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Probit function technical support document

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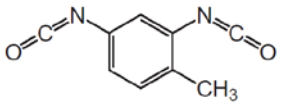
substance name	CAS number
2,4-Toluene Diisocyanate **2,6-Toluene Diisocyanate**	**584-84-9** **91-08-7**

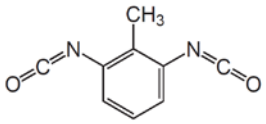
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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 Toluene Diisocyanate (TDI)

1. Substance identification

CAS-number:	584-84-9 (2,4-TDI) 91-08-7 (2,6-TDI)
IUPAC name:	Toluene diisocyanate
Synonyms:	TDI, 2,4-toluene diisocyanate, 2,4-TDI, 2,6-diisocyanate, 2,6-TDI, 4-methyl-m-phenylene diisocyanate, 2-methyl-m-phenylene diisocyanate
Molecular formula:	$C_9H_6N_2O_2$
Molecular weight:	174.2 g/mol
Physical state:	Liquid (at 20°C and 101.3 kPa)
Boiling point:	253°C (2,4-TDI)/247°C (2,6-TDI) (at 101.3 kPa)
Vapour pressure:	0.02 kPa (at 20°C)
Saturated vapor conc:	200 ppm = 1449 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.138 ppm (at 20°C and 101.3 kPa) 1 ppm = 7.246 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H315, H317, H319, H330, H334, H335, H351

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

Special considerations: TDI exists as both the 2,4- and 2,6-isomers. These are available commercially in ratios of 65/35 or 80/20. There is no indication of a difference between the isomers in acute inhalation lethality, and most guidelines or standards apply to both isomers equally. For the purpose of lethality probit functions, the isomers will be considered equally toxic and only one probit function will be developed for both isomers and the mixtures.

TDI readily reacts with water vapour resulting in a “fall-out” of reaction product that is probably TDI-dimer. Deposition and reaction with moisture can act to reduce the atmospheric concentration of TDI. This phenomenon is responsible for large differences in theoretical vs analytical exposure concentrations.

Acute effects: The main target organ for inhalation exposure to TDI is the respiratory tract. Inhaled TDI causes irritation and sensitization of the respiratory tract; irritation of cornea, conjunctiva and skin can also occur. The health endpoints of acute exposure are related to the irritative and corrosive properties of TDI to the respiratory tract. Symptoms of high exposure are laboured breathing, secretions from nose, mouth and eyes and prostration.

Damage occurs in the respiratory system, particularly the respiratory tract resulting in mucus secretion, upper airway and/or pulmonary oedema and bronchospasm. The resulting hypoxemia will cause CNS and cardiovascular (myocardial ischemia) effects. Lethality results when the respiratory damage proceeds to inflammation, degeneration and necrosis of affected tissue, atelectasis, emphysema and death.

Long-term effects: TDI may induce sensitization. Sensitization with the risk to develop subsequent allergic reactions can occur from respirable exposure over a long period of time to relatively low concentrations or from at least one exposure at a high concentration. In addition, chronic exposure produces irritative effects similar to acute exposure. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition may well develop after single exposure to TDI. Symptoms occur within minutes to hours after the initial exposure and may persist as non-specific bronchial hyper-responsiveness for months to years.

[1] AEGL, 2004.

3. Human toxicity data

No informative reports on human toxicity following acute inhalation exposure were identified in which details about both health effects and the exposure have been documented in sufficient detail.

AEGL (2004 reports the following experimental study in humans:
Henschler *et al.* (1962) exposed six healthy male volunteers to 2,4-TDI, 2,6-TDI, or a mixture of 2,4- and 2,6-TDI (65:35) at measured concentrations ranging from 0.01 ppm to 1.3 ppm (0.07 to 9.42 mg/m^3) for 30 min. The volunteers were exposed at all concentrations, but at only one concentration per day, and the concentrations were randomly selected. Volunteers had no prior knowledge of the isomer or concentration selected. A concentration-dependent increase in sensory irritation was reported. There was slight eye and nose irritation at 0.1 ppm and marked discomfort at ≥0.5 ppm (0.36 mg/m^3). 2,6-TDI appeared slightly more irritating than the 2,4-isomer, but was similar to the mixture.

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 TDI, 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. Five studies were identified -with eight datasets for four species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, one dataset was assigned status B and seven were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of 4 animal studies were identified in which sensory irritation was studied. In these studies the following RD_{50} values were observed:

Species/strain	*RD_{50} (mg/m^3)*	*Duration (min)*	*Author/year*
Rat, Sprague-Dawley	9.93^{P}	3-hr 2,4-TDI	Shiotsuka 1987a
Rat, Sprague-Dawley**	15.4^{S}	3-hr (2,4 / 2,6; 80:20)	Shiotsuka 1987b
Mouse, Swiss-Webster	5.89^{P}	10-min 2,4-TDI	Sangha 1979
Mouse, Swiss-Webster	3.61^{P}	30-min 2,4-TDI	Sangha 1979
Mouse, Swiss-Webster	1.44^{P}	3-hr 2,4-TDI	Sangha 1979
Mouse, Swiss-Webster	1.88ND	3-hr 2,6-TDI	Weyel 1982

P: a plateau was reached, S: second decrease during exposure, ND: no data to indicate if a plateau in response was reached.
**: secondary data from draft AETL document (product of ACUTEX project)

5. Probit functions from individual studies

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

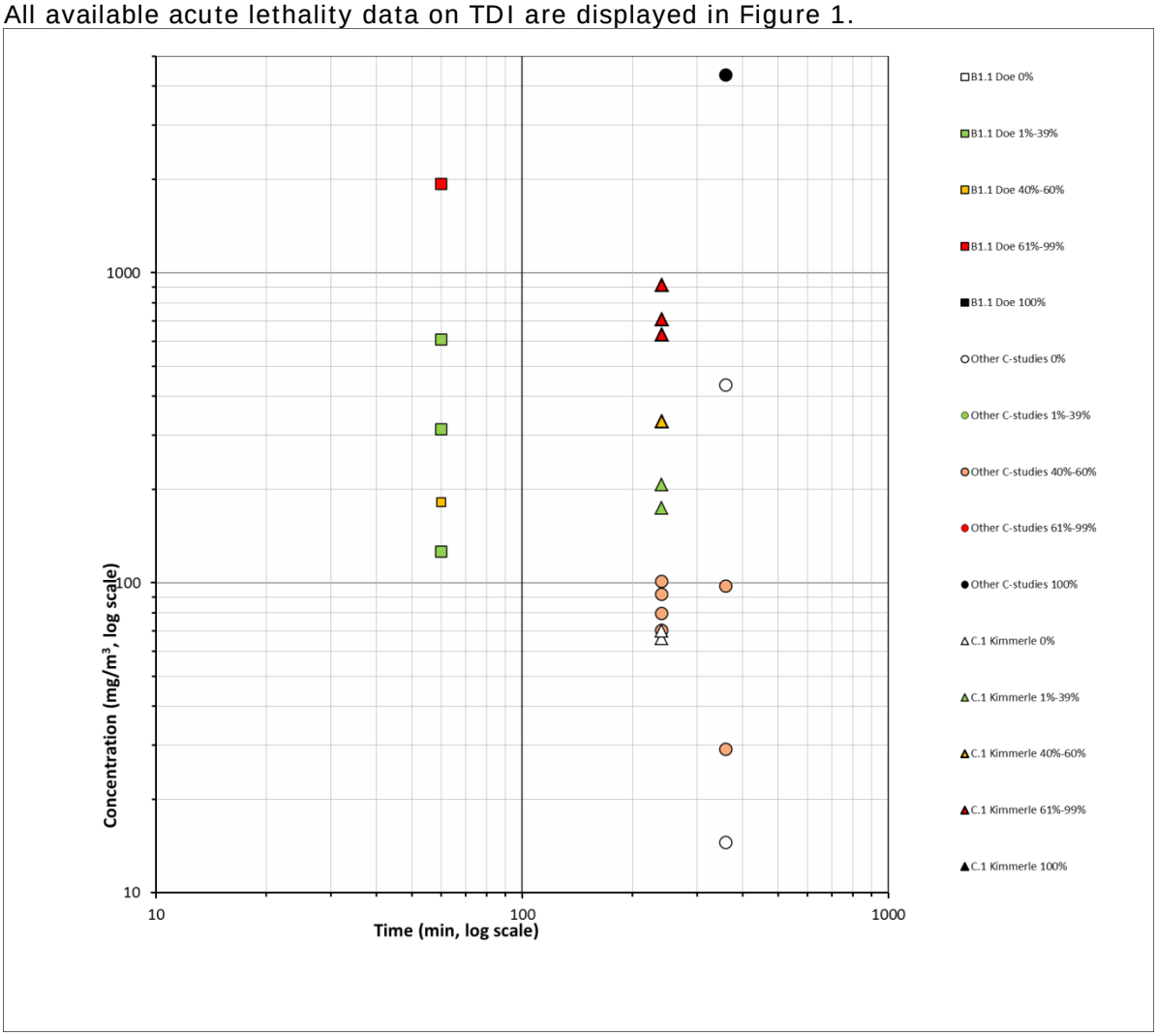


Figure 1 *All available acute lethality data for TDI.*

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

It was possible to derive a probit function for TDI based on the only available study with B1 quality. However, this B1 study did not enable to produce a concentration-time-lethality relationship.

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

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (60 min.)	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	475 (206-1981)	N/A

The data of study B1.1 with rats are presented graphically below.

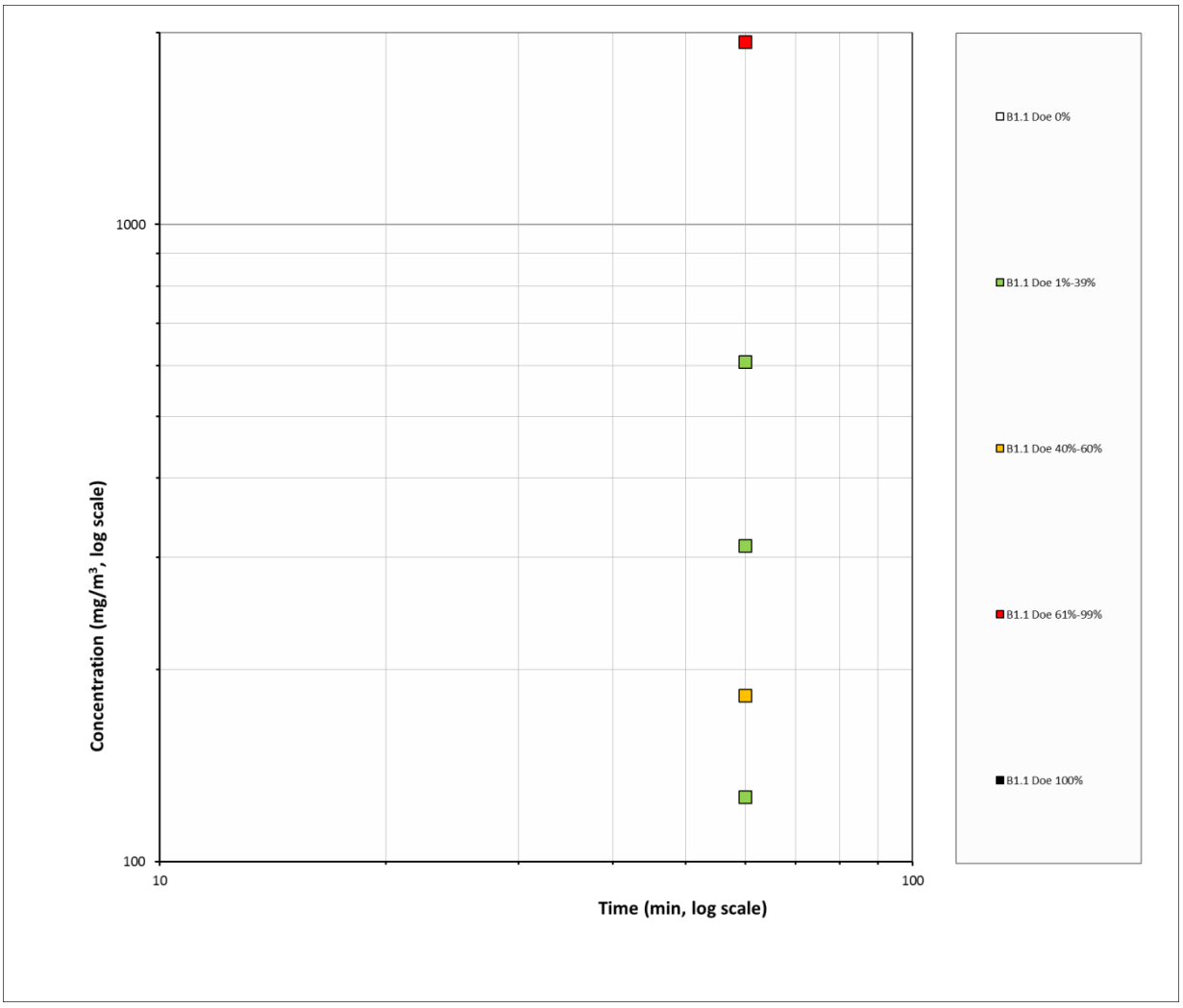


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of TDI.*

Based on criteria outlined in the guideline the data from study B1.1 were selected for the final dataset for the derivation of the animal probit function.
The data that were selected for final analysis of the animal probit function are presented in Table 2 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 2 *Data selected for the derivation of the animal probit function of TDI (identical to table 1).*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (60 min.)	n-value 95% C.I.
B1.1		*60-min LC_{50}*	475 (206-1981)	N/A

The data of the selected datasets are presented graphically below.

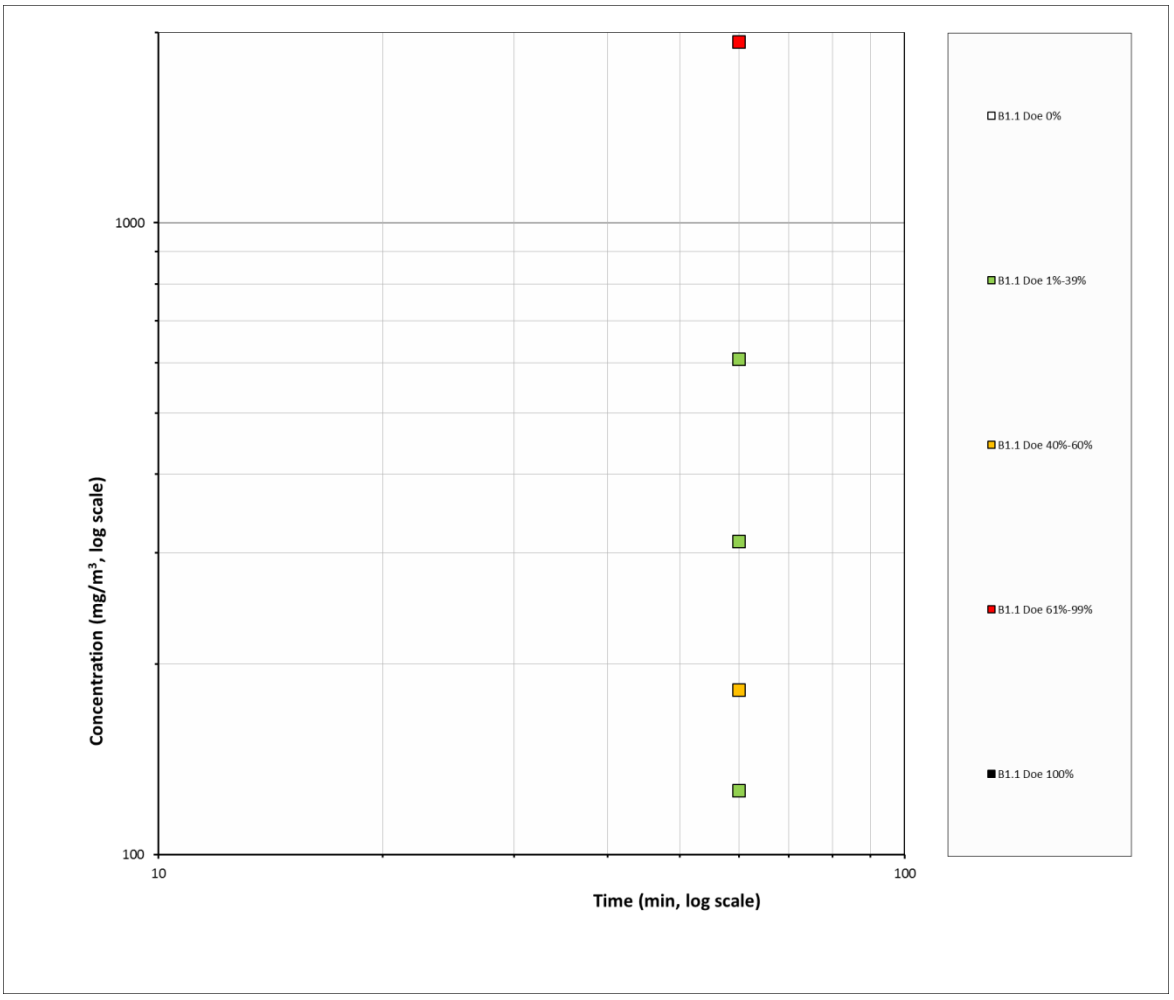


Figure 3 *Final data selected for derivation of the animal probit function of TDI (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from study B1.1 (Doe, 1980) 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 475 mg/m^3 and a default n-value of 2.

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

Table 3 Rationale for the applied assessment factors.

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	Default
Nominal concentration	1	B1-study with analytically determined concentrations
Adequacy of database:	2	Only one limited B1-study was found.

The estimated human equivalent 60-minute LC_{50} value is 475 / 6 = **79 mg/m^3**.

No reliable experimentally determined n-value was available, so the default n-value of **2.0** was used. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.0**.

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): $5 = a + 1 \times \ln (79^2 \times 60)$ resulting in the a-value of **-7.84**.

$Pr = -7.84 + 1 \times \ln (C^2 \times t)$ 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, including 40 animals, an exposure duration of 60 minutes and response rates between 0 and 100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 17 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 25 mg/m^3.

Table 4 *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	24	17
1% lethality, this probit	35	25
AEGL-3[2] (2004, final)	4.71	3.70
ERPG-3[2] (2016)	-	4.35
LBW (2017)	4.7	3.7

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

[2] AEGL 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: Doe, 1980
Substance: TDI (80% 2,4-TDI, 20% 2,6-TDI)
Species, strain, sex: Male and female Alderly Park Rats
Number/sex/conc. group: 4/concentration
Age and weight: 6-10 weeks old, 150-300 grams
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	*Not specified. TDI reacts with water vapour. TDI was introduced into the test chamber to allow high vapour concentrations. An aerosol/vapour mixture was likely present in the exposure chamber at high concentrations*
Use of vehicle (other than air)	*Dried air (4% relative humidity)*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution	*No information on pressure distribution*
Homogeneity of test atmosphere in breathing zone of animals	*TDI was dispensed into a syringe atomizer. The test atmosphere passed through a heated glass tube (circa 120 C), mixed with diluting air and led into the animal exposure chamber. All air was dried to less than 4% relative humidity*
Number of air changes per hour	*Animals were exposed in a 17 L inhalation chamber; air flow not specified*
Equilibration time (t95)	*Insufficient data to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*One 5-minute sample with 2 impringers in series midway through the 1-hour exposure period (in breathing zone), followed by HPLC analysis*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*Presence or absence of aerosol was not reported, but test atmosphere was generated as vapour. Measurement of particle size distribution was not specified.*
Assessment of Reliability	***B1*** *Study with limitations, because limited to one exposure duration/Particle size was not determined*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	Dead/tested
Rat	126	N/A	60	0/4	1/4
Rat	182	N/A	60	1/4	3/4
Rat	313	N/A	60	2/4	1/4
Rat	608	N/A	60	1/4	2/4
Rat	1935	N/A	60	4/4	3/4

Probit function

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

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

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

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	1.16	0.60	0.30	-
Sexes combined	Rat	1.35	0.59		-

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

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
60	615 (200-5716)	375 (89-1741)	475 (206-1981)

The study authors reported a 60 min LC_{50} value (sexes combined) of 479 (225-1022) mg/m^3.

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

Study ID: C.1

Author, year: Kimmerle, 1976
Substance: TDI
Species, strain, sex: Male and female Rats, Wistar II
Number/sex/conc. group: 10/sex/concentration
Age and weight: age not specified, 170-190 grams
Observation period: 28 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)	*40% TDI was mixed in xylene and ethylene glycol acetate (1 :1).*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution	*No information on pressure distribution*
Homogeneity of test atmosphere in breathing zone of animals	*A colouring agent was introduced at a known concentration. This mixture was sprayed in a 10L mixing vessel at a rate of 10L/min. The resulting aerosol was metered into the test chamber*
Number of air changes per hour	*Animals were exposed in a 20 L inhalation chamber; air flow not specified*
Equilibration time (t95)	*Insufficient data to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Up to 4 times per exposure condition, the amount of adsorbed colorant on cotton in the test chamber was photometrically determined and was used to calculate the concentration, expressed as mg solid/m^3 air*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*No information*
Assessment of Reliability	***C*** *Limited to one exposure duration, unreliable concentration measurement, particle size not determined.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	Dead/tested
Rat	66	N/A	240	0/10	0/10

Rat	70	N/A	240	0/10	0/10
Rat	174	N/A	240	2/10	0/10
Rat	207	N/A	240	4/10	0/10
Rat	332	N/A	240	3/10	7/10
Rat	634	N/A	240	7/10	9/10
Rat	708	N/A	240	8/10	10/10
Rat	917	N/A	240	9/10	10/10

Probit function

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

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

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

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-5.15	1,72	0.20	-
Sexes combined	Rat	-5.03	1.71	-	-

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

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
240	370 (293-467)	329 (259-416)	351 (300-413)

The study author calculated 4 hour LC_{50} values of 350 (255-479) and 360 (259-439) for males and females, respectively.

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

Study ID: other C studies

Albino rats (n=6) were exposed by whole body for 6h to analysed concentrations of TDI at 2, 4, or 13.5 ppm (14.5, 29.0, 97.8 mg/m^3) (mixed isomer, ratio not specified) (Wazeter, 1964). At both the middle and high concentrations, three of six rats died, those deaths occurring by post-exposure days 7 and 15, respectively. No deaths occurred at 2 ppm. Ocular and nasal irritation and laboured breathing were observed at all concentrations within 2h of initiation of exposure. Deaths resulted from severe pulmonary haemorrhage, emphysema, and pneumonia. When TDI vapour is metered into a small chamber containing rats, one observes an immediately heavy “fall-out” of TDI-water reaction product, which may be TDI-dimer as described by Zapp (1957). As a result, the actual exposure for TDI rats is only a fraction of the amount vaporized into the air stream.

Rats, mice, guinea pigs and rabbits (n=76, number, strain and sex unspecified) were exposed whole body for 4h to measured concentrations of 0.1, 1.0, 2, 5, 10, 20, or 34 ppm (0.73, 7.23, 14.5, 36.2, 72.5, 145 or 246 mg/m^3) (Duncan, 1962). The specific TDI isomers studies were not identified. Air sampling appeared to take place in animal breathing zone, but number and duration of samples is not specified. TDI is captured in absorber medium (capture efficiency unknown) and analysed with the Marcali method (chemical reaction and colorimetry). Presence of the aerosol was reported, but the particle size was not provided. Animals exhibited concentration-dependent signs of toxicity, such as mouth-breathing, lacrimation, profuse salivation, and restlessness, during exposure. At concentrations above 5 ppm, mouth-breathing was observed after 1h of exposure. Histopathologic examinations of the respiratory tracts of five animals per group per time point revealed focal coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group. Advanced bronchiolitis fibrosia obliterans and bronchopneumonia were evident at the higher concentrations. The reported 4h-LC50 value for rats was 101 mg/m^3, for mice 70.3 mg/m^3, for guinea pigs 92 mg/m^3, and for rabbits 79.7 mg/m^3.

Zapp presented an overview of toxicity data of TDI. A concentration of 600 ppm (4348 mg/m^3) of 2,4-TDI for 6h resulted in pulmonary congestion and edema and was lethal to rats (Zapp, 1957). No deaths were reported in rats exposed to a calculated concentration of 2,4-TDI at 60 ppm (435 mg/m^3) for 6h. Description of study characteristics (including the length of the observation period) is limited.

Appendix 2 Reference list

Baur, X. Isocyanate hypersensitivity. Final report to the International Isocyanate Institute. III File No. 10349; III Project E-AB-19, 1985 (as cited in AEGL (2004)).

Brorson, T., Skarping, G. and Carsten, S. Biological monitoring of isocyanates and related amines IV. 2,4- and 2,6-toluene diamine in hydrolyzed plasma and urine after test-chamber exposure of humans to 2,4- and 2,6-toluene diisocyanate. Int. Arch. Occup. Environ. Health. 1991;63:253-259 (as cited in AEGL (2004)).

Chemiekaarten. Ed 33. Den Haag. TNO/SDU uitgevers, 2018.

Doe, J.E. and G.M. Horpsool. Toluene di-isocyanate: acute inhalation toxicity in the rat. Imperial Chemical Industries, report no CTL/T/1097. (February 1980).

Duncan, B., L.D. Scheel, E.J. Fairchild, *et al.* (1962). Toluene Diisocyanate Inhalation Toxicity: Pathology and Mortality. Ind Hyg J 23;1962:447-456.

Henschler, D., W. Assman, and K.-O. Meyer. 1962. On the toxicology of toluene diisocyanate [in German]. Archiv für Toxikologie 19:364-387 (as cited in AEGL (2004)).

Kimmerle, G. 1976. Acute inhalation toxicity of diisocyanates, polymer isocyanates and coating systems on rats. Bayer AG, Institute for Toxicology. Report no 6200.

National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 4. Washington, DC. The National Academies Press, 2004.

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

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

Sangha, G.K. and Y. Alarie. Sensory irritation by toluene diisocyanate vapour in single and repeated exposures. Toxicol. Appl. Pharmacol. 1979;50:533-547.

Shiotsuka, R.N. (1987a). Sensory irritation study of MONDUR TDS in male Sprague-Dawley rats. Study no. 86-341-01. Stilwell, KS: Mobay Corp (as cited in AEGL (2004)).

Shiotsuka, R.N. (1987b). Sensory irritation study of MONDUR TD-80 in male Sprague-Dawley rats. Study no. 86-341-02. Stilwell, KS: Mobay Corp (as cited in draft AETL document).

Wazeter, F.X. 1964. Six-hour acute inhalation toxicity study in rats. No. 100-012. International Research and Developmental Corp.

Weyel D.A., B.S. Rodney, Y. Alarie. Sensory irritation, pulmonary irritation, and acute lethality of a polymeric isocyanate and sensory irritation if 2,6-toluene diisocyanate. Toxicol. Appl. Pharmacol. 64;1982:423-430.

Zapp J.A. (1957). Hazards of Isocyanates in Polyuterathane Foam Plastic Production. AMA Arch Indust Health 15;1957:324-39.