

Probit function technical support document

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substance name	CAS number
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).

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, have been approved by the scientific expert panel on probit functions on scientific grounds. The status of this document was therefore raised to "interim", pending a decision on its formal implementation.

Subsequently the Ministry of Housing, Spatial Planning and the Environment (VROM) will perform a second tier evaluation to decide whether the probit function will be formally implemented. The decision on actual implementation will primarily be based on the results of a consequence analysis.

Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the e-mail address mentioned above.

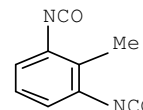
Detailed information on the procedures for derivation, evaluation and formalization of probit functions is available at

<http://www.rivm.nl/milieuportaal/bibliotheek/databases/probitrelaties.jsp>.

1 Technical support document Toluene Diisocyanate

1. Substance identification

4	CAS-number:	584-84-9 (2,4-TDI), 91-0807 (2,6-TDI)
5	IUPAC name:	Toluene diisocyanate
6	Synonyms:	TDI, 2,4-toluene diisocyanate, 2,6-toluene diisocyanate,
7		2,4-TDI, 2,6-TDI
8	Molecular formula:	C ₉ H ₆ N ₂ O ₂ . Structural formula 2,6-TDI:
9	Molecular weight:	174.2
10	Physical state:	liquid (at 20°C and 101.3 kPa)
11	Boiling point:	251°C (at 101.3 kPa)
12	Vapour pressure:	0.004 kPa (at 20°C)
13	Saturated vapour conc:	290 mg/m ³ (at 20°C and 101.3 kPa)
14	Conversion factor:	1 mg/m ³ = 0.138 ppm (at 20°C and 101.3 kPa)
15		1 ppm = 7.246 mg/m ³ (at 20°C and 101.3 kPa)
16	Labelling:	R26-36/37/38-40-42/43-52/53



2. Mechanism of action and toxicological effects following acute exposure¹

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

27 **Acute effects:** The main consequence of inhalation exposure to TDI is irritation and
 28 sensitization of the respiratory tract; irritation of cornea, conjunctiva and skin can also
 29 occur. The health endpoints of acute exposure are related to the irritative and
 30 corrosive properties of TDI. Symptoms of high exposure are laboured breathing,
 31 secretions from nose, mouth and eyes and prostration.

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

37 **Long-term effects:** Sensitization to TDI is believed to be the consequence of long-
 38 term exposure. In addition chronic exposure produces irritative effects similar to acute
 39 exposure. Reactive Airways Dysfunction Syndrome, an acquired asthma-like
 40 condition may well develop after single exposure to TDI. Symptoms occur within
 41 minutes to hours after the initial exposure and may persist as non-specific bronchial
 42 hyper-responsiveness for months to years.

3. Human toxicity data

45 No informative reports on health effects in humans following acute inhalation
 46 exposure were identified. Such reports are considered informative if both health
 47 effects as well as the exposure have been documented in sufficient detail.

¹ National Research Council: AEGL Volume 4, AHLS Provider manual 3rd ed.

48 **4. Animal acute toxicity data**

49 Animal lethal toxicity data considering acute exposure are described in Appendix 1. A
50 total of 5 studies were identified -with 8 datasets for 4 species- with data on lethality
51 following acute inhalation exposure. No datasets were assigned status A for deriving
52 the human probit function, 1 dataset was assigned status B and 7 were assessed to be
53 unfit (status C) for human probit function derivation.

54 During a literature search the following technical support documents and databases
55 have been consulted:

- 56 1. AEGL final TSD and ERPG documents and reference database for TDI, covering
57 references before 1995.
- 58 2. An additional search covering data from 1995 - 2008 was performed in HSDB,
59 MEDline/PubMed, Toxcenter, IUCLID, RTECS, with the following search terms:
60
 - 61 • TDI, toluene diisocyanate and synonyms
 - 62 • CAS number
 - 63 • lethal*
 - 64 • mortal*
 - 65 • LC₅₀ and LC
 - 66 • probit
- 67 3. Unpublished data were sought through networks of toxicological scientists.

69 **Sensory irritation**

70 A total of 4 studies were identified in which sensory irritation was studied. In these
71 studies the following RD₅₀ values were observed:

<i>Species/strain</i>	<i>RD₅₀ (mg/m³)</i>	<i>Duration (min)</i>	<i>Author/year</i>
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	1.88 ND	3-hr 2,6-TDI	Weyel 1982

72 P: a plateau was reached, S: second decrease during exposure, ND no data to indicate
73 if a plateau in response was reached.

74 **: secondary data from draft AETL document

77 **5. Probit functions**

78 No probit functions have been calculated and reported in Appendix 1 for any of the
79 reported individual studies.

80
81 Due to the lack of adequate data (only 1 B-study with a single exposure duration of 1
82 hour), a graphical representation of the data is not informative.

83
84

85 6. Evaluation

86 Only one LC₅₀ value is available, and by current standards not a very good one. If a
87 value should be set on the basis of these data, an additional assessment factor of 2
88 should be applied to the LC₅₀ value to account for database inadequacy.

89

90 As point of departure for deriving the human probit function the 60 minute LC₅₀ value
91 of **475 mg/m³** for the rat from the Doe (1980) study was taken. The human equivalent
92 LC₅₀ was calculated by applying the following assessment factors:

93

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	
RD ₅₀	3	RD ₅₀ less than 20% of LC ₅₀
Nominal concentration	1	Analytical concentration reported
Adequacy of database:	2	only 1 B-study with 1 exposure duration available

94

95 The estimated human equivalent 60-minute LC₅₀ value is $475 / 18 = \mathbf{26.4 \text{ mg/m}^3}$.

96

97 There was no experimentally determined n-value, the **default n-value of 2** will be
98 taken. Assuming a regression coefficient of 2 for the slope of the curve, the b-value
99 can be calculated using the $2 / n$ as **b = 1**.

100

101 The human probit function is then calculated on the human equivalent 60 min LC₅₀
102 and using the above parameters to solve the following equation to obtain the a-value
103 (the intercept): $5 = a + 1 \times \ln(26.4^2 \times 60)$ resulting in the a-value of **-5.64**.

104

105 **Pr = -5.64 + 1 × ln(C² × t)** with C in mg/m³ and t in min.

106

107 The derived human probit function has a scientifically weak basis. The probit function
108 is only based on one old study with one exposure duration in the rat.

109

110 The human 60 min LC₁ (Pr = 2.67) calculated with this probit equation is 8.2 mg/m³
111 and the calculated human 60 min LC_{0.1} (Pr = 1.91) is 5.6 mg/m³.

112

Estimated level	30 min (mg/m ³)	60 min (mg/m ³)
1% lethality, this probit	11.6	8.2
0.1% lethality, this probit	8.0	5.6
AEGL-3 (2004, final)	4.6	3.6
ERPG-3 (1998)		4.3
LBW (2007)		5

113

114 Comparing to equivalent (inter)national guideline levels as presented in the table
115 below, the lethal levels derived with this probit function are 2 times higher. The fact
116 that AEGL and ERPG use a different study (Duncan 1962) and a different species
117 (AEGL: mouse, most susceptible) as point of departure probably plays a major role.

118 **Appendix 1 Animal experimental research**

119

120 **Study ID: 1.B.1**

121 **Author, year: Doe 1980**

122 Substance: TDI (80% 2,4-TDI, 20% 2,6-TDI)

123 Species, strain, sex: Male and female Alderly Park Rats

124 Number/sex/concentration group: 4/concentration

125 Age and weight: 150-300 grams, 6-10 weeks old

126 Observation period: 14 days

127

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>Not specified. TDI reacts with water vapour. TDI was passed through a tube at a temperature of 120 °C before introduction into the test chamber to allow high vapour concentrations. An aerosol/vapour mixture was likely present in the exposure chamber</i>
Use of vehicle (other than air)	<i>Dried air (4% Relative Humidity)</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body, equilibration time unspecified</i>
Pressure distribution.	<i>No information on pressure distribution</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified; air sampling appears to take place in animal breathing zone</i>
Number of air changes per hour	<i>No information</i>
Actual concentration measurement	<i>One 5-minute sample with 2 impingers in series midway through the 1-hour exposure period (in breathing zone), followed by HPLC analysis</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>Presence or absence of aerosol was not reported, but test atmosphere was generated as vapour. Particle size distribution was not measured.</i>
Assessment of Reliability	B This study received B status because only 1 exposure duration was studied.

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129

130 **Results**

131

Species	Concentration (mg/m ³)	Exposure duration (min)	Physical state	Lethality	
				male	Female
Rat	126	60	Vapour/aerosol	0/4	1/4
Rat	182	60	Vapour/aerosol	1/4	3/4
Rat	313	60	Vapour/aerosol	2/4	1/4
Rat	608	60	Vapour/aerosol	1/4	2/4
Rat	1935	60	Vapour/aerosol	4/4	3/4

132

133

134 **Probit function**

135 No C × t probit function could be calculated from these data alone. LC₅₀ values for
 136 males, females and sexes combined have been calculated.

137

138 Depending on the analysis, the LC₅₀ differed by a factor 2 -3 between males and
 139 females, but in an analysis with sex as covariate no statistically significant differences
 140 between sexes were found. The overall statistical power of the probit model was low.
 141 The authors also concluded that the LC₅₀ values for males and females were equal.
 142 For this reason the data from males and females were pooled and analyzed to derive
 143 the animal LC₅₀.

144

145 The authors report a 60-min LC₅₀ of 66 ppm (478 mg/m³) for sexes combined; our
 146 analysis estimated a 60-min LC₅₀ of 475 mg/m³.

147

148

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%-C.I. female</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Combined</i>
60	507 (245 - 2189)	381 (data do not allow to calculate a cfd-i)	475 (206 - 1978)

149

150

151 **Study ID: 1.C.1**
 152 **Author, year: Wazeter 1964**
 153 Substance: TDI
 154 Species, strain, sex: Manor Farms rats, sex unspecified
 155 Number/sex/concentration group: 6/concentration
 156 Age and weight: 245-280 grams, adult (age further unspecified)
 157 Observation period: 15 days
 158

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food,, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>TDI was passed through a tube at a temperature of 65 °C before introduction into the test chamber, to allow high vapour concentrations. Therefore, exposure to vapour in pre-dried air. Even so, an 'immediate heavy fall out of TDI-water reaction product' was observed.</i>
Use of vehicle (other than air)	<i>Dried air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body, equilibration time unspecified</i>
Pressure distribution.	<i>No information on pressure distribution</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified; air sampling appears to take place in animal breathing zone.</i>
Number of air changes per hour	<i>No information</i>
Actual concentration measurement	<i>One 5-minute sample midway through the 1 hour exposure period (in breathing zone) in an impinger, followed by colorimetric analysis. Analytical concentration was about 5% of the nominal concentration. The large difference between actual and nominal concentration indicates with some certainty that a large fraction of the test atmosphere had not been captured for analysis.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>Presence of aerosol likely but presence or absence and particle size not reported.</i>
Assessment of Reliability	C This study received C status because only 1 exposure duration was studied, and because the analytical concentration assessment was highly uncertain.

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160

161 **Results**

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Species	Concentration (mg/m ³)	Exposure duration (min)	Physical state	Lethality	
				Sex unknown	
Rat	98	360	Vapour/aerosol	3/6	
Rat	29	360	Vapour/aerosol	3/5	
Rat	14.5	360	Vapour/aerosol	0/5	
Rat	14.5	360	Vapour/aerosol	0/5	
Rat	< 7	360	Vapour/aerosol	0/5	

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165 **Probit function**

166 No $C \times t$ probit function could be calculated from these data alone. No LC_{50} value
 167 was calculated because of questionable concentration assessment.

168

169 No calculation of LC_{50} for C- studies. The report states that this study was mainly for
 170 range-finding for multiple-exposure studies.

171

172 **Study ID: 1.C.2**
 173 **Author, year: Kimmerle 1976**
 174 Substance: TDI
 175 Species, strain, sex: Male rats, Wistar II
 176 Number/sex/concentration group: 10 / sex / concentration
 177 Age and weight: adult males, 170-190 gr.
 178 Observation period: 28 days
 179

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>40% TDI mixed in xylene and ethylene glycol acetate. A colouring agent was introduced at a known concentration. This mixture was sprayed in a 10 l mixing vessel at a rate of 10 l/min. The resulting aerosol was metered into the test chamber.</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>No information</i>
Actual concentration measurement	<i>Up to 4 times per exposure condition. The amount of adsorbed colorant on cotton in the test chamber was used to calculate the concentration, expressed as mg solid/m³ air.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C <i>Only 1 exposure duration, concentration assessment not reliable</i>

180

181 **Results**

182

Species	Concentration (mg/m ³)	Exposure duration (min)	Physical state	Lethality	
				male	Female
Rat	66	240	Aerosol	0/10	0/10
Rat	70	240	Aerosol	0/10	0/10
Rat	174	240	Aerosol	2/10	0/10
Rat	207	240	Aerosol	4/10	0/10
Rat	332	240	Aerosol	3/10	7/10
Rat	634	240	Aerosol	7/10	9/10
Rat	708	240	Aerosol	8/10	10/10
Rat	917	240	Aerosol	9/10	10/10

183

184

185 **Probit function**

186 No $C \times t$ probit function could be calculated from these data alone. The LC_{50} values
 187 calculated from the data (table below) compare well with those reported in the
 188 original report (male LC_{50} 350 mg/m³, female LC_{50} 360 mg/m³).

189

190

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. male</i>	<i>LC₅₀ (mg/m³) 95%-C.I. female</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Combined</i>
240	370 (277 – 502)	336 (278 – 415)	351 (297 – 414)

191

192

193 **Study ID: 1.C.3**
 194 **Author, year: Duncan 1962**
 195 Substance: TDI
 196 Species, strain, sex: Rats, mice, guinea pigs and rabbits, strain and sex unspecified
 197 Number/sex/concentration group: unknown number / concentration
 198 Age and weight: not specified
 199 Observation period: 14 days
 200

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>Not specified. TDI was dispensed as an aerosol from a nebulizer. Exposure was probably to aerosol and vapour.</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body, equilibration time unspecified</i>
Pressure distribution.	<i>0.1 inch negative water pressure in the chamber</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Claimed to be uniform due to inlet and outlet vents.</i>
Number of air changes per hour	<i>60 air changes / hour</i>
Actual concentration measurement	<i>Air sampling appears to take place in animal breathing zone. Capture of TDI in absorber medium (vapour/aerosol capture efficiency unknown) and analysis with Marcali method (chemical reaction and colorimetry). Number and duration of samples not specified.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>TDI reacts with water vapour. Presence of aerosol was reported, but particle size was not provided.</i>
Assessment of Reliability	C This study received C status because only 1 exposure duration was studied, and exposure assessment was questionable.

201

202

203 **Results**

204 This study only reports a figure with a lethality probit function and LC₅₀ values for all
205 tested species. For rats, the graphs seems to indicate about 1% lethality at an exposure
206 level of 5 ppm (36 mg/m³). It is highly unlikely that such a low response could be
207 observed when the total number of rats for all exposure concentrations is stated to be
208 86. The LC₅₀ values reported by the authors for all tested species are presented below.
209

Species	LC ₅₀ (mg/m ³)	Exposure duration (min)	Physical state
Rat	101	240	Aerosol/vapour
Mouse	70.3	240	Aerosol/vapour
Guinea Pig	92.0	240	Aerosol/vapour
Rabbit	79.7	240	Aerosol/vapour

210

211

212 **Probit function**

213 No C × t probit function could be calculated from these data alone. LC₅₀ values as
214 presented by the authors are listed above.

215

216 **Study ID: 1.C.4**
 217 **Author, year: Zapp 1957**
 218 Substance: TDI
 219 Species, strain, sex: Rats, strain and sex unspecified
 220 Number/sex/concentration group: unknown number / concentration
 221 Age and weight: not specified
 222 Observation period: not specified
 223

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>No information.</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>No information</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>No information</i>
Actual concentration measurement	<i>Some concentrations were calculated (nominal), others were claimed to be analytical but analysis method unspecified.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>TDI reacts with water vapour. Aerosol was probably present, but the particle size was not reported.</i>
Assessment of Reliability	C This range-finding study received C status because very sketchy description of all relevant test conditions.

224
 225

226 **Results**

227 This study only some range-finding results for acute and subacute inhalation
228 exposures. Only acute inhalation data are presented here.

229

Species	Concentration (mg/m ³)	Exposure duration (min)	Physical state	Lethality	
Rat	4348	360	Aerosol/vapour	Lethal	
Rat	435	240	Aerosol/vapour	Non lethal	

230

231

232 **Probit function**

233 No $C \times t$ probit function could be calculated from these data alone.

234

Appendix 2 Reference list

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