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Toluene diisocyanates – Addendum for evaluation of a BAT value

Assessment Values in Biological Material – Translation of the German version from 2021

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Keywords

toluene diisocyanates; 2,4-toluene diisocyanate; 2,6-toluene diisocyanate; toluenediamine; biological tolerance value; BAT value

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated 2,4-toluene diisocyanate (2,4-TDI) [584-84-9], 2,6-toluene diisocyanate (2,6-TDI) [91-08-7] and toluene diisocyanates, mixture [26471-62-5] and derived a biological tolerance value (BAT value) for the combined urinary concentration of the two metabolites 2,4-toluenediamine (2,4-TDA) and 2,6-toluenediamine (2,6-TDA) to characterise the internal exposure at the workplace.

The evaluation of the BAT value was based on the relationship between 2,4-/2,6-TDI uptake by inhalation at the level of the MAK value and the corresponding urinary excretion rate of 2,4-/2,6-TDA. Biomonitoring field studies were applied in which the excretion of 2,4- and 2,6-TDA in urine of persons occupationally exposed to 2,4-/2,6-TDI was examined as well as the concentration of TDI in the air. An eight-hour exposure to the present MAK value of 0.001 ml 2,4-/2,6-TDI/m³ (7 µg 2,4-/2,6-TDI/m³) correlated with a mean urinary sum of 2,4- and 2,6-TDA concentration (after hydrolysis) of approximately 5 µg/g creatinine. Therefore, a BAT value of 5 µg Σ2,4- and 2,6-TDA (after hydrolysis)/g creatinine was evaluated. Sampling time is at the end of exposure or the end of the working shift.

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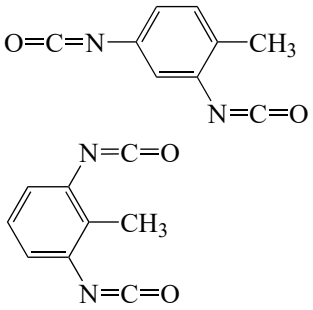
BAT value (2020)	**5 µg Σ 2,4- and 2,6-TDA (after hydrolysis)/g creatinine** Sampling time: end of exposure or end of shift
MAK value (2020)	**0.001 ml/m³ (ppm) ≙ 0.007 mg/m³**
Carcinogenicity	–
Absorption through the skin	–
Sensitization (2014)	Sah
Prenatal toxicity (2020)	Pregnancy Risk Group C
Germ cell mutagenicity	–
Synonyms of 2,4-toluene diisocyanate	2,4-Diisocyanato-1-methylbenzene 2,4-Diisocyanatotoluene 4-Methyl-m-phenylene diisocyanate Toluene-2,4-diisocyanate
Synonyms of 2,6-toluene diisocyanate	1,3-Diisocyanato-2-methylbenzene 2,6-Diisocyanatotoluene 2-Methyl-m-phenylene diisocyanate Toluene-2,6-diisocyanate
CAS numbers	2,4-TDI: 584-84-9 2,6-TDI: 91-08-7 TDI, mixture: 26471-62-5
Formula	 $C_9H_6N_2O_2$

Toluene diisocyanate (TDI) is one of the most important isocyanates worldwide. It is used in large quantities in the production of flexible polyurethane foam. TDI is generally used as a technical isomer mixture. The main components are 2,4- and 2,6-TDI. The ratio of 2,4- to 2,6-TDI in the isomer mixture is usually either 80:20% or 65:35%.

Information on the formation of toluenediamine (TDA) from 2,4- and 2,6-TDI in the air: In a study on the formation of TDA from 2,4- and 2,6-TDI in the air, no 2,4- + 2,6-TDA was detected in the air in a concentration range from 0.36 mg TDI/m³ to 4.3 mg TDI/m³ (temperature 27 °C, humidity 7% to 70%) (Holdren et al. 1984). During the generation of air concentrations of 2,4- and 2,6-TDI, the concentration of 2,4- + 2,6-TDA in the air was also determined. In a concentration range of 20 to 50 µg 2,4- + 2,6-TDI/m³ no 2,4- + 2,6-TDA was detected in the air. The detection limit was 0.2 to 0.5 µg 2,4- + 2,6-TDA/m³ (Brorson et al. 1989). Likewise, no 2,4- + 2,6-TDA (detection limit 0.5 µg/m³) was detected in the air in a study with test persons after exposure to 40 µg 2,4- + 2,6-TDI/m³ (Skarping et al. 1991).

1 Metabolism and Toxicokinetics

TDI preferentially forms adducts with NH_2, OH and SH groups of proteins. Isocyanates can be hydrolysed to form the corresponding amines or carbamic acid esters, which react with isocyanate (and moisture) in a sequence of further reaction steps to form complex polyurea mixtures. Such polymerized, mostly precipitated material of high molar mass is removed by mucociliary clearance, swallowed and excreted via the gastrointestinal tract. The formation of TDA is pH dependent. At a pH of 7, little TDA is formed in the lungs. In the stomach, comparatively much more TDA is produced due to the low pH in the range of 2. Studies indicate an overall low dermal absorption of TDI. The systemic availability of the substance or of its active metabolite TDA seems to be considerably reduced due to the high reactivity of TDI and its affinity to structural components of the skin. However, it should be considered that high or prolonged dermal exposure may possibly lead to or contribute to respiratory sensitization (Hartwig and MAK Commission 2021).

In addition to the binding of TDI to macromolecules in blood plasma, binding to haemoglobin also occurs in mammals (Mhike et al. 2016).

In one volunteer exposed for 90 minutes to an average of 78 µl 2,4-TDI/m^3, TDA was released from a purified haemoglobin fraction after hydrolysis even 45 days after exposure. The highest value was measured 14 days after the end of exposure (Wilson 1995).

Metabolism and toxicokinetics are described in detail in the MAK documentation of 1999 (translated in Greim 2003), more recent studies in the MAK documentation of 2021 (Hartwig and MAK Commission 2021).

2 Critical Toxicity

At the workplace, TDI can be taken up by inhalation or skin contact. From an occupational health point of view, the effect of TDI on the respiratory tract is of primary importance. After inhalation exposure, coughing, bronchospasm, tracheitis, bronchitis, bronchiolitis obliterans, bronchopneumonia and pulmonary oedema have been reported. It is known that exposure to TDI can lead to a specific bronchial hypersensitivity ("isocyanate asthma", early type, late type or dual type) (Moller et al. 1986). Both specific, IgE-mediated and non-specific mechanisms are held responsible for this. Occasionally, isolated hypersensitivity after a single high exposure has been described and classified as reactive airways dysfunction syndrome (RADS) (Shakeri et al. 2008). The induction of sensitization is individually dose-dependent. Using a variety of exposure patterns (variation of concentration and duration) in TDI-sensitized subjects, it has been shown that the total dose and not only the concentration or duration is of decisive importance for the induction of an asthmatic reaction (Vandenplas et al. 1999). It has also been described that massive, extensive skin contact with isocyanates can result in isocyanate asthma (Bello et al. 2007).

From the three available cohort studies, no reliable evidence of a carcinogenic effect in humans can be deduced (Mikoczy et al. 2004; Pinkerton et al. 2016; Sorahan and Nichols 2002). In addition, no substance-related increased tumour incidences in rats and mice after inhalation exposure to TDI occurred. A possible carcinogenic potential of TDI depends crucially on the extent of TDA formation in vivo. From animal experiments (Timchalk et al. 1994) it can be deduced that 1.3% of the TDI is metabolized to TDA after inhalation. Assuming that this rate of metabolism also applies to humans, the amount of TDA formed after exposure at the MAK value of 7 µg TDI/m^3 (0.001 ml/m^3) is many times lower than that after oral administration of the carcinogenic dose of 60 mg/kg body weight, which is why TDI was not classified as a carcinogen (Hartwig and MAK Commission 2021). A detailed description of the toxicity of TDI can be found in the MAK documentations (Greim 2003; Hartwig and MAK Commission 2021).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

There are several studies with data on both external exposure to TDI and internal exposure to 2,4-/2,6-TDA in urine (see Table 1).

In a study with nine men (age 35–45 years) from TDI monomer production, TDI concentrations in the air during the 8-hour shift and TDA levels in post-shift urine were determined. The TDI air values ranged from 9.5 to 94 µg 2,4-/2,6-TDI/m³, with 2,6-TDI accounting for 42%–87%. Twenty percent of the absorbed amount was metabolized to TDA, whereby absorption through the skin was also assumed. After an 8-hour shift, between 6.5 and 31.7 µg TDA/g creatinine was determined in urine. There was a linear correlation between TDI in the air and TDA in urine (Maître et al. 1993).

In a collective of 81 employees (age 18–63 years, 66 men, 15 women), the median TDI exposure was 4 µg/m³ for 2,4- and 2,6-TDI (personal measurement). A non-exposed control group of 121 persons was included. Urine samples were collected within the last four hours on the working day on which air concentrations were also determined. The median urine level was 9.7 µg TDA/l; a linear relationship between external and internal exposure was found (Sennbro et al. 2004).

In a collective of 18 male factory workers, 2,4-/2,6-TDI concentrations were measured on an individual basis and correlated with urinary concentrations of 2,4- and 2,6-TDA. Data were analysed separately for pre- and post-shift, and for 2,4- and 2,6-TDA. No 2,4- or 2,6-TDA was detected in the urine of a concomitant control group of 20 persons not exposed to TDI. The individually determined air and urine concentrations were not reported, nor were mean values given. The data were evaluated under different corrections (creatinine level, specific gravity). A linear relationship between external and internal exposure was observed for both the pre-shift and post-shift values (Sakai et al. 2005).

In a study of 400 workers in five polyurethane factories in Iran exposed to up to 81 µg TDI/m³, mean urinary TDA concentrations (post-shift) of 2.95 to 3.2 µmol/mol creatinine were measured in 100 samples. The control group consisted of 100 office workers. The authors state that the measured air concentrations correlated linearly with the urinary TDA concentrations. Individual values were not reported (Mirmohammadi et al. 2009).

In a factory where polyurethane foam blocks were produced, out of 16 factory workers (age 25–53 years), who also used respiratory protection and gloves for a short period of time, eight persons were exposed to an average of 20 µg TDI/m³ (personal measurement) in the foam production area. The sum of 2,4- and 2,6-TDA concentrations in urine was determined at the beginning of the working week and after four working days before and after the shift. At the beginning of the week, TDA concentrations in urine of eleven persons from the foam production area averaged 2.65 ± 1.96 µg TDA/g creatinine, after four days the pre-shift value was 4.32 ± 3.12 µg TDA/g creatinine and the post-shift value was 9.19 ± 6.09 µg/g. This showed an accumulation of TDA in urine over the working week. The air concentrations of the sum of 2,4- and 2,6-TDI correlated linearly with the urinary TDA concentrations at the end of the shift (De Palma et al. 2012).

Average 2,4-/2,6-TDI concentrations of 39.5 µg/m³ were determined on Friday in nine factory workers by personal measurements. Urine samples were collected during four representative shifts on two consecutive Fridays, both before and after the shift, and additionally after the exposure-free weekend on each Monday before and after the shift. Urinary (post-shift) TDA concentrations were 37.46 µg/l on average. After double logarithmic plotting the air concentration of TDI during the shift against the difference between the post-shift TDA value in urine and the pre-shift TDA value, a linear correlation was obtained (r = 0.816) (Geens et al. 2012).

In the following studies no regression equations are given; these are briefly mentioned here for the sake of completeness.

In 17 employees in flexible foam production, a total of 133 air concentrations were determined by personal and stationary measurements for 5 to 250 minutes on days 2 and 3 of a working week. Urine samples were collected at the beginning, middle and end of the shift. A good correlation between TDI concentrations in workplace air and TDA

concentrations in post-shift urine was obtained by multiplying the sampling times by the observed concentrations (Kääriä et al. 2001).

In various polyurethane processing operations, 21 employees were exposed to < 1.75 up to a maximum of 14 µg TDI/m³, determined by personal and stationary measurements. On two consecutive days, mainly the second and third day of the working week, the air concentrations were measured and the concentrations of TDA in urine were determined on Monday morning, before and after the shift. The total TDA concentrations over all shifts were in the range of < 0.02 to 0.76 nmol/mmol creatinine (Rosenberg et al. 2002).

The 136 employees from a total of eleven polyurethane foam-producing companies were exposed to an average of up to 18.2 µg/m³ (2,4-TDI) and 0.07 to 25.2 µg/m³ (2,6-TDI) (personal measurement). For the sum of both isomers a concentration range of 0.028 to 36.4 µg/m³ was given (person-related, eight hours). In urine, concentrations of up to 623 nmol 2,4-TDA/l (detection limit: 0.41 nmol/l) and up to 353 nmol 2,6-TDA/l, and in plasma up to 254 nmol 2,4-TDA/l and up to 509 nmol 2,6-TDA/l were determined. The authors state that personal air concentrations of TDI correlated well with urine and plasma concentrations of TDA (Littorin et al. 2007).

In polyurethane foam-producing factories, 24 employees were examined. Six of the workers were exposed only to TDI in the range of 0.4 to 29 µg 2,4-TDI/m³ and 3.6 to 58 µg 2,6-TDI/m³ (personal measurement). Urine and blood samples were collected on Monday morning before the working week. Urinary TDA concentrations in these workers ranged from 0.5 to 1.0 µg 2,4-TDA/l and 0.8 to 4.7 µg 2,6-TDA/l urine. Plasma samples were in the range from 0.5 to 2.0 µg 2,4-TDA/l plasma and 2.0 to 12 µg 2,6-TDA/l plasma. A good correlation between TDA plasma levels and TDA urine levels was observed (Tinnerberg et al. 2014).

No correlation between TDI concentrations in workplace air and TDA levels in urine was observed in 20 workers (age 23–58) in a polyurethane foam factory. Urinary TDA concentrations were measured before and after the shift. The authors suggest that no correlation could be found due to the respiratory protection used (Świerczyńska-Machura et al. 2015).

Tab. 1 TDA concentrations in the urine of persons occupationally exposed to TDI

Persons	TDI in air [µg/m³]		TDA in urine		Regression equation	TDA in urine at 7 µg/m³	References
(n)	Range	Mean value	Range	Mean value		[µg/g crea]	
9	9.5–94	n. d.	6.5–31.7 µg/g crea	15.7 ± 8.3 µg/g crea	$\log Y$ [µg/g crea] = 0.5795 $\log X$ [µg/m³] + 0.3278; r = 0.91	**6.57**	Maître et al. 1993
81	< 0.02–44	median: 4	0.1–162 µg/l	median: 9.7 µg/l, 6.9 µg/g crea	Y_{TDA} [µg/l] = 2.2 X [µg/m³] + 0.1	**12.9**	Sennbro et al. 2004
18	n. d.		n. d.	n. d.	$Y_{2,4\text{-TDA}}$ [µg/g crea] = 3.2 X [ppb] + 0.39; r = 0.64 $Y_{2,6\text{-TDA}}$ [µg/g crea] = 6.6 X [ppb] –1.43; r = 0.91	2,4-TDA: 3.59 2,6-TDA: 5.17 sum: **8.76**	Sakai et al. 2005
100[a)]	53–81	67	n. d.	2.95–3.20 µmol/mol crea	Y_{TDA} [µmol/mol crea] = 0.028 X [µg/m³] + 1.666; r = 0.88	**2.01**	Mirmohammadi et al. 2009
16	9.04–64.96[b)]	20.22[b)]	n. d.	9.19 ± 6.09 µg/g crea[c)]	$Y_{2,4+2,6\ TDA}$ [µg/g crea] = 0.314 $X_{2,4+2,6\ TDI}$ [µg/m³] + 2.185, r^2 = 0.829	**4.4**	De Palma et al. 2012
9	10.40–141.90	39.45	pre-shift: 3.6–19.5 µg/l post-shift: 10–142.6 µg/l	pre-shift: 10.95 µg/l post-shift: 37.46 µg/l	Y_{TDA} [µg/g crea] = 0.547 X [µg/m³] – 1.636	**2.19**	Geens et al. 2012

Tab. 1 *(continued)*

Persons	TDI in air [µg/m³]		TDA in urine		Regression equation	TDA in urine at 7 µg/m³	References
(n)	Range	Mean value	Range	Mean value		[µg/g crea]	
136	2,4-TDI: < 18.2; 2,6-TDI: 0.07–25.2 sum: 0.028–36.4	n. d.	2,4-TDA: 0.41 nmol/l (LOD)–623 nmol/l 2,6-TDA: 0.41 nmol/l (LOD)–353 nmol/l	n. d.	qualitative correlation		Littorin et al. 2007
17	factory 1: < 0.2–230 factory 2: < 0.2–41	1.6–76 1.7–16	factory 1: 0.11–39 nmol/mmol crea factory 2: < 0.05–7.1 nmol/mmol crea	n. d. n. d.	good correlation after multiplying the sampling times with the observed concentrations		Kääriä et al. 2001
21	< 1.75–14	n. d.	< 0.02–0.76 nmol/mmol crea	0.23 nmol/mmol crea	n. d.		Rosenberg et al. 2002
6[d]	2,4-TDI: 0.4–29 2,6-TDI: 3.6–58	n. d.	2,4-TDA: 0.5–1.0 µg/l 2,6-TDA: 0.8–4.7 µg/l	median 2,4-TDA: 0.5 µg/l median 2,6-TDA: 1.7 µg/l	good correlation between TDA plasma levels and TDA urine levels		Tinnerberg et al. 2014
20	n = 10: 0.6–11.3 n = 3: 0.2–6.5 n = 2: 9.9–41.5 n = 5: 0.3–58.7	3.7 3.6 25.7 26.3	< LOD–1.9 µmol/mol crea 0.6–2.1 µmol/mol crea 1.7–3.9 µmol/mol crea 0.2–2.9 µmol/mol crea	0.6 µmol/ mol crea 1.1 µmol/mol crea 3.0 µmol/mol crea 1.0 µmol/mol crea	no correlation, probably due to use of respiratory protection		Świerczyńska-Machura et al. 2015

[a] 400 workers examined, samples from 100 workers; [b] n = 8; [c] n = 11; [d] 24 workers in the study, 6 exposed only to TDI
crea: creatinine; LOD: limit of detection; n. d.: no data

3.2 Relationship between internal exposure and effects

It is not possible to establish a dose–response relationship for the concentration of TDA in urine. The detection of 2,4-/2,6-TDA in urine should be considered solely as an exposure marker. The detection of TDI-specific IgE can be seen as an effect marker, even if no correlation to the level of exposure or effects (symptoms such as runny nose, cough, bronchial asthma) could be established so far.

4 Selection of Indicators

The detection of 2,4-/2,6-TDA after hydrolysis in urine has proven to be effective in detecting TDI exposure (Brorson et al. 1991; Geens et al. 2012; Leng et al. 2015; Lind et al. 1996; Rosenberg et al. 2002; Sennbro et al. 2004). Based on the marker TDA, however, it is not possible to distinguish between simultaneous exposure to TDI and TDA.

Another marker of TDI exposure is the corresponding haemoglobin adduct in the blood (Mhike et al. 2016; Wilson 1995). This allows the exposure of the last three months to be detected. However, the few data currently available are not sufficient for the derivation of a limit value.

5 Analytical Methods

For the determination of 2,4-/2,6-TDA in urine, tested methods of the working group "Biomonitoring" are available (Cocker et al. 2017; Lewalter et al. 1994, 2000). GC-MS methods have been developed on the basis of these methods (Sennbro et al. 2003). Urine is hydrolysed with concentrated hydrochloric acid or sodium hydroxide to produce 2,4-TDA as well as 2,6-TDA. The diamines are extracted with toluene and then derivatised (for example with heptafluorobutyric anhydride). The detection limit for TDA is 0.1 µg/l in urine.

6 Background Exposure

A biological reference value (BAR) has not yet been established for either 2,4-TDI (Nasterlack 2010) or 2,4-TDA (Nasterlack 2016). In a collective of 120 unexposed individuals the median TDA value was below the detection limit of 0.1 µg/l, the maximum value was 0.4 µg/l (Sennbro et al. 2005).

7 Evaluation

In some of the available studies, equations are given for the correlation between TDI concentrations in the air and 2,4-/2,6-TDA concentrations in urine:

The study by Maître et al. (1993) showed a good correlation between external and internal exposure (r = 0.91). The equation was given as log Y = 0.5795 log X + 0.3278. If the MAK value of 7 µg TDI/m³ is taken as a basis, the TDA value in urine is 6.57 µg TDA/g creatinine.

In the study by Sennbro et al. (2004), the equation for the correlation between TDI values in the air and TDA values in urine was given as Y_{TDA} [µg/l] = 2.2 X + 0.1. For an exposure at the MAK value of 7 µg TDI/m³, the TDA value in urine is 15.5 µg/l urine. With an assumed median creatinine level of 1.2 g/l and a conversion factor of 0.83 (Bader et al. 2020), this results in a TDA value of 12.9 µg TDA/g creatinine.

In the study by Sakai et al. (2005), two equations for exposure to 2,4- and 2,6-TDA were given: $Y_{2,4\text{-TDA}}$ [µg/g creatinine] = 3.2 X [ppb] + 0.39 and $Y_{2,6\text{-TDA}}$ [µg/g creatinine] = 6.6 X [ppb] – 1.43. Assuming a TDI exposure of 7 µg/m³ (≈ 1 ppb), values for 2,4-TDA of 3.59 µg/g creatinine and for 2,6-TDA of 5.17 µg/g creatinine are obtained, which results in a sum value of 8.76 µg TDA/g creatinine.

In the study by Mirmohammadi et al. (2009), a correlation equation was given with Y_{TDA} [µmol/mol creatinine] = 0.028 X + 1.666. At a TDI exposure at the level of the MAK value of 7 µg/m³, the regression equation yields a value of 1.862 µmol TDA/mol creatinine. At a molar mass for TDA of 122.17 g/mol and for creatinine of 113.12 g/mol, this corresponds to 2.01 µg TDA/g creatinine.

De Palma et al. (2012) reported the following equation for the correlation between external TDI and internal TDA exposure in their study: $Y_{2,4+2,6\ TDA}$ [µg/g creatinine] = 0.314 $X_{2,4+2,6\ TDI}$ [µg/m³] + 2.185. For an inhalation exposure at the level of the MAK value of 7 µg/m³, the resulting value is 4.4 µg/g creatinine.

Geens et al. (2012) described the following correlation equation in their study: Y_{TDA} [µg/g creatinine] = 0.547 X [µg/m³] – 1.636. This correlation results in a urinary TDA value of 2.19 µg TDA/g creatinine for an inhalation exposure of 7 µg/m³ (≈ 1 ppb).

The studies described here give an average value of 6.13 µg 2,4/2,6-TDA/g creatinine. This value is in the same order of magnitude as the Biological Exposure Index (BEI) of 5 µg/g creatinine of the American Conference of Governmental Industrial Hygienists (ACGIH 2016) and as the Biological Monitoring Guidance Value (BMGV) of 1 µmol isocyanate-derived diamine/mol creatinine (corresponding to 4 µg/g creatinine) of the HSE's Health & Safety Laboratory (Cocker 2011).

On this basis, in correlation to the MAK value of 7 µg/m³

a BAT value of 5 µg Σ 2,4- and 2,6-TDA (after hydrolysis)/g creatinine

is derived. Sampling takes place at the end of exposure or end of shift.

TDI were assigned to Pregnancy Risk Group C. Since the BAT value was derived in correlation to the MAK value, no prenatal toxicity is to be expected if the BAT value of 5 µg Σ 2,4- und 2,6-TDA (after hydrolysis)/g creatinine is adhered to.

8 Interpretation

The BAT value relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l (Bader et al. 2016). As a rule, where urine samples are outside the above-mentioned limits, a repetition of the measurement in normally hydrated test persons is recommended.

Notes

Competing interests

The established rules and measures of the commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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