 psig) was attached to the filling tube. When nitrogen was introduced into the cylinder, it was saturated with MIC and the resultant N<sub>2</sub>-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The N<sub>2</sub>-MIC mixture was metered into a stainless-steel manifold line leading to the chambers. The valves, fittings, pipings, and manifold connected to the storage cylinder were thermally controlled due to the latent heat of vaporization. The N<sub>2</sub>-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the N<sub>2</sub>-MIC mixture occurred. The concentration of MIC in the cylinder head space was lowered by cooling the storage cylinder. After each exposure, the chamber manifold line was flushed with nitrogen. This was accomplished by replacing the two metering valves located at the top of the storage cylinder with two-way ball valves and attaching a tube between the ball valves.</i>
Number of air changes per hour	<i>An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour</i>
Equilibration time (t95)	<i>13.05 min</i>
Start of exposure relative to equilibration	<i>Not specified</i>
Actual concentration measurement	<i>Chamber air was sampled one to five times an hour with an automatic gas sampling system. Samples were drawn with a vacuum pump from a sampling line located in the centre of the chamber. Analysis was performed with a gas chromatograph equipped with either a nitrogen-phosphorus detector.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>B1</b> <i>Well performed study. Limited to one exposure duration.</i>

1  
2**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality*
	Measured	Adjusted		
				Dead/tested
Guinea pig	2.4	N/A	360	0/12
Guinea pig	5.7	N/A	360	0/12
Guinea pig	13	N/A	360	5/12
Guinea pig	25	N/A	360	12/12

3 \* Dodd et al. (1985, 1986) presented the 6-hour lethality data on a combined male and female analysis  
4 only

5  
6**Probit function**

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

$$9 \text{ Pr} = a + b \times \ln C + d \times S$$

10 with C for concentration in mg/m<sup>3</sup>.

11  
12  
13

Probit function	Species	a	b	n-value
Sexes combined	Guinea pig	-24.1	11.3	N/A

14

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Combined *
360	13.1 (C.I. could not be calculated)

15 \* Dodd et al (1985,1986) derived a 6h LC<sub>50</sub> value of 12.8 (10.5-15.9) mg/m<sup>3</sup>.

16

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

1 **Study ID: B1.6**

2  
3 **Author, year:** **Varma et al. (1988)**  
4 Substance: methyl isocyanate  
5 Species, strain, sex: mouse, Swiss-Webster, male  
6 Number/sex/conc. group: 8-12  
7 Age and weight: age not specified; 20-25 g  
8 Observation period: 14 days  
9

10 **Evaluation of study quality<sup>#</sup>**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>N/A</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>The desired exposure concentrations were obtained by passing dry air through a 500-mL bottle containing 10 ml methyl isocyanate liquid held in a 0°C ice bath. Thus, air saturated with methyl isocyanate vapor was delivered to the central glass chamber of the exposure system. The exposure concentration was established by varying the airflow into the evaporating bottle or adjusting the exhaust of the central chamber. *</i>
Number of air changes per hour	<i>Dependent on the desired concentration, the air flow in the chamber was between 10 and 100 liters/min (desired concentrations between 0.9 and 7.6 ppm) or 6.5 liters/min (desired concentrations of less than 0.9 ppm). For a concentration &gt;7.6 ppm, this was not specified. *</i>
Equilibration time (t95)	<i>Insufficient information to calculate t95</i>
Start of exposure relative to equilibration	<i>No information</i>
Actual concentration measurement	<i>The concentration of methyl isocyanate in exposure chambers was monitored throughout the duration of exposure with a gas chromatograph equipped with a nitrogen-phosphorus detector.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>

Assessment of Reliability	<b>B1</b> <i>Well performed study. Limited to one exposure duration.</i>
---------------------------	---

# this study focussed on the effect of starvation, dexamethasone, sodium thiosulfate, atropine and ethanol on methylisocyanate inhalation toxicity. The data presented below are those of the control animals (i.e. saline-treated)

\* Varma et al. (1988) refer to earlier publications of Ferguson et al. (1986) and Varma et al. (1987) for details on the experimental setup.

## Results

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Male
				Dead/tested
Mouse	21.4	N/A	180	0/8
Mouse	42.8	N/A	180	5/11
Mouse	95.0	N/A	180	31/41

## 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<sup>3</sup>.

Probit function	Species	a	b	n-value
	Mouse	-0.974	1.47	N/A

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
180	57.5 (38.6-73.2)

The study authors calculated a 3-h LC<sub>50</sub> value of 64.0 mg/m<sup>3</sup>.

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

1 **Study ID: B1.7**2  
3 **Author, year:** **ManTech Environmental 1992**

4 Substance: methyl isocyanate

5 Species, strain, sex: Rat, Fischer 344, male

6 Number/sex/conc. group: 20

7 Age and weight: approximately 7-8 weeks and 166-241 g at start of  
8 exposure

9 Observation period: 14 days

10  
11 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	Yes
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)	Nitrogen
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution	A tent constructed of a plastic covered wooden frame with a plexiglass door was built to house the exposure chamber and MIC generator hood. The tent was operated negative to the exposure room.
Homogeneity of test atmosphere in breathing zone of animals	A "flash evaporator" was used to generate vapours. Liquid MIC was collected from a steel cylinder in a bottle and further drawn into a syringe connected to a U-Tube (which was partially filled with glass beads) with Kovar ends. Nitrogen entered one end of the U-Tube and was heated as it passed over the hot glass beads. A stainless steel Tee was connected to the other end of the U-Tube. Liquid IMC entered one port of the Tee, dripped onto the hot beads and was vaporized. The heated nitrogen carried the vapors out to the other port of the Tee and into a Teflon delivery line connected to the exposure chamber inlet. The MIC/air mixture entered the top of the chamber, was drawn past the rats and was exhausted at the bottom of the chamber.
Number of air changes per hour	Exposures were conducted in 0.3 m <sup>3</sup> stainless steel and glass chamber. Airflow was approximately 250-295 L/min. This results in 61-72 air changes per hour.
Equilibration time (t95)	3.1-3.6 min

Start of exposure relative to equilibration	<i>No information</i>
Actual concentration measurement	<i>Chamber concentrations were determined by gas-chromatography (equipped with flame ionization detector); air samples were continuously drawn from the chamber (near the breathing zone of the animals).</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>B1</b> <i>Well-performed study. Limited to one exposure duration.</i>

1  
2  
3**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	54	N/A	60	0/20
Rat	80	N/A	60	4/20
Rat	110	N/A	60	7/20
Rat	118	N/A	60	16/20
Rat	148	N/A	60	16/20

4

**Probit function**

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

$$7 \text{ Pr} = a + b \times \ln C$$

8 with C for concentration in mg/m<sup>3</sup>.

9  
10

Probit function	Species	a	b	n-value
	Rat	-9.94	3.19	-

11

12

13

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
60	109 (98.2-120)

14

15

16

17

15 ManTech Environmental (1992) reported 1-hour LC<sub>50</sub> values of 107 (92-125) mg/m<sup>3</sup>.

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



1 **Study ID: B1.8**

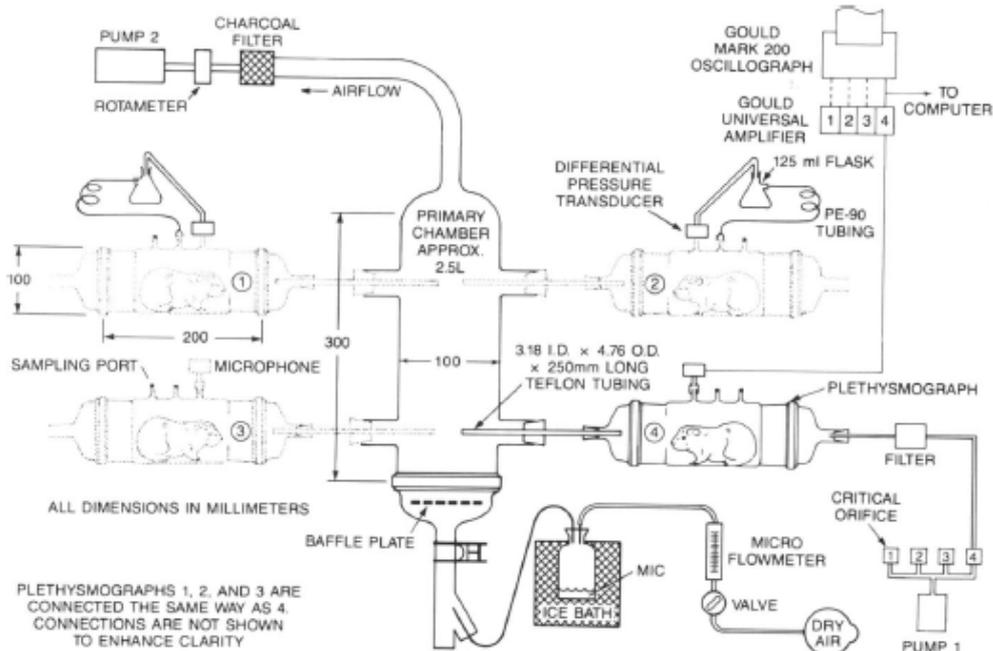
2  
3 **Author, year:** **Ferguson and Alarie (1991)**  
4 Substance: methyl isocyanate  
5 Species, strain, sex: guinea pig, English short-haired, amle  
6 Number/sex/conc. group: 8/group  
7 Age and weight: age not specified; 275-325 g  
8 Observation period: up to 1 year  
9

10 **Evaluation of study quality\***

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>The desired exposure concentrations were obtained by passing dry air through a 500-ml bottle containing 10 ml MIC liquid held in a 0°C ice bath. Thus air saturated with MIC vapor was delivered to the central glass chamber of the exposure system. The exposure concentration was established by varying the airflow into the evaporating bottle or adjusting the exhaust of the central chamber. Each guinea pig was placed in a whole body plethysmograph. Once the desired exposure concentration was achieved and remained stable, exposure was initiated by attaching the plethysmographs to the central chamber.</i>
Number of air changes per hour	<i>1.8 l/min; volume of inhalation chamber not specified</i>
Equilibration time (t95)	<i>Insufficient information to calculate t95</i>
Start of exposure relative to equilibration	<i>Exposure started after complete equilibration</i>
Actual concentration measurement	<i>Using a gas-tight syringe, 1 ml samples were drawn from each animal exposure chamber for direct injection into a gas chromatograph equipped with a nitrogen-phosphorus detector. Samples were obtained every 3-5 minutes during exposure. The average concentration was determined for each exposure and coefficients of variation for each mean exposure concentration were below 20%.</i>

Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	<b>B1</b> <i>Well-performed study. Limited to one exposure duration.</i>

1 \* the details of the vapour generation system and the analytical determination of MIC  
 2 exposure concentrations have been described by Alarie et al. (1987).  
 3



4 System used for exposure of guinea pigs (Alarie et al. 1987).  
 5  
 6  
 7  
 8

**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Male
				Dead/tested
Guinea pig	14	N/A	180	0/8
Guinea pig	31	N/A	180	0/8
Guinea pig	45	N/A	180	2/8
Guinea pig	64	N/A	180	8/8
Guinea pig	88	N/A	180	6/8

9  
 10 **Probit function**

11 The probit function and associated LC-values have been calculated using the  
 12 DoseResp program (Wil ten Berge, 2016) as  
 13  $Pr = a + b \times \ln C$   
 14 with C for concentration in mg/m<sup>3</sup>.  
 15

Probit function	Species	a	b	n-value
	Guinea pig	-6.58	2.78	-

20180719- methyl isocyanate -PROPOSED

1  
2

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
180	54.4 (43.4-67.8)

3  
4

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

1 **Study ID: B1.9**

2  
3 **Author, year:** **IRDC (1964)**  
4 Substance: methyl isocyanate  
5 Species, strain, sex: rat, Sprague-Dawley, male  
6 Number/sex/conc. group: 4-6  
7 Age and weight: no information  
8 Observation period: 15 days  
9

10 **Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to OECD 403 guideline(s)	<i>OECD guideline 403 did not exist at the time</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>The concentration within the chamber was maintained by the use of a constant metering syringe which delivered a known amount of compound into the vaporizing unit where it was vaporized, picked up by a moving air stream, and carried into the exposure chamber.</i>
Number of air changes per hour	<i>Air flow and volume of inhalation chamber not specified.</i>
Equilibration time (t95)	<i>Insufficient information to calculate t95</i>
Start of exposure relative to equilibration	<i>Not specified</i>
Actual concentration measurement	<i>Only nominal concentrations presented. According to the authors, adequate analytical methods were not available for sampling such low concentrations. The ppm exposure has been calculated on the basis of the airflow through the chamber and the amount of material vaporized.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>

Assessment of Reliability	<p><b>B1</b></p> <p><i>Well-performed study, though some details on study characteristics are missing. Limited to one exposure duration.</i></p> <p><i>No actual concentrations presented, though nominal concentrations calculated. Nominal concentrations were &lt; 25% of the saturated vapour concentration.</i></p>
---------------------------	--

1  
2  
3

### Results

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	19		360	0/4
Rat	38		360	1/4
Rat	76		360	5/6
Rat	152		360	6/6

4  
5

### Probit function

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

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

with C for concentration in mg/m<sup>3</sup>.

10

Probit function	Species	a	b	n-value
	Rat	-5.11	2.57	N/A

11  
12

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
360	51.0 (24.3-80.3)

13  
14

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

1 **Study ID: C.1**

2  
3 **Author, year:** *Dodd et al. (1987)*  
4 Substance: Methyl isocyanate  
5 Species, strain, sex: rat, Sprague-Dawley, male and female  
6 Number/sex/conc. group: not clearly specified  
7 Age and weight: 200-300 g/ 195-265 g (m/f)  
8 Observation period: 14 days  
9

10 **Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>N/A</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>Both the chamber and the glove box are maintained at a negative pressure with respect to the room.</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>Vapor exposures were statically generated. The test material was introduced into the chamber with a glass syringe through a ¼ inch stainless-steel bulkhead sampling port containing a gas chromatogram septum. Following injection of liquid methyl isocyanate into the chamber, evaporation of the sample occurred in a matter of seconds. The following information on the exposure chamber design was presented by Dodd et al. (1987): A static exposure chamber (135 L) with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate (see figure below). This static exposure chamber was placed in a dynamic 900-L exposure chamber (with an airflow of 350 L/min), constructed of stainless-steel and glass, providing a double chamber exposure design. Attached to this dynamic exposure chamber was a 940 L stainless-steel and glass glove-box operated with a dynamic airflow of approximately 350 L/min (see figure below).</i>
Number of air changes per hour	<i>Vapor exposures were statically generated in a 135 L inhalation chamber.</i>

Equilibration time (t95)	<i>t95 in minutes cannot be calculated (as a static test atmosphere generation was applied, i.e. no air flow). However, it was stated by Dodd et al. (1987) that "Chamber concentration reached equilibrium within approximately 1 min".</i>
Start of exposure relative to equilibration	<i>It was stated by Dodd et al. (1987) that "The sliding cage drawer mechanism prevented the animals' introduction into the chamber until mixing of methyl isocyanate with air had equilibrated. Thus, the chamber concentrations were determined prior to animal exposure".</i>
Actual concentration measurement	<i>Chamber air was sampled manually with a glass gastight syringe two to four times per exposure and analysed with a gas chromatograph with flame ionization detector. It was stated by Dodd et al. (1987) that "The analytical to nominal chamber concentrations for the static exposure ranged between 0.5 and 0.9".</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	<b>C</b> <i>Limited to one exposure duration. Because no individual mortality data are available the study was given C status.</i>

1  
2  
3  
4  
5  
6

Additional remark: this study included also an experiment in which early mortality was evaluated. As only the number of deaths during exposure or within 10 minutes postexposure was provided by Dodd et al. (1987), these data are not presented here.

The figures below are copied from Dodd et al. (1987):

### STATIC EXPOSURE CHAMBER

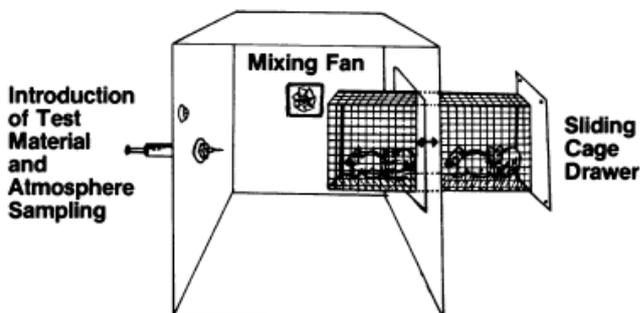


FIGURE 1. A static exposure chamber with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

7

### DOUBLE CHAMBER EXPOSURE DESIGN

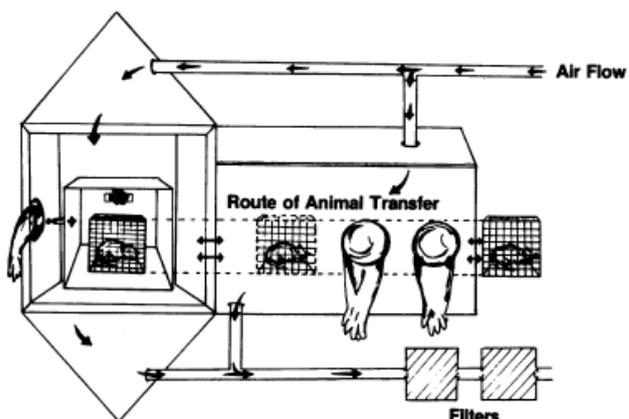


FIGURE 2. A static exposure chamber was placed in a dynamic exposure chamber/glove box assembly providing a double chamber exposure design to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

1  
2  
3  
4  
5  
6

### Results

Dodd et al. (1987) presented 15-min LC<sub>50</sub> values:

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Reported by Dodd et al. (1987)
15	406 (271-608)

7  
8  
9

The individual animal lethality data were not available.  
No C × t probit function could be calculated from these data alone.

1 **Study ID: C.2**

2  
3 **Author, year:** *Dodd et al. (1987)*  
4 Substance: Methyl isocyanate  
5 Species, strain, sex: guinea pigs, Hartley, sex not specified  
6 Number/sex/conc. group: not clearly specified  
7 Age and weight: age not specified; 300-650 g  
8 Observation period: 14 days  
9

10 **Evaluation of study quality**

<b>Criteria</b>	<b>Comment</b>
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>N/A</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>Both the chamber and the glove box are maintained at a negative pressure with respect to the room.</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>Vapor exposures were statically generated. The test material was introduced into the chamber with a glass syringe through a ¼ inch stainless-steel bulkhead sampling port containing a gas chromatogram septum. Following injection of liquid methyl isocyanate into the chamber, evaporation of the sample occurred in a matter of seconds. The following information on the exposure chamber design was presented by Dodd et al. (1987): A static exposure chamber (135 L) with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate (see figure below). This static exposure chamber was placed in a dynamic 900-L exposure chamber (with an airflow of 350 L/min), constructed of stainless-steel and glass, providing a double chamber exposure design. Attached to this dynamic exposure chamber was a 940 L stainless-steel and glass glove-box operated with a dynamic airflow of approximately 350 L/min (see figure below).</i>
Number of air changes per hour	<i>Vapor exposure were statically generated in a 135 L inhalation chamber.</i>

Equilibration time (t <sub>95</sub> )	<i>t<sub>95</sub> in minutes cannot be calculated (static test atmosphere generation). However, it was stated by Dodd et al. (1987) that "Chamber concentration reached equilibrium within approximately 1 min".</i>
Start of exposure relative to equilibration	<i>It was stated by Dodd et al. (1987) that "The sliding cage drawer mechanism prevented the animals' introduction into the chamber until mixing of methyl isocyanate with air had equilibrated. Thus, the chamber concentrations were determined prior to animal exposure".</i>
Actual concentration measurement	<i>Chamber air was sampled manually with a glass gastight syringe two to four times per exposure and analysed with a gas chromatograph with flame ionization detector. It was stated by Dodd et al. (1987) that "The analytical to nominal chamber concentrations for the static exposure ranged between 0.5 and 0.9".</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	N/A
Assessment of Reliability	<b>C</b> <i>Limited to one exposure duration. Because no individual mortality data are available the study was given C status</i>

1  
2  
3  
4  
5  
6  
7

Additional remark: this study included also an experiment in which early mortality was evaluated. As only the number of deaths during exposure or within 10 minutes postexposure was provided by Dodd et al. (1987), these data are not presented here.

The figures below are copied from Dodd et al. (1987):

### STATIC EXPOSURE CHAMBER

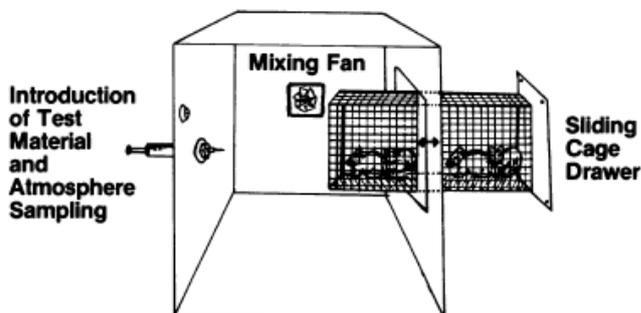


FIGURE 1. A static exposure chamber with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

8

### DOUBLE CHAMBER EXPOSURE DESIGN

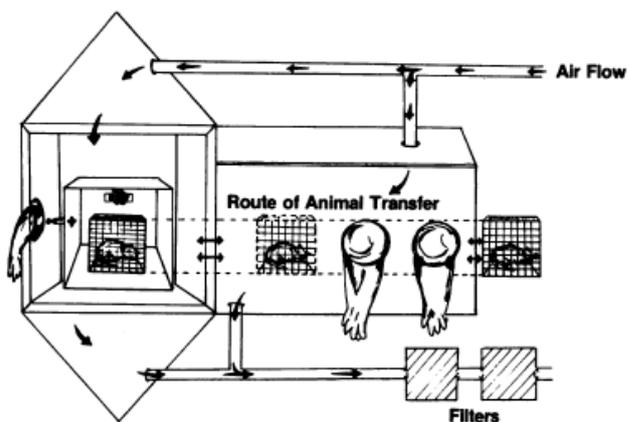


FIGURE 2. A static exposure chamber was placed in a dynamic exposure chamber/glove box assembly providing a double chamber exposure design to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

1  
2  
3  
4  
5  
6

### Results

Dodd et al. (1987) presented 15-min LC<sub>50</sub> values:

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Reported by Dodd et al. (1987)
15	266 (145-485)

7  
8  
9

The individual animal lethality data were not available.  
No C × t probit function could be calculated from these data alone.

1 **Study ID: C.3**

2

3 **Author, year:** **Salmon et al., 1985**

4 Substance: methyl isocyanate

5 Species, strain, sex: rat, Lister hooded, male

6 Number/sex/conc. group: 2

7 Age and weight: age not specified / 170-200 g

8 Observation period: at least 14 days\*

9

10 \* The surviving animals of this study were observed for up to 14 months by Gassert et al.  
11 (1986). It is noticed that two animals died after 6 and 8 months observation period. These two  
12 animals were not considered in the analysis below.

13

14 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to OECD 403 guideline(s)	<i>No statement of compliance with OECD guideline 403 provided</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>Methylisocyanate was introduced from a microsyringe into the airstream at a steady rate by infusion pump. Effluent airflow from the system was directed through a scrubber system with a continuous flow of water to remove MIC from the airstream before discharge to the atmosphere.</i>
Number of air changes per hour	<i>Air flow of 10 L/min; air flow was maintained by a stainless steel bellows pump. No information on volume of inhalation chamber.</i>
Equilibration time (t95)	<i>Insufficient information to calculate t95.</i>
Start of exposure relative to equilibration	<i>Not specified.</i>
Actual concentration measurement	<i>The atmospheric concentration was monitored at the chamber outlet by a Miran infrared spectrometer. A continuous chart record of concentration was obtained.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>C</b> <i>Limited to one exposure duration and a limited number of animals included (i.e. only 2 animals/group, 4 groups, resulting in a total of 8 animals) with either zero or 100% mortality.</i>

1  
2  
3  
4**Results**

Species	Concentration (mg/m <sup>3</sup> )		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Male
				Dead/tested
Rat	26		120	0/2
Rat	50		120	0/2
Rat	74		120	0/2
Rat	154		120	2/2 #

5 # one rat died 45 h after exposure and the other was killed in extremis at 50 h. Necropsy of  
6 these animals revealed hemorrhagic patches on the lungs and pulmonary edema.

7  
8**Probit function**

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

11  $Pr = a + b \times \ln C + c \times \ln t + d \times S$   
12 with C for concentration in mg/m<sup>3</sup>.

13  
14

Probit function	Species	a	b	n-value
	Rat	-43.2	10.3	N/A

15  
16

Duration (min.)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
120	106 (CI could not be estimated)

17  
18  
19  
20

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

1 **Study ID: C.4**2  
3 **Author, year:** **Mellon Institute 1970**

4 Substance: Methyl isocyanate

5 Species, strain, sex: Rat, Wistar, male

6 Number/sex/conc. group: 6

7 Age and weight: no information

8 Observation period: 14 days

9  
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to OECD 403 guideline(s)	<i>OECD guideline 403 did not exist at the time</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere in breathing zone of animals	<i>Animals were exposed to flowing streams of metered concentrations of methyl isocyanate</i>
Number of air changes per hour	<i>No information</i>
Equilibration time (t95)	<i>Insufficient information to calculate t95</i>
Start of exposure relative to equilibration	<i>No information</i>
Actual concentration measurement	<i>Gas chromatography was used to analytically determine the concentrations to which the animals were exposed.*</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	<i>N/A</i>
Assessment of Reliability	<b>C</b> <i>Multiple concentration levels and duration were tested. Few study details are available. LC<sub>50</sub> values and confidence intervals are provided for 6 exposure durations. No individual animal data presented.</i>

11 \* The analytical method was not fully developed until exposures were completed.  
 12 Analyses of a range of metered concentrations showed the analytically determined  
 13 concentrations to average 38.31% of the metering indications. The concentration data  
 14 (as presented in the table below) have been adjusted for this value by the study  
 15 authors and it is stated by the study author to "represent analytically verified  
 16 concentrations".

1 **Results**

Species	Exposure duration (min)	LC <sub>50</sub> (mg/m <sup>3</sup> ) 95%-C.I. Male
Rat	7.5	1285 (572-2888)
Rat	15	513 (385-679)
Rat	30	182 (145-228)
Rat	60	98 (56-169)
Rat	120	65 (49-86)
Rat	240	42 (no C.I. presented)

2

3 The authors stated that the behavior of the animals in the inhalation chamber  
 4 indicated eye, nose and lung irritation proportional to the exposure concentration.  
 5 Symptoms and gross pathology after the exposures were primarily explainable on the  
 6 basis of lung irritation, with death resulting from lung edema.

7

8 Further, a range finding study was shortly described by the study authors:

9 Rat 4-hour inhalation of metered (nominal) concentrations:

10 62.5 ppm (148 mg/m<sup>3</sup>) killed 6 of 6

11 31.2 ppm (74.1 mg/m<sup>3</sup>) killed 0 of 6

12 2 mg/liter (857 ppm) killed 6 of 6 after 1 hour

13

14 **Probit function**

15 No C × t probit function could be calculated from these data alone. However, as LC<sub>50</sub>  
 16 values were provided for different exposure durations an n-value could be calculated  
 17 using the following formula (AEGL SOP):

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

18

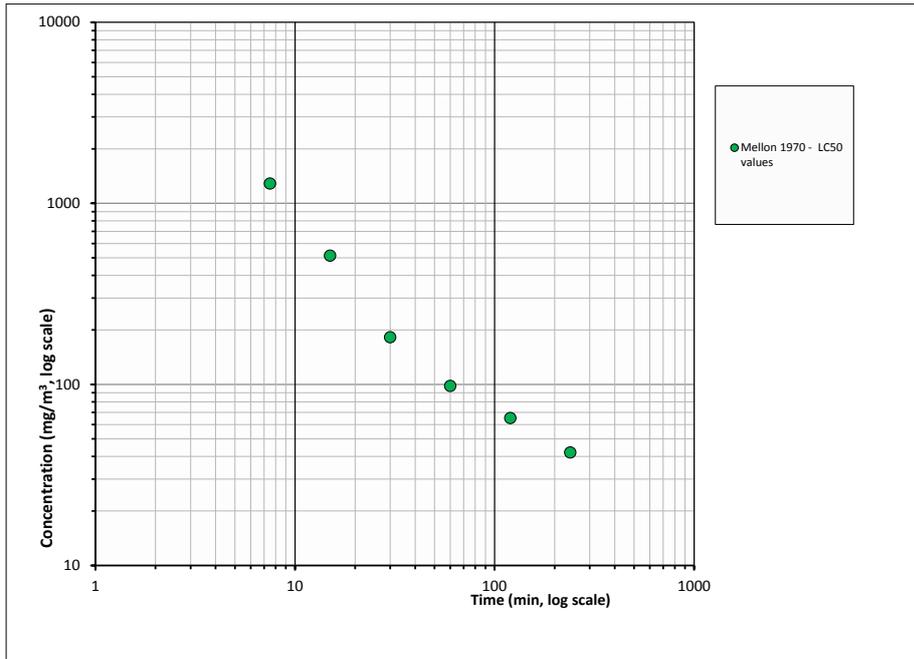
19 The calculated n-value was 1.0.

20

21 A graphical overview of the LC<sub>50</sub> values is presented below.

22

20180719- methyl isocyanate -PROPOSED



1  
2

## 1 Study ID: other C studies

2  
3 The acute inhalation toxicity database of methyl isocyanate includes also includes  
4 many studies focussing on the mechanism of action. These studies are not further  
5 considered here.

6  
7 Bucher et al. (1987a/b)/Boorman et al. (1987a/b) exposed male and female F344/N  
8 rats and B6C3F1 mice whole body to methylisocyanate for 2 hours. Exposure was  
9 conducted using whole-body in flow-through chambers. Chamber concentrations were  
10 monitored continuously. Details of the generation, monitoring, and safety aspects are  
11 reported by Adkins et al. (1987). Within 3 hours following the exposures (day 0), and  
12 again on days 1, 3, 7, 14, 49 and 91 after exposure, five predesignated animals per  
13 group were killed by pentobarbital overdose and given a complete gross necropsy. No  
14 animals died during the 2 hour exposures. Deaths of mice were observed within 15 to  
15 18 hour following exposures to 30 ppm (71 mg/m<sup>3</sup>), and rats began to die within a  
16 similar period after exposures to as low as 20 ppm (47.5 mg/m<sup>3</sup>).

17 Gross examination of animals dying during this early period (days 1-3) revealed  
18 profuse edema and exudate in the nasal cavity and upper airways, and extending into  
19 the trachea and large bronchi. Although mortality varied from one exposure to the  
20 next, several general patterns were consistent between experiments. A higher  
21 proportion of male rats and mice than females died during the first 1 to 3 days  
22 following exposure to 20 or 30 ppm (47.5 or 71 mg/m<sup>3</sup>), and females in particular  
23 showed a biphasic survival curve. Initial deaths were followed by a 5- to 7-day period  
24 in which few deaths occurred. Deaths then resumed, and cumulative mortality was  
25 similar between the sexes after about 3 weeks. This delay in onset of mortality was  
26 also seen in male and female rats exposed to 10 ppm (23.8 mg/m<sup>3</sup>) MIC for 2 hr (Fig.  
27 2). Deaths began on day 8, and overall survival of male and female rats exposed to  
28 10 ppm (23.8 mg/m<sup>3</sup>) for 2 hr was similar. No mice died after exposure to 10 ppm.  
29 Most deaths of exposed animals occurred during the first month after the exposures,  
30 and were preceded by periods of severe respiratory distress. The last deaths occurred  
31 on days 49 and 78 after exposure. These were both male mice exposed to 30 ppm  
32 (71 mg/m<sup>3</sup>). No deaths of control animals occurred during the studies.

33 Because animal survival was presented in graphic form, the exact numbers could not  
34 be discerned. Moreover, the study included scheduled deaths at multiple timepoints  
35 after exposure starting at day 0 up to day 91 (including post-exposure observation  
36 periods <14 days), which made it difficult to assess the true mortality rate.

37  
38 Dow Chemical (1990) exposed rats and rabbits to methylisocyanate via whole body  
39 inhalation. Two rabbits per group were exposed to MIC at 12.8 mg/m<sup>3</sup> for 6.75, 3.5,  
40 or 2 h or at 4.3 mg/m<sup>3</sup> for 7 h. Although the concentrations were listed as nominal,  
41 the report stated that the analytical method (infrared absorption) was adequate for  
42 monitoring concentrations as low as 4.3 mg/m<sup>3</sup>. A description of the exposure  
43 chamber was not included. All rabbits exposed at 12.8 mg/m<sup>3</sup> died 1-2 wk  
44 postexposure, apparently due to respiratory infections. Animals exposed at 4.3  
45 mg/m<sup>3</sup> for 7 hour survived. At 12.8 mg/m<sup>3</sup> for durations of 3.5 h, the eyes were red  
46 and had evidence of corneal injury when observed with fluorescein. Ocular damage  
47 was slight in animals exposed at 12.8 mg/m<sup>3</sup> for 2 h and equivocal in animals  
48 exposed at 4.3 mg/m<sup>3</sup> for 7 h. No experimental details or further discussion was  
49 included.

50 Female rats (strain not specified; N = 4) were exposed to concentrations of MIC  
51 ranging from 4.3 to 546 mg/m<sup>3</sup> for durations of 0.1-7 h. Although the concentrations  
52 were listed as nominal, the report stated that the analytical method (infrared  
53 absorption) was adequate for monitoring concentrations as low as 4.3 mg/m<sup>3</sup>;  
54 however, the analytical concentrations were not reported. A description of the  
55 exposure chamber was not included. Exposures at 546 mg/m<sup>3</sup> for 0.5 h, 214 mg/m<sup>3</sup>  
56 for 2 h, 83 mg/m<sup>3</sup> for 4 h, and 32.8 mg/m<sup>3</sup> for 4 h resulted in the deaths of all  
57 animals. Exposures resulting in some or no mortalities are as follows: 546 mg/m<sup>3</sup> for

1 0.2 h, 1/4; 546 mg/m<sup>3</sup> for 0.1 h, 0/4; 214 mg/m<sup>3</sup> for 1 h, 3/4; 83 mg/m<sup>3</sup> for 2 h,  
2 3/4; 83 mg/m<sup>3</sup> for 1 h, 0/4; 32.8 mg/m<sup>3</sup> for 2 h, 0/4; 12.8 mg/m<sup>3</sup> for 7 h, 3/4; 12.8  
3 mg/m<sup>3</sup> for 4 h, 0/4; 4.3 mg/m<sup>3</sup> for 7 h, 0/4. At concentrations 12.8 mg/m<sup>3</sup>, clinical  
4 signs indicated eye and nasal irritation, and necropsy revealed moderate to slight lung  
5 congestion. Liver and kidney pathology was also stated, but not defined, for most of  
6 these animals. No irritation was observed from exposures at 4.3 mg/m<sup>3</sup> for 4 or 7 h  
7 with questionable to slight lung pathology observed at necropsy.

8  
9 Eastman Kodak (1966) exposed groups of three rats under a whole body protocol to  
10 high concentrations of MIC until death. The exposure concentration and time-to-death  
11 for all animals in each group were 407,550 mg/m<sup>3</sup> for 7 min (flowthrough), 15720  
12 mg/m<sup>3</sup> for 18 min (flow-through), 20378 mg/m<sup>3</sup> for 30 min (static), 1976 mg/m<sup>3</sup> for  
13 110 min (static), and 815 mg/m<sup>3</sup> for 196 min (static).  
14 Static exposure at 121 mg/m<sup>3</sup> for 6 h resulted in deaths of two of three rats by 8 d  
15 postexposure. Clinical signs included lacrimation, dyspnea, nasal discharge, and  
16 gasping (Eastman Kodak 1966).

17  
18 The surviving animals of the study of Salmon et al. (1985) were followed for up to 14  
19 months (Gassert et al. 1986). One rat exposed at 74 mg/m<sup>3</sup> died at 6 months, and  
20 one exposed at 26 mg/m<sup>3</sup> died at 8 months, following sudden onset of respiratory  
21 distress. Necropsy of exposed animals at 14 months showed a history of mild  
22 respiratory infection in all animals as evidenced by lymphoid hyperplasia adjacent to  
23 bronchiolar airways. Mild interstitial fibrosis in the peribronchiolar regions was seen in  
24 all animals. In the eyes, eosinophil and lymphoid infiltrate was most prominent in the  
25 animals exposed at 50 mg/m<sup>3</sup>.

26  
27 Jeevaratnam and Sriramachari (1994) reported a rat 30-min LC<sub>50</sub> value of 465 ppm  
28 (1104 mg/m<sup>3</sup>), but details concerning this value were not presented.

29  
30 Kimmerle and Eben (1964) exposed rats (strain not specified) for two and four hours  
31 in a dynamic inhalation chamber (methylene chloride or dimethyl sulfoxide was used  
32 as vehicle; further details of the experimental design are not provided). Animals were  
33 exposed for 2 hours to 5.2, 49 and 50 mg/m<sup>3</sup> with resultant mortality of 0/20, 10/20  
34 and 10/20, respectively, and for 4 hours to 12, 21 and 64 mg/m<sup>3</sup> with resultant  
35 mortality of 10/20, 16/20 and 20/20, respectively. The authors reported 2-hour and  
36 4-hour LC<sub>50</sub> values of 50 and 12 mg/m<sup>3</sup>, respectively. It is not clear what the duration  
37 of the post-exposure observation was, though it was reported that animals died at up  
38 to 8 days postexposure. The contribution of the vehicles methylene chloride or  
39 dimethylsulfoxide to the observed mortality cannot be excluded.

40  
41 Mellon Institute (1963) exposed Wistar rats for four hours to methyl isocyanate.  
42 Exposure of 148 mg/m<sup>3</sup> killed 6/6 animals within 2 d, but no deaths occurred  
43 following exposure at 74.1 mg/m<sup>3</sup>. A description of the exposure chamber was not  
44 included. The result of this range-finding study was used as the basis for following  
45 LC<sub>50</sub> studies (see Mellon Institute 1970).

46  
47 Mellon Institute (1966) exposed groups of four male guinea pigs to "metered"  
48 (nominal) concentrations of methyl isocyanate at 37.1, 74.2, or 148.4 mg/m<sup>3</sup> for 4 h  
49 followed by a 14-d observation period. A description of the exposure chamber was not  
50 included. All animals died following exposure to the highest concentration, 3/4 died  
51 after exposure at 74.2 mg/m<sup>3</sup>, and 0/4 died after exposure at 37.1 mg/m<sup>3</sup>; deaths  
52 occurred within 48 h. Animals showed immediate signs of ocular and nasal irritation  
53 at the "higher" concentrations and were gasping after 10 min at 148.4 mg/m<sup>3</sup>. Gross  
54 necropsy revealed haemorrhage of the lungs. Further experimental details were not  
55 given.

1 Nemery et al. (1985) and Dinsdale (1987) exposed male LAC:P rats whole body to  
2 methyl isocyanate in a static exposure chamber. Nominal chamber concentrations  
3 were 0.02, 0.1, 0.25, 0.5, 1 or 10 mg/L. Exposure lasted one hour, except at the  
4 highest concentration used when it was 15 minutes. Eight rats were exposed for 15  
5 minutes to 10 mg/L; four died during exposure and two shortly afterwards. Upon one  
6 hour exposure, no deaths were noticed in the 0.02, 0.1 and 0.25 mg/L exposure  
7 groups (despite severe respiratory distress). One rat of the nine exposed one hour to  
8 0.5 mg/L died within 24 hours. Three rats exposed one hour to 1 mg/L died within 24  
9 hours and four others were moribund and killed at this time.

10 One additional group of rats were exposed one hour to 0.25 mg/L and their lungs  
11 were histopathologically examined up to 3 weeks postexposure. All 30 rats in this  
12 group survived their exposure to methyl isocyanate, but one animal died 10 days  
13 after exposure and another died after 6 weeks (Dinsdale, 1987).

14 It is stated by Nemery et al. (1985) that methyl isocyanate concentrations, as  
15 determined by gas chromatography, were found to be below those expected from  
16 total evaporation and uniform distribution of the injected compound. A consistent  
17 decrease in concentration with time occurred even when there were no animals in the  
18 tank; it was not due to the presence of water vapour or to stratification of the gas and  
19 probably resulted from leakages. The concentrations given in their paper were  
20 calculated initial concentrations which must be reduced by a factor of 4 to obtain a  
21 time weighted average concentration over one hour.

22 Given the uncertainty on the actual exposure, this study was not further evaluated  
23 and was given the C-status.

24  
25 Pairs of Charles Foster rats were exposed to MIC at 3.52 or 35.32 ppm (8.36 and 83.9  
26 mg/m<sup>3</sup>) for 10 min and necropsied immediately after death (Sethi et al. 1989). During  
27 exposure, dyspnea, congestion in the eyes, bloody lacrimation, and nasal secretion  
28 were observed. Animals exposed at 83.9 mg/m<sup>3</sup> died within 4 min of exposure, and  
29 animals exposed at 8.36 mg/m<sup>3</sup> died 39 min and 293 min postexposure. Lung  
30 hemorrhages, dilated and congested trachea, pulmonary edema, and brain edema  
31 were observed at necropsy. The main histological findings were necrosis of the  
32 bronchial epithelium, lung edema, and congestion of the vessels in several visceral  
33 organs. It should be noted that for these exposure concentrations, the effects are  
34 more severe than (and are not consistent with) those reported in other similar  
35 studies. Additional details on the exposure system, generation of the test  
36 atmospheres, and monitoring of chamber concentrations were not provided.

37  
38 Troup et al. (1987) exposed male Sprague-Dawley rats and Hartley guinea pigs to  
39 methyl isocyanate for 15 minutes. Details of the chamber design, exposure  
40 conditions, and analytical procedures are described by Dodd et al. (1987). The target  
41 methyl isocyanate concentrations were 100, 600 or 1000 ppm (237.5, 1425, 2375  
42 mg/m<sup>3</sup>) for rats and 25, 125, or 225 ppm (59.4, 297, 534 mg/m<sup>3</sup>) for guinea pigs.  
43 Animals were sacrificed immediately following the 15 min exposure (0 hour) or at 1,  
44 2, 4, or 16 hour postexposure. The aim of the study was to investigate the  
45 pathogenesis of mortality resulting from overexposure to methyl isocyanate vapor.  
46 All guinea pigs in the 534 mg/m<sup>3</sup> group died prior to the 16-h sample, and only one  
47 animal in the 297 mg/m<sup>3</sup> group survived; time to death was not stated. Some rats in  
48 the 2375 mg/m<sup>3</sup> group died prior to the 16-h sample, but the number and time to  
49 death were not stated.

50  
51 Vijayaraghavan and Kaushik (1987) reported 30-min LC<sub>50</sub> values of 1046.5 mg/m<sup>3</sup>  
52 (95% C.I.: 903.6-1211.8 mg/m<sup>3</sup>) for rats and 267.6 mg/m<sup>3</sup> (95% C.I.: 215.3-331.6  
53 mg/m<sup>3</sup>) for mice. Female Wistar rats and male Swiss albino mice were exposed whole  
54 body for 30 minutes to methyl isocyanate in a static inhalation chamber. A post-  
55 exposure observation period of 48h was included, which is considered not sufficient to  
56 cover for possible delayed deaths.

## Appendix 2 Reference list

- 1  
2  
3  
4 Adkins, B., R.W. O'Connor, and J.M. Dement. 1987. Inhalation exposure system used  
5 for acute and repeated-dose methyl isocyanate exposures of laboratory animals.  
6 Environ. Health Perspect. 72:45-51.  
7  
8 Alarie, Y., J.S. Ferguson, M.F. Stock, D.A. Weyel, and M. Schaper. 1987. Sensory and  
9 pulmonary irritation of methyl isocyanate in mice and pulmonary irritation and  
10 possible cyanidelike effects of methyl isocyanate in guinea pigs. Environ. Health  
11 Perspect. 72:159-167.  
12  
13 Boorman, G.A., R. Brown, B.N. Gupta, L.C. Uraih, and J.R. Bucher. 1987a.  
14 Pathological changes following acute methyl isocyanate inhalation and recovery in  
15 B6C3F1 mice. Toxicol. Appl. Pharmacol. 87:446-456.  
16  
17 Boorman, G.A., L.C. Uraih, B.N. Gupta, and J.R. Bucher. 1987b. Two-hour methyl  
18 isocyanate inhalation and 90-day recovery study in B6C3F1 mice. Environ. Health  
19 Perspect. 72:63-69.  
20  
21 Bucher, J.R., B.N. Gupta, B. Adkins, Jr., M. Thompson, C.W. Jameson, J.E. Thigpen,  
22 and B.A. Schwetz. 1987a. Toxicity of inhaled methyl isocyanate in F344/N rats and  
23 B6C3F1 mice. I. Acute exposure and recovery studies. Environ. Health Perspect.  
24 72:53-61.  
25  
26 Bucher, J.R., G.A. Boorman, B.N. Gupta, L.C. Uraih, L.B. Hall, and S.A. Stefanski.  
27 1987b. Two-hour methyl isocyanate inhalation exposure and 91-day recovery: A  
28 preliminary description of pathologic changes in F344 rats. Environ. Health Perspect.  
29 72:71-75.  
30  
31 Chemiekaarten. Ed 32. Den Haag. TNO/SDU uitgevers, 2017.  
32  
33 Dinsdale, D., B. Nemery, and S. Sparrow. 1987. Ultrastructural changes in the  
34 respiratory tract of rats following methyl isocyanate inhalation. Arch. Toxicol. 59:385-  
35 390.  
36  
37 Dodd, D.E., E.H. Fowler, W.M. Snellings, I.M. Pritts, and R.L. Baron. 1985. Acute  
38 inhalation studies with methyl isocyanate. Bushy Run Research Center. Sponsored by  
39 Union Carbide Corporation. EPA/OTS; Doc #88-8600039. 100 Pp.  
40  
41 Dodd, D.E., E.H. Fowler, W.M. Snellings, I.M. Pritts, and R.L. Baron. 1986. Acute  
42 inhalation studies with methyl isocyanate vapor. I. Methodology and LC50  
43 determinations in guinea pigs, rats, and mice. Fundam. Appl. Toxicol. 6:747-755.  
44  
45 Dodd, D.E., F.R. Frank, E.H. Fowler, C.M. Troup, and R.M. Milton. 1987. Biological  
46 effects of short-term, high-concentration exposure to methyl isocyanate. I. Study  
47 objectives and inhalation exposure design. Environ. Health Perspect. 72:13-19.  
48  
49 Dow Chemical. 1990. The Dow Chemical Company. Results of single exposure of rats  
50 and rabbits to the vapors of methyl isocyanate. Dow report identification number  
51 D004632. EPA/OTS; Doc #86-910000362S. 7 pp.  
52  
53 Eastman Kodak. 1966. Eastman Kodak Company. Toxicity and health hazard  
54 summary. Lab. No. 63-832. EPA/OTS; Doc #86-910000056. 6 pp.  
55  
56 ERPG (2005). Emergency Response Planning Guidelines. Methyl Isocyanate. American  
57 Industrial Hygiene Association.

- 1  
2 Fait, D.W. and D.E. Dodd. 1981. Methyl isocyanate four-hour acute LC50 inhalation  
3 study on rats and guinea pigs. Bushy Run Research Center. Sponsored by Union  
4 Carbide Corporation. EPA/OTS; Doc #86-920000613. 6 pp.  
5  
6 Ferguson, J.S., M. Schaper, M.F. Stock, D.A. Weyel, and Y. Alarie. 1986. Sensory and  
7 pulmonary irritation with exposure to methyl isocyanate. *Toxicol. Appl. Pharmacol.*  
8 82: 329-335.  
9  
10 Ferguson, J.S., and Y. Alarie. 1991. Long term pulmonary impairment following a  
11 single exposure to methyl isocyanate. *Toxicol. Appl. Pharmacol.* 107: 253-268.  
12  
13 Fowler, E.H. and D.E. Dodd, 1987. Respiratory tract changes in guinea pigs, rats and  
14 mice following a single six-hour exposure to methyl isocyanate vapor. *Environmental*  
15 *Health Perspectives* 72, 109-116.  
16  
17 Gassert, T., C. MacKenzie, M. Kerr Muir, N. Andersson, and A.G. Salmon. 1986. Long  
18 term pathology of lung, eye, and other organs following acute exposure of rats to  
19 methyl isocyanate. *Lancet* 2: 1403.  
20  
21 IRDC (International Research and Development Corporation). 1964. Six-hour acute  
22 inhalation toxicity study in rats. Report 203-001. Sponsored by The Carwin Co.  
23 EPA/OTS; Doc #86-870002225. 6pp.  
24  
25 James, J.T., L.C. Buettner, and S.S. Hsu. 1987. Sensory irritation of methylisocyanate  
26 vapor. *J. Appl. Toxicol.* 7: 147-148.  
27  
28 Jeevaratnam, K., and S. Sriramachari. 1994. Comparative toxicity of methyl  
29 isocyanate and its hydrolytic derivatives in rats. I. Pulmonary histopathology in the  
30 acute phase. *Arch. Toxicol.* 69: 39-44.  
31  
32 Kimmerle, G., and A. Eben. 1964. On the toxicity of methyl isocyanate and its  
33 quantitative determination in air [in German]. *Arch. Toxikol.* 20: 235-241.  
34  
35 ManTech Environmental (ManTech Environmental Technology, Inc). 1992. Acute 1-  
36 hour inhalation toxicity study of methyl isocyanate in rats. Project No. 6030-003.  
37 Sponsored by Rhone-Poulenc Ag Company. EPA/OTS; Doc #86-920000962. 25 pp.  
38  
39 Mellon Institute. 1963. Range finding tests on methyl isocyanate. Report 26-75.  
40 Sponsored by Union Carbide Chemicals, Co. EPA/OTS; Doc #86-910000658.  
41 6 pp.  
42  
43 Mellon Institute. 1966. Miscellaneous acute toxicity data. Report 28-141. Sponsored  
44 by Union Carbide Chemicals, Co. EPA/OTS; Doc #86-910000267. 2pp.  
45  
46 Mellon Institute. 1970. Acute inhalation toxicity, human response to low  
47 concentrations, guinea pig sensitization, and cross sensitization to other isocyanates.  
48 Report 33-19. Sponsored by Union Carbide Chemicals, Co. EPA/OTS; Doc #86-  
49 910000268. 8 pp.  
50  
51 National Research Council. Acute Exposure Guideline Levels for Selected Airborne  
52 Chemicals. Volume 3. Washington, DC. The National Academies Press, 2003.  
53  
54 Nemery, B., S. Dinsdale, S. Sparrow, and D.E. Ray. 1985a. Effects of methyl  
55 isocyanate on the respiratory tract of rats. *Br. J. Ind. Med.* 42: 799-805.  
56

- 1 RIVM 2016. Interventiewaarden gevaarlijke stoffen.  
2 [http://www.rivm.nl/rvs/Normen/Rampen\\_en\\_incidenten/Interventiewaarden](http://www.rivm.nl/rvs/Normen/Rampen_en_incidenten/Interventiewaarden)  
3
- 4 Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard, P.M.J. Bos, H. Muijser, A. Wijbenga.  
5 Methods for the derivation of probit functions to predict acute lethality following  
6 inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.  
7
- 8 Salmon, A.G., M. Kerr Muir, and N. Andersson. 1985. Acute toxicity of methyl  
9 isocyanate: A preliminary study of the dose response for eye and other effects. Br. J.  
10 Ind. Med. 42:795-798.  
11
- 12 Sethi, N., R. Dayal, and R.K. Singh. 1989. Acute and subacute toxicity study of  
13 inhaled methyl isocyanate in Charles Foster rats. Ecotoxicol. Environ. Safety 18:68-  
14 74.  
15
- 16 Troup, C.M., D.E. Dodd, E.H. Fowler, and F.R. Frank. 1987. Biological effects of short-  
17 term, high-concentration exposure to methyl isocyanate. II. Blood chemistry and  
18 hematologic evaluations. Environ. Health Perspect. 72:21-28.  
19
- 20 Varma, D.R., J.S. Ferguson, and Y. Alarie 1987. Reproductive toxicity of  
21 methylisocyanate in mice. J. Tox. Env. Health 21: 265-275.  
22
- 23 Varma, D.R., J.S. Ferguson, and Y. Alarie. 1988. Inhibition of methyl isocyanate  
24 toxicity in mice by starvation and dexamethasone but not by sodium thiosulfate,  
25 atropine, and ethanol. J. Toxicol. Environ. Health 24:93-101.  
26
- 27 Vijayaraghavan, R., and M.P. Kaushik. 1987. Acute toxicity of methyl isocyanate  
28 and ineffectiveness of sodium thiosulphate in preventing its toxicity. Ind. J.  
29 Exp. Biol. 25:531-534.