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Probit function technical support document

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| substance name | CAS number |
|---|---|
| **Methyl isocyanate** | **624-83-9** |

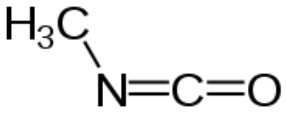
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have had the opportunity to comment on the derivation of the proposed probit function. The status of this document has now been raised to "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 Methyl isocyanate



## 1. Substance identification

| | |
|---|---|
| CAS-number: | 624-83-9 |
| IUPAC name: | Isocyanatomethane |
| Synonyms: | Methyl carbylamines; MIC |
| Molecular formula: | $C_2H_3NO$ |
| Molecular weight: | 57.1 g/mol |
| Physical state: | liquid (at 20°C and 101.3 kPa) |
| Boiling point: | 38°C (at 101.3 kPa) |
| Vapour pressure: | 46.4 kPa (at 20°C) |
| Saturated vapour conc: | 464,000 ppm = 1,102 g/m$^3$ (at 20°C) |
| Conversion factor: | 1 mg/m$^3$ = 0.421 ppm (at 20°C and 101.3 kPa) |
| | 1 ppm = 2.375 mg/m$^3$ (at 20°C and 101.3 kPa) |
| Labelling: | H301-311-315-317-318-330-334-335-361d |

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

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

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

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

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

## 3. Human toxicity data

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

[1] AEGL (2003)

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

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

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

## 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 methyl isocyanate, covering references before and including 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA, RTECS, IRIS and ToxNet with the following search terms:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - $LC_{50}$, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

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

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

## Sensory irritation

Two 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 methyl isocyanate*

| Species/strain | $RD_{50}$ ($mg/m^3$) | Exposure duration (min) | Author/year |
|---|---|---|---|
| Mouse, Swiss-Webster | $3.1^{P}$ | 90 | Ferguson et al., 1986; Alarie et al., 1987 |
| Mouse, ICR | $6.9^{p}$ | 30 | James et al., 1987 |

P: a plateau was reached

# 5. Probit functions from individual studies

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

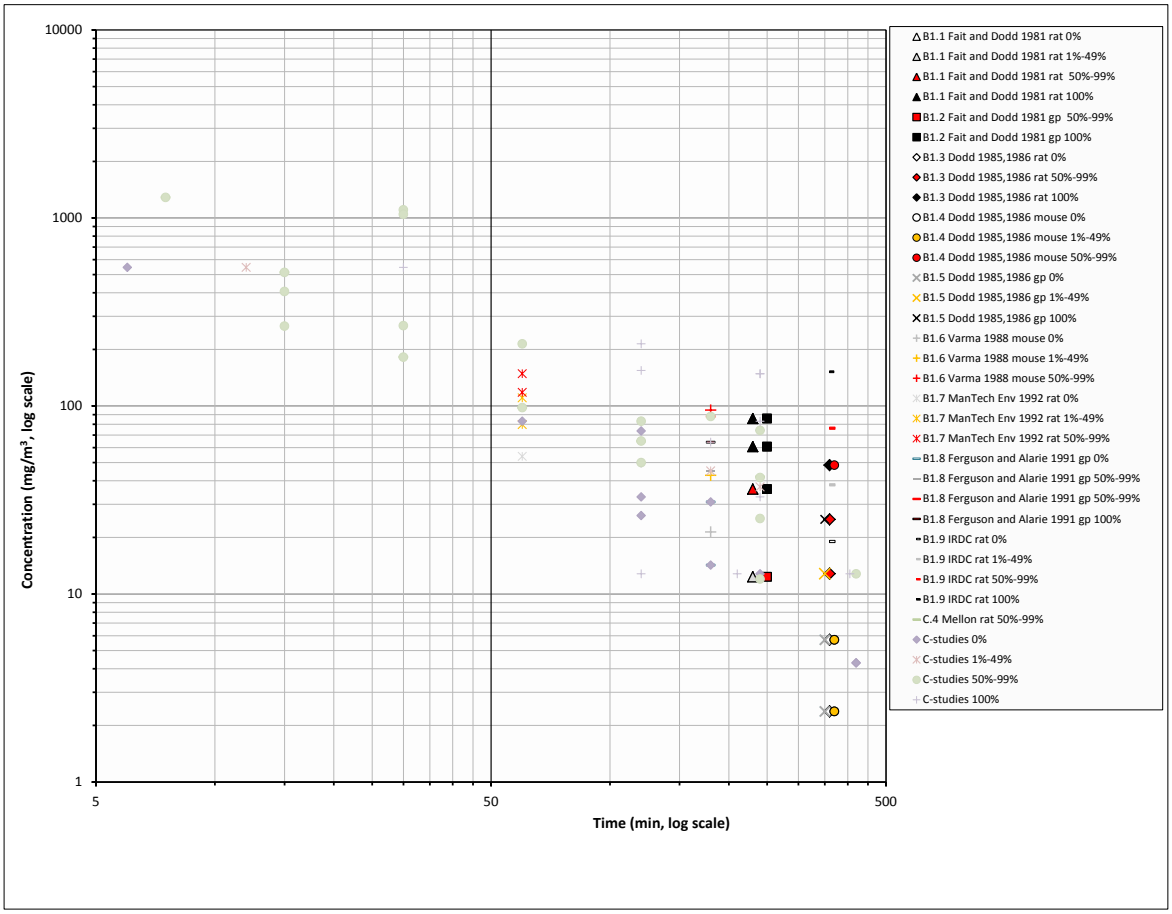



***Figure 1*** *All available acute lethality data for methyl isocyanate.*

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

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

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

Although the Mellon 1970 study was classified as a C-study the n-value of 1.01 found in that study was preferred over the default value (n=2) to scale the $LC_{50}$ values of the B1-studies. This was also supported by species-specific n-values when $LC_{50}$ values of the various B!-studies were pooled. This resulted in n-values of 1.24 (rat), 0.54 (guinea pig), and 1.04 (mouse) (analyses not shown). To enable intra-species pooling, $LC_{50}$-values of B1-studies were scaled using the species specific (overall) n-value of 1.01 (study C.4; Mellon 1970) with the following formula (section 6):

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

With $LC_{50,c}$ = scaled $LC_{50}$ value for common exposure duration $t_c$
$LC_{50,test}$ = observed $LC_{50}$ value for tested exposure duration
$t_c$ = common exposure duration for intra-species pooling
$t_{test}$ = tested exposure duration
n = 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/m³, t in min)* | LC50 at tested exposure duration (mg/m³) 95% C.I. | LC50, 60 minutes (mg/m³) 95% C.I. (underline italic for scaled values) | n-value 95% C.I. |
|---|---|---|---|---|---|
| B1.1 | Rat | *240-min LC50* | 25.9 (17.5-34.2) | 102 | N/A |
| B1.3 | Rat | *360-min LC50* | 14.3 (10.6-18.6) | 84 | 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) | 301 | N/A |
| B1.2 | Guinea pig | *240-min LC50* | 9.42 (0.812-16.43) | 37 | N/A |
| B1.5 | Guinea pig | *360-min LC50* | 13.1 (C.I. could not be calculated) | 77 | N/A |
| B1.8 | Guinea pig | *180-min LC50* | 54.4 (43.4-67.8) | 161 | N/A |
| B1.4 | Mouse | *360-min LC50* | 29.6 (22.3-42.1) | 175 | N/A |
| B1.6 | Mouse | *180-min LC50* | 57.5 (38.6-73.2) | 171 | N/A |

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.

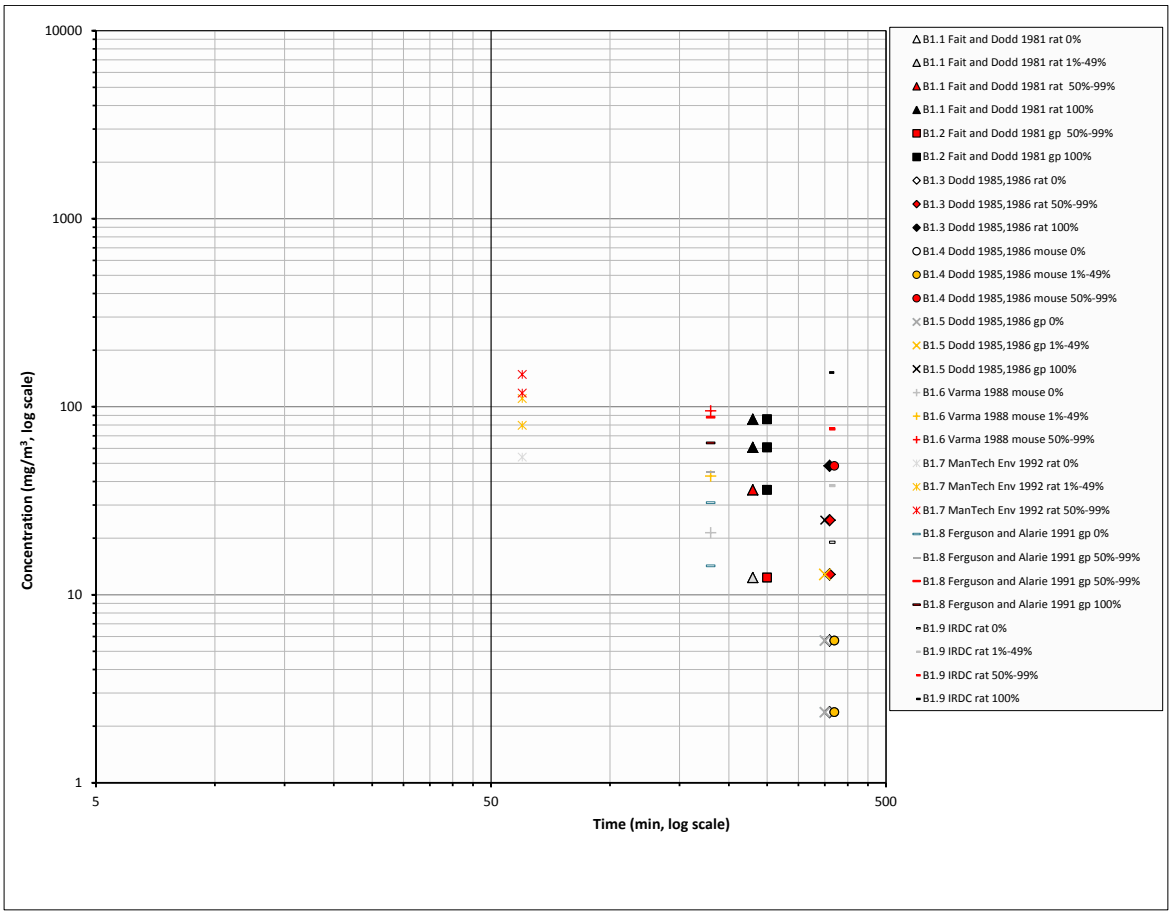



***Figure 2*** *Data selected for the initial analysis for the derivation of the animal probit function of methyl isocyanate.*

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.

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

| Study ID | Species | Probit (C in mg/m$^3$, t in min) | $LC_{50}$ at tested exposure duration (mg/m$^3$) 95% C.I. | n-value 95% C.I. |
|---|---|---|---|---|
| B1.7 | Rat | *60-min $LC_{50}$* | 109 (98-120) | N/A |

The data of the selected datasets are presented graphically below.

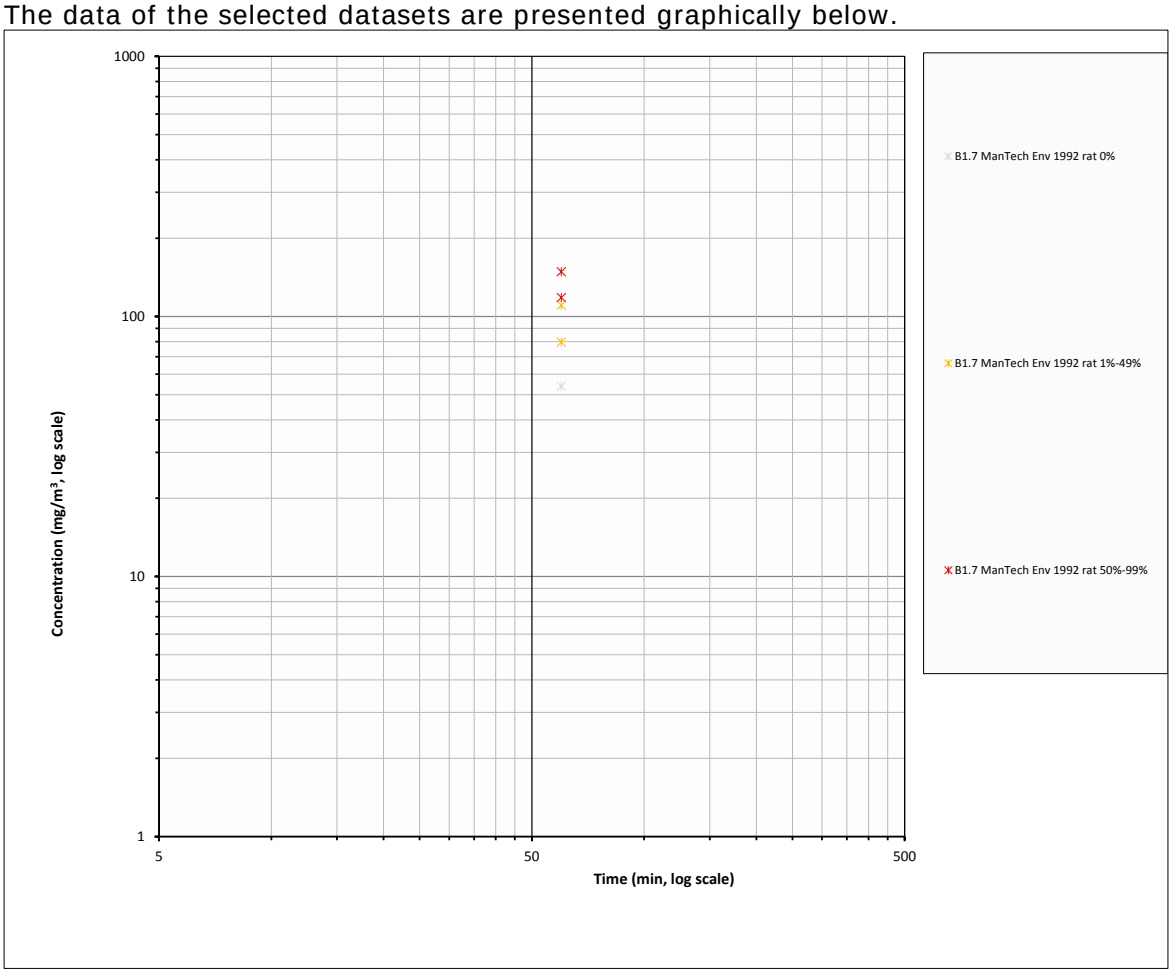



***Figure 3*** *Final data selected for derivation of the animal probit function of methyl isocyanate.*

# 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 $LC_{50}$ value of 109 mg/m$^3$ 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 $LC_{50}$ 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 |
| Nominal concentration | 1 | Analytical concentrations available |
| Adequacy of database: | 1 | In total nine B1-studies available. |

The estimated human equivalent 60-minute $LC_{50}$ value is 109 / 3 = **36 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 $LC_{50}$ 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**.

**$Pr = -10.3 + 1.98 \times \ln(C^{1.01} \times t)$ with C in mg/m$^3$ and t in min.**

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

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 8 mg/m$^3$ and the calculated human 60 min $LC_1$ (Pr = 2.67) is 11 mg/m$^3$.

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

| Estimated level | 30 min (mg/m$^3$) | 60 min (mg/m$^3$) |
|---|---|---|
| 0.1% lethality, this probit | 15 | 8 |

| | | |
|---|---|---|
| 1% lethality, this probit | 23 | 11 |
| AEGL-3[2] (2003, final) | 0.95 | 0.48 |
| ERPG-3[2] (2005) | - | 3.6 |
| LBW (2016) | 6.6 | 3.3 |

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.

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

# Appendix 1 Animal experimental research

## Study ID: B1.1

***Author, year:*** ***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 | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *stable* |
| Use of vehicle (other than air) | *Nitrogen* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *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 $N_2$-MIC mixture was regulated at approximately 5 psig, and was needle-valve controlled (measured with a rotameter). The $N_2$-MIC vapour was further diluted with filtered room air and drawn through the chambers.* |
| Number of air changes per hour | *An airflow of approximately 1100 L/min and a 4350 L inhalation chamber: ca. 15 air changes/hour* |
| Equilibration time (t95) | *11.9 min* |
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *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.* |

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

**Results**

| Species | Concentration (mg/m$^3$) | | 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 |

**Probit function**

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

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

with C for concentration in mg/m$^3$, and S for sex (0 = 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 |

| Duration (min.) | $LC_{50}$ (mg/m$^3$) 95%-C.I. Male * | $LC_{50}$ (mg/m$^3$) 95%-C.I. Female * | $LC_{50}$ (mg/m$^3$) 95%-C.I. Combined |
|---|---|---|---|
| 240 | 23.9 (14.3-36.2) | 27.5 (16.6-40.7) | 25.9 (17.5-34.2) |

* Fait and Dodd (1981) derived 4h $LC_{50}$ values of 26.4 (17.8-39.2) mg/m$^3$ and 26.1 (14.5-47.3) mg/m$^3$ for males and females, respectively.

The 4-hour $LC_{50}$ values for both sexes did not differ by more than a factor of 2. This does not support the proposition that sex differences exist in the lethal response. For this reason the 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.

# Study ID: B1.2

***Author, year:*** ***Fait and Dodd (1981)****
Substance: methyl isocyanate
Species, strain, sex: Guinea pigs, Hartley albino, male and female
Number/sex/conc. group: 6
Age and weight: 4-5 weeks of age 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 | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *stable* |
| Use of vehicle (other than air) | *Nitrogen* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *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 $N_2$-MIC mixture was regulated at approximately 5 psig, and was needle-valve controlled (measured with a rotameter). The $N_2$-MIC vapour was further diluted with filtered room air and drawn through the chambers.* |
| Number of air changes per hour | *An airflow of approximately 1100 L/min and a 4350 L inhalation chamber: ca. 15 air changes/hour* |
| Equilibration time (t95) | *11.9 min* |
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *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.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |

| | |
|---|---|
| Assessment of Reliability | ***B***<br>*Well-performed study. Limited to one exposure duration.* |

**Results**

| Species | Concentration (mg/m$^3$) | | 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 |

**Probit function**

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

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

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

| 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 |

| Duration (min.) | $LC_{50}$ (mg/m$^3$) 95%-C.I. Male * | $LC_{50}$ (mg/m$^3$) 95%-C.I. Female * | $LC_{50}$ (mg/m$^3$) 95%-C.I. Combined |
|---|---|---|---|
| 240 | 7.13 (0.420-15.84) | 12.69 (1.649-23.67) | 9.42 (0.812-16.43) |

* Fait and Dodd (1981) reported 4h $LC_{50}$ values of < 12.4 mg/m$^3$ (males and females combined).

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

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

# Study ID: B1.3

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

Substance: Methyl isocyanate

Species, strain, sex: rat, Fischer 344, male and female

Number/sex/conc. group: 6

Age and weight: 10-11 weeks (6-h experiment); weight not specified

Observation period: 14 days

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

**Evaluation of study quality**

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

| | |
|---|---|
| Homogeneity of test atmosphere in breathing zone of animals | *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 $N_2$-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The $N_2$-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 $N_2$-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the $N_2$-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.* |
| Number of air changes per hour | *An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour* |
| Equilibration time (t95) | *13.05 min* |
| Start of exposure relative to equilibration | *Not specified* |
| Actual concentration measurement | *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.*<br>*Analysis was performed with a gas chromatograph equipped with a nitrogen-phosphorus detector.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***B1***<br>*Well performed study; limited to one exposure duration.* |

1

**Results**

| Species | Concentration ($mg/m^3$) | | 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 |

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

**Probit function**

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

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

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Combined * |
|---|---|
| 360 | 14.3 (10.6-18.6) |

* Dodd et al (1985,1986) derived a 6h $LC_{50}$ value of 14.5 (10.9-19.5) $mg/m^3$.

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

# Study ID: B1.4

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

Substance: Methyl isocyanate

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

Number/sex/conc. group: 6

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

Observation period: 14 days

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

**Evaluation of study quality**

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

| | |
|---|---|
| Homogeneity of test atmosphere in breathing zone of animals | *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 $N_2$-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The $N_2$-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 $N_2$-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the $N_2$-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.* |
| Number of air changes per hour | *An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour* |
| Equilibration time (t95) | *13.05 min* |
| Start of exposure relative to equilibration | *Not specified* |
| Actual concentration measurement | *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.*<br>*Analysis was performed with a gas chromatograph equipped with either a nitrogen-phosphorus detector.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***B1***<br>*Well performed study. Limited to one exposure duration.* |

1

**Results**

| Species | Concentration ($mg/m^3$) | | 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 |

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

**Probit function**

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

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

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Combined * |
|---|---|
| 360 | 29.6 (22.3-42.1) |

* Dodd et al (1985,1986) derived a 6h $LC_{50}$ value of 29.0 (20.0-41.6) $mg/m^3$.

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

# Study ID: B1.5

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

Substance: Methyl isocyanate

Species, strain, sex: guinea pig, Hartley albino, male and female

Number/sex/conc. group: 6

Age and weight: 10 weeks (6-h experiment); weight not specified

Observation period: 14 days

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

**Evaluation of study quality**

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

| | |
|---|---|
| Homogeneity of test atmosphere in breathing zone of animals | *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 $N_2$-MIC mixture, obtained from the cylinder head space, was regulated at approximately 5 psig. The $N_2$-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 $N_2$-MIC flow rate was then metered with a rotameter located adjacent to the chamber air intake duct, where further dilution of the $N_2$-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.* |
| Number of air changes per hour | *An airflow of approximately 1000 L/min and a 4350 L inhalation chamber: ca. 14 air changes/hour* |
| Equilibration time (t95) | *13.05 min* |
| Start of exposure relative to equilibration | *Not specified* |
| Actual concentration measurement | *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.*<br>*Analysis was performed with a gas chromatograph equipped with either a nitrogen-phosphorus detector.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***B1***<br>*Well performed study. Limited to one exposure duration.* |

1

**Results**

| Species | Concentration ($mg/m^3$) | | 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 |

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

**Probit function**

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

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

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Combined * |
|---|---|
| 360 | 13.1 (C.I. could not be calculated) |

* Dodd et al (1985,1986) derived a 6h $LC_{50}$ value of 12.8 (10.5-15.9) $mg/m^3$.

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

# Study ID: B1.6

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

**Evaluation of study quality#**

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *N/A* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *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.* ***** |
| Number of air changes per hour | *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 >7.6 ppm, this was not specified.* ***** |
| Equilibration time (t95) | *Insufficient information to calculate t95* |
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *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.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |

| Assessment of Reliability | ***B1***<br>*Well performed study. Limited to one exposure duration.* |
|---|---|

# 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 ($mg/m^3$) | | 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

$Pr = a + b \times lnC$

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Male |
|---|---|
| 180 | 57.5 (38.6-73.2) |

The study authors calculated a 3-h $LC_{50}$ value of 64.0 $mg/m^3$.

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

# Study ID: B1.7

***Author, year:*** ***ManTech Environmental 1992***
Substance: methyl isocyanate
Species, strain, sex: Rat, Fischer 344, male
Number/sex/conc. group: 20
Age and weight: approximately 7-8 weeks and 166-241 g at start of exposure
Observation period: 14 days

**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 $m^3$ stainless steel and glass chamber. Airflow was approximately 250-295 L/min.*<br>*This results in 61-72 air changes per hour.* |
| Equilibration time (t95) | *3.1-3.6 min* |

| | |
|---|---|
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *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).* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***B1***<br>*Well-performed study. Limited to one exposure duration.* |

**Results**

| Species | Concentration (mg/m$^3$) | | 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 |

**Probit function**

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

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

with C for concentration in mg/m$^3$.

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

| Duration (min.) | $LC_{50}$ (mg/m$^3$) 95%-C.I. Male |
|---|---|
| 60 | 109 (98.2-120) |

ManTech Environmental (1992) reported 1-hour $LC_{50}$ values of 107 (92-125) mg/m$^3$.

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

1

# Study ID: B1.8

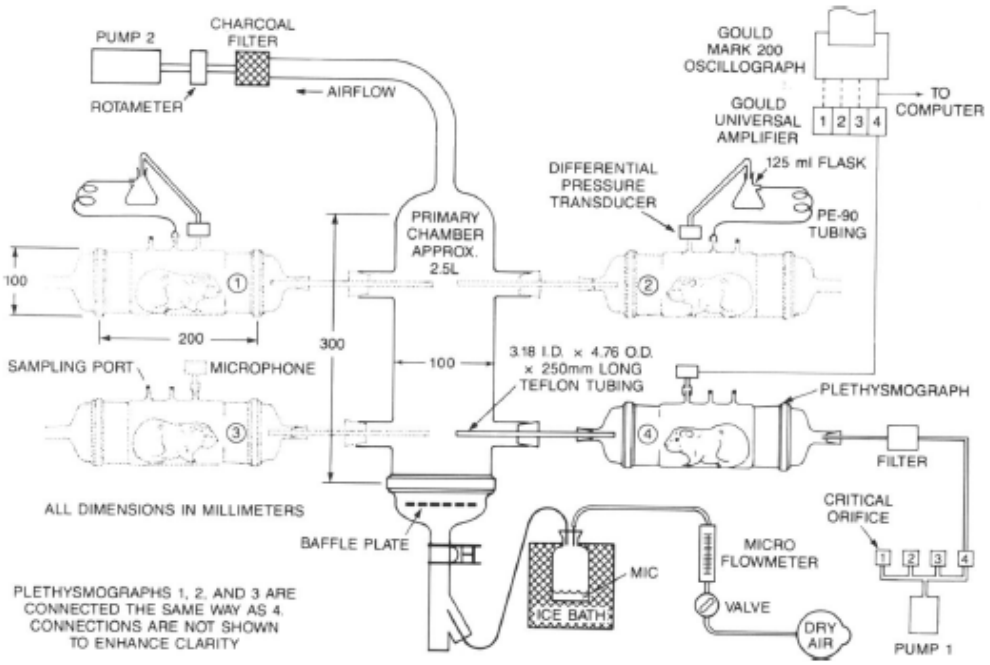
***Author, year:*** ***Ferguson and Alarie (1991)***
Substance: methyl isocyanate
Species, strain, sex: guinea pig, English short-haired, amle
Number/sex/conc. group: 8/group
Age and weight: age not specified; 275-325 g
Observation period: up to 1 year

**Evaluation of study quality***

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *The 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.* |
| Number of air changes per hour | *1.8 l/min; volume of inhalation chamber not specified* |
| Equilibration time (t95) | *Insufficient information to calculate t95* |
| Start of exposure relative to equilibration | *Exposure started after complete equilibration* |
| Actual concentration measurement | *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%.* |

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

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




System used for exposure of guinea pigs (Alarie et al. 1987).

**Results**

| Species | Concentration (mg/m$^3$) | | 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 |

**Probit function**

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

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

with C for concentration in mg/m$^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Male |
|---|---|
| 180 | 54.4 (43.4-67.8) |

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

# Study ID: B1.9

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

**Evaluation of study quality**

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *GLP did not exist at the time* |
| Study carried out according to OECD 403 guideline(s) | *OECD guideline 403 did not exist at the time* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *No* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *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.* |
| Number of air changes per hour | *Air flow and volume of inhalation chamber not specified.* |
| Equilibration time (t95) | *Insufficient information to calculate t95* |
| Start of exposure relative to equilibration | *Not specified* |
| Actual concentration measurement | *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.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |

| | |
|---|---|
| Assessment of Reliability | ***B1***<br>*Well-performed study, though some details on study characteristics are missing. Limited to one exposure duration.*<br>*No actual concentrations presented, though nominal concentrations calculated. Nominal concentrations were < 25% of the saturated vapour concentration.* |

**Results**

| Species | Concentration ($mg/m^3$) | | 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 |

**Probit function**

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

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

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Male |
|---|---|
| 360 | 51.0 (24.3-80.3) |

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

# Study ID: C.1

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

**Evaluation of study quality**

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *N/A* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *Both the chamber and the glove box are maintained at a negative pressure with respect to the room.* |
| Homogeneity of test atmosphere in breathing zone of animals | *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.*<br>*The following information on the exposure chamber design was presented by Dodd et al. (1987):*<br>*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).* |
| Number of air changes per hour | *Vapor exposures were statically generated in a 135 L inhalation chamber.* |

| | |
|---|---|
| Equilibration time (t95) | *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".* |
| Start of exposure relative to equilibration | *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".* |
| Actual concentration measurement | *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.*<br>*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".* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***C***<br>*Limited to one exposure duration. Because no individual mortality data are available the study was given C status.* |

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):

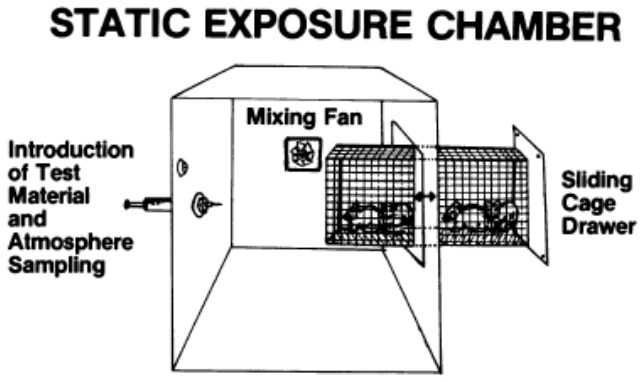



FIGURE 1. A static exposure chamber with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

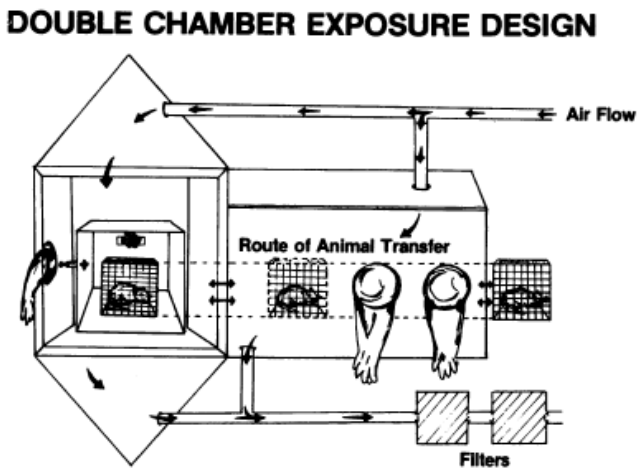



FIGURE 2. A static exposure chamber was placed in a dynamic exposure chamber/glove box assembly providing a double chamber exposure design to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

**Results**

Dodd et al. (1987) presented 15-min $LC_{50}$ values:

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Reported by Dodd et al. (1987) |
|---|---|
| 15 | 406 (271-608) |

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

# Study ID: C.2

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

**Evaluation of study quality**

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *N/A* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *Both the chamber and the glove box are maintained at a negative pressure with respect to the room.* |
| Homogeneity of test atmosphere in breathing zone of animals | *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.*<br>*The following information on the exposure chamber design was presented by Dodd et al. (1987):*<br>*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).* |
| Number of air changes per hour | *Vapor exposure were statically generated in a 135 L inhalation chamber.* |

| | |
|---|---|
| Equilibration time (t95) | *t95 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".* |
| Start of exposure relative to equilibration | *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".* |
| Actual concentration measurement | *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.*<br>*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".* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***C***<br>*Limited to one exposure duration. Because no individual mortality data are available the study was given C status* |

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):

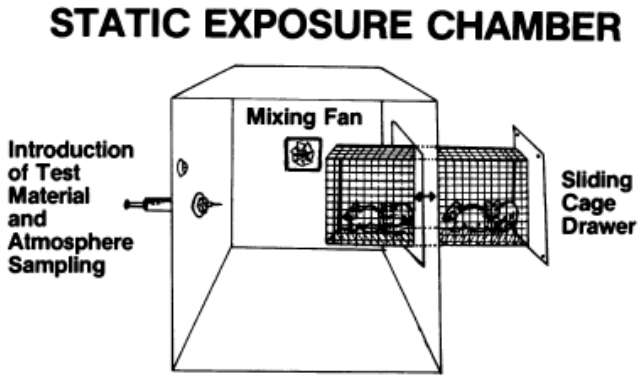



FIGURE 1. A static exposure chamber with sliding cage drawer mechanism was used to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

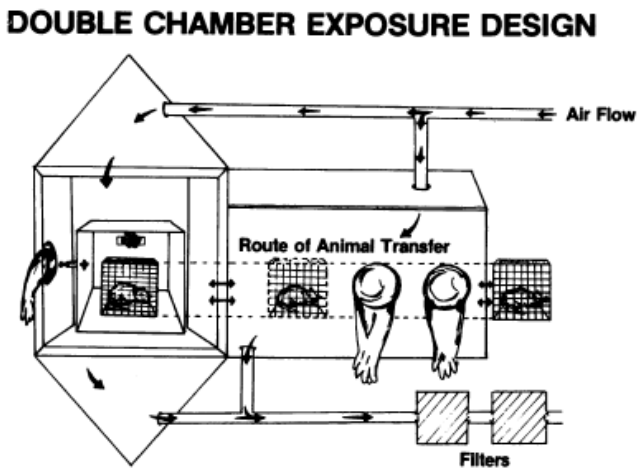



FIGURE 2. A static exposure chamber was placed in a dynamic exposure chamber/glove box assembly providing a double chamber exposure design to expose rats and guinea pigs to atmospheres containing methyl isocyanate vapor.

**Results**

Dodd et al. (1987) presented 15-min $LC_{50}$ values:

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Reported by Dodd et al. (1987) |
|---|---|
| 15 | 266 (145-485) |

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

# Study ID: C.3

***Author, year:*** ***Salmon et al., 1985***
Substance: methyl isocyanate
Species, strain, sex: rat, Lister hooded, male
Number/sex/conc. group: 2
Age and weight: age not specified / 170-200 g
Observation period: at least 14 days*

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

**Evaluation of study quality**

| **Criteria** | ***Comment*** |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to OECD 403 guideline(s) | *No statement of compliance with OECD guideline 403 provided* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *No* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *N/A* |
| Pressure distribution | *No information* |
| Homogeneity of test atmosphere in breathing zone of animals | *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.* |
| Number of air changes per hour | *Air flow of 10 L/min; air flow was maintained by a stainless steel bellows pump. No information on volume of inhalation chamber.* |
| Equilibration time (t95) | *Insufficient information to calculate t95.* |
| Start of exposure relative to equilibration | *Not specified.* |
| Actual concentration measurement | *The atmospheric concentration was monitored at the chamber outlet by a Miran infrared spectrometer. A continuous chart record of concentration was obtained.* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure | *N/A* |
| | |
| Assessment of Reliability | ***C*** *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.* |

**Results**

| Species | Concentration ($mg/m^3$) | | 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 # |

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

**Probit function**

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

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

with C for concentration in $mg/m^3$.

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

| Duration (min.) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Male |
|---|---|
| 120 | 106 (CI could not be estimated) |

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

# Study ID: C.4

***Author, year:*** ***Mellon Institute 1970***
Substance: Methyl isocyanate
Species, strain, sex: Rat, Wistar, male
Number/sex/conc. group: 6
Age and weight: no information
Observation period: 14 days

**Evaluation of study quality**

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

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

**Results**

| Species | Exposure duration (min) | $LC_{50}$ ($mg/m^3$) 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) |

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

Further, a range finding study was shortly described by the study authors:
Rat 4-hour inhalation of metered (nominal) concentrations:
62.5 ppm (*148 mg/m³*) killed 6 of 6
31.2 ppm (*74.1 mg/m³*) killed 0 of 6
2 mg/liter (857 ppm) killed 6 of 6 after 1 hour

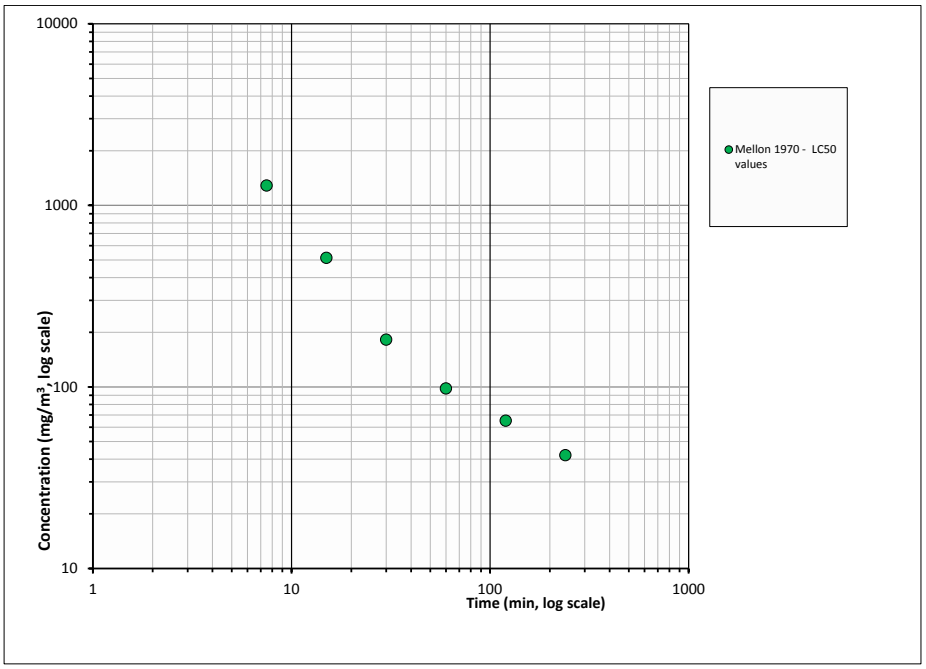
**Probit function**

No C × t probit function could be calculated from these data alone. However, as $LC_{50}$ values were provided for different exposure durations an n-value could be calculated using the following formula (AEGL SOP):

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

The calculated n-value was 1.0.

A graphical overview of the $LC_{50}$ values is presented below.


10000
1000
100
10
Concentration (mg/m³, log scale)
1
10
100
1000
Time (min, log scale)
Mellon 1970 - LC50 values

1
2

## Study ID: other C studies

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

Bucher et al. (1987a/b)/Boorman et al. (1987a/b) exposed male and female F344/N rats and B6C3F1 mice whole body to methylisocyanate for 2 hours. Exposure was conducted using whole-body in flow-through chambers. Chamber concentrations were monitored continuously. Details of the generation, monitoring, and safety aspects are reported by Adkins et al. (1987). Within 3 hours following the exposures (day 0), and again on days 1, 3, 7, 14, 49 and 91 after exposure, five predesignated animals per group were killed by pentobarbital overdose and given a complete gross necropsy. No animals died during the 2 hour exposures. Deaths of mice were observed within 15 to 18 hour following exposures to 30 ppm (71 mg/m$^3$), and rats began to die within a similar period after exposures to as low as 20 ppm (47.5 mg/m$^3$).
Gross examination of animals dying during this early period (days 1-3) revealed profuse edema and exudate in the nasal cavity and upper airways, and extending into the trachea and large bronchi. Although mortality varied from one exposure to the next, several general patterns were consistent between experiments. A higher proportion of male rats and mice than females died during the first 1 to 3 days following exposure to 20 or 30 ppm (47.5 or 71 mg/m$^3$) , and females in particular showed a biphasic survival curve. Initial deaths were followed by a 5- to 7-day period in which few deaths occurred. Deaths then resumed, and cumulative mortality was similar between the sexes after about 3 weeks. This delay in onset of mortality was also seen in male and female rats exposed to 10 ppm (23.8 mg/m$^3$) MIC for 2 hr (Fig. 2). Deaths began on day 8, and overall survival of male and female rats exposed to 10 ppm (23.8 mg/m$^3$) for 2 hr was similar. No mice died after exposure to 10 ppm. Most deaths of exposed animals occurred during the first month after the exposures, and were preceded by periods of severe respiratory distress. The last deaths occurred on days 49 and 78 after exposure. These were both male mice exposed to 30 ppm (71 mg/m$^3$). No deaths of control animals occurred during the studies.
Because animal survival was presented in graphic form, the exact numbers could not be discerned. Moreover, the study included scheduled deaths at multiple timepoints after exposure starting at day 0 up to day 91 (including post-exposure observation periods <14 days), which made it difficult to assess the true mortality rate.

Dow Chemical (1990) exposed rats and rabbits to methylisocyanate via whole body inhalation. Two rabbits per group were exposed to MIC at 12.8 mg/m$^3$ for 6.75, 3.5, or 2 h or at 4.3 mg/m$^3$ for 7 h. Although the concentrations were listed as nominal, the report stated that the analytical method (infrared absorption) was adequate for monitoring concentrations as low as 4.3 mg/m$^3$. A description of the exposure chamber was not included. All rabbits exposed at 12.8 mg/m$^3$ died 1-2 wk postexposure, apparently due to respiratory infections. Animals exposed at 4.3 mg/m$^3$ for 7 hour survived. At 12.8 mg/m$^3$ for durations of 3.5 h, the eyes were red and had evidence of corneal injury when observed with fluorescein. Ocular damage was slight in animals exposed at 12.8 mg/m$^3$ for 2 h and equivocal in animals exposed at 4.3 mg/m$^3$ for 7 h. No experimental details or further discussion was included.
Female rats (strain not specified; N = 4) were exposed to concentrations of MIC ranging from 4.3 to 546 mg/m$^3$ for durations of 0.1-7 h. Although the concentrations were listed as nominal, the report stated that the analytical method (infrared absorption) was adequate for monitoring concentrations as low as 4.3 mg/m$^3$; however, the analytical concentrations were not reported. A description of the exposure chamber was not included. Exposures at 546 mg/m$^3$ for 0.5 h, 214 mg/m$^3$ for 2 h, 83 mg/m$^3$ for 4 h, and 32.8 mg/m$^3$ for 4 h resulted in the deaths of all animals. Exposures resulting in some or no mortalities are as follows: 546 mg/m$^3$ for

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

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

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

Jeevaratnam and Sriramachari (1994) reported a rat 30-min $LC_{50}$ value of 465 ppm (1104 mg/m$^3$), but details concerning this value were not presented.

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

Mellon Institute (1963) exposed Wistar rats for four hours to methyl isocyanate. Exposure of 148 mg/m$^3$ killed 6/6 animals within 2 d, but no deaths occurred following exposure at 74.1 mg/m$^3$. A description of the exposure chamber was not included. The result of this range-finding study was used as the basis for following $LC_{50}$ studies (see Mellon Institute 1970).

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

Nemery et al. (1985) and Dinsdale (1987) exposed male LAC:P rats whole body to methyl isocyanate in a static exposure chamber. Nominal chamber concentrations were 0.02, 0.1, 0.25, 0.5, 1 or 10 mg/L. Exposure lasted one hour, except at the highest concentration used when it was 15 minutes. Eight rats were exposed for 15 minutes to 10 mg/L; four died during exposure and two shortly afterwards. Upon one hour exposure, no deaths were noticed in the 0.02, 0.1 and 0.25 mg/L exposure groups (despite severe respiratory distress). One rat of the nine exposed one hour to 0.5 mg/L died within 24 hours. Three rats exposed one hour to 1 mg/L died within 24 hours and four others were moribund and killed at this time.
One additional group of rats were exposed one hour to 0.25 mg/L and their lungs were histopathologically examined up to 3 weeks postexposure. All 30 rats in this group survived their exposure to methyl isocyanate, but one animal died 10 days after exposure and another died after 6 weeks (Dinsdale, 1987).
It is stated by Nemery et al. (1985) that methyl isocyanate concentrations, as determined by gas chromatography, were found to be below those expected from total evaporation and uniform distribution of the injected compound. A consistent decrease in concentration with time occurred even when there were no animals in the tank; it was not due to the presence of water vapour or to stratification of the gas and probably resulted from leakages. The concentrations given in their paper were calculated initial concentrations which must be reduced by a factor of 4 to obtain a time weighted average concentration over one hour.
Given the uncertainty on the actual exposure, this study was not further evaluated and was given the C-status.

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

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

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

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