ANNEX 1

in support of the Committee for Risk Assessment (RAC) for evaluation of limit values for diisocyanates at the workplace

ECHA/RAC/A77-O-0000006826-64-01/F

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LITERATURE

This report is based on international evaluations such as: (DECOS, 2018, ATSDR, 2018, AGS, 2006, DFG, 2003, DFG, 2008, IARC, 1999, IPCS, 1987, Montelius, 2001, OECD, 2001, OEHHA, 2019, ACGIH, 2016). In addition, information is used from ECHA's published opinion and Annex I on the Annex XV dossier proposing restrictions for diisocyanates (ECHA 2018). This has been complemented by a review of the REACH registrations and a literature search of published papers from the last ten years, with the exception of the inclusion of also some older articles in Chemical Agent Identification and Physico-Chemical Properties.

1. Chemical Agent Identification and Physico-Chemical Properties

1.1 Diisocyanates

Isocyanates are organic compounds that contain one or more functional groups with the molecular formula -N=C=O. The term polyisocyanate is commonly used when referring to an isocyanate containing multiple isocyanate functional groups. The isocyanates considered in this report have two isocyanate functional groups and are referred to as diisocyanates.

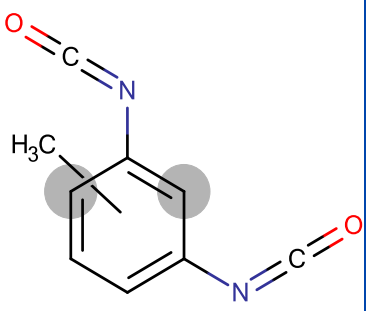
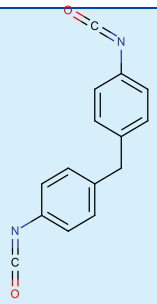
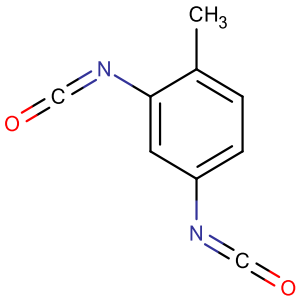
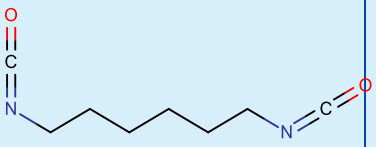
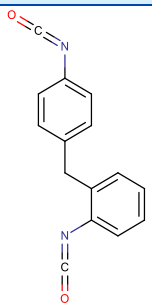
Diisocyanates are the most common group of isocyanates used at the workplace (ECHA, 2018a). They are highly reactive compounds and undergo rapid exothermic reactions with all kinds of nucleophiles. In the reactive group (R-N=C=O) R can be aliphatic, cycloaliphatic or an aromatic group. Aromatic isocyanates are more reactive than aliphatic isocyanates.

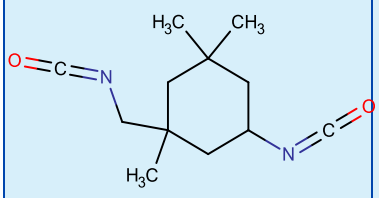
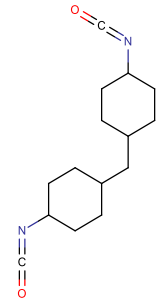
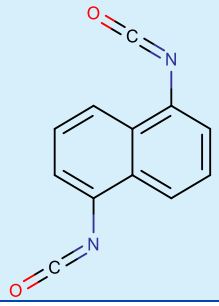
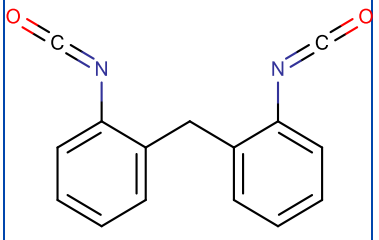
The diisocyanates considered in this proposal are those for which safety data are available, for which use at higher tonnages is known and which data could be extracted from registration dossiers.

In total there are 28 diisocyanates either registered or with harmonised classification. The substance identification and physico-chemical properties are described in tabulated summaries in Appendix 1 (Table 33 and Table 34).

There are 11 registered diisocyanates, which account for > 99.9 % of the registered tonnage and which are individually registered for at least 1 000 t/a. For 9 out of these 11 diisocyanates, a harmonised classification is available (see section 0). The substance identification and physico-chemical properties of these 11 diisocyanates are described in Table 1 and Table 2.

Table 1: Substance identification

Structure	EC/list number	CAS	Substance name	Abbreviation
	247-722-4	26471-62-5	m-tolylidene diisocyanate; toluene diisocyanate; reaction mass of 2,4-diisocyanato-1-methylbenzene (2,4-TDI) and 2,6-diisocyanato-1-methylbenzene (2,6-TDI)	TDI
	202-966-0	101-68-8	4,4'-methylenediphenyl diisocyanate	4,4'-MDI
	209-544-5	584-84-9	4-methyl-m-phenylene diisocyanate; 2,4-toluene diisocyanate	2,4-TDI
	212-485-8	822-06-0	hexamethylene diisocyanate	HDI
	227-534-9	5873-54-1	o-(p-isocyanatobenzyl)phenyl isocyanate; 2,4’-methylenediphenyl diisocyanate	2,4'-MDI

Structure	EC/list number	CAS	Substance name	Abbreviation
	223-861-6	4098-71-9	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	IPDI
	225-863-2	5124-30-1	4,4'-methylenedicyclohexyl diisocyanate	hydrogenated 4,4'-MDI (H12-MDI)
	221-641-4	3173-72-6	1,5-naphthylene diisocyanate	1,5-NDI
	219-799-4	2536-05-2	2,2'-methylenediphenyl diisocyanate	2,2'-MDI

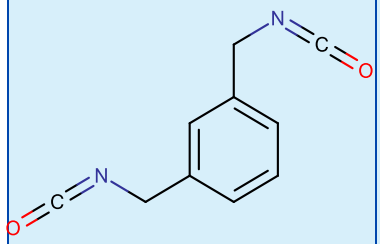
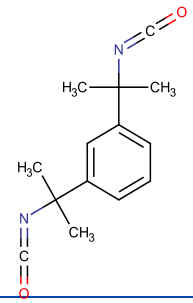
Structure	EC/list number	CAS	Substance name	Abbreviation
	222-852-4[1]	3634-83-1	1,3-bis(isocyanatomethyl)benzene	m-XDI
	220-474-4[1]	2778-42-9	1,3-bis(1-isocyanato-1-methylethyl)benzene	m-TMXDI

Table 2: Physico-chemical properties

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³[2]
TDI	247-722-4	m-tolylidene diisocyanate	21 °C	251 °C	1.5 Pa (20 °C)[r]	7.12
4,4'-MDI	202-966-0	4,4'-methylenediphenyl diisocyanate	38 °C	314 °C	$1.2 \cdot 10^{-3}$ Pa (25 °C)	10.23
2,4-TDI	209-544-5	4-methyl-m-phenylene diisocyanate	21 °C	251 °C	2.8 Pa (25 °C)	7.12
HDI	212-485-8	Hexamethylene diisocyanate	-67 °C	255 °C	2.2 Pa (25 °C)	6.88
2,4'-MDI	227-534-9	o-(p-isocyanatobenzyl)phenyl isocyanate	34-38 °C[r]	decomp 241 °C[r]	$9.7 \cdot 10^{-4}$ Pa (25 °C)	10.23

[1] No harmonised classification available

[2] The conversion factor is derived from the assumption of ideal gas behaviour as

$$1\ ppm\ in \frac{mg}{m3} = \left[molar\ weight\ in \frac{g}{mol}\right] \cdot \frac{1000}{10^6} \cdot \frac{[pressure\ in\ Pa]}{[temperature\ in\ K] \cdot \left[gas\ constant = 8.314 \frac{m^3 \cdot Pa}{K \cdot mol}\right]}$$

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³[32]
IPDI	223-861-6	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	-60 °C	158-159 °C (15 Torr)	0.34 Pa (25 °C)	9.09
H12-MDI	225-863-2	4,4'-methylenedicyclohexyl diisocyanate	no crystalisation	167-168 °C (1.5 Torr)	$2.3 \cdot 10^{-3}$ Pa (25 °C)	10.73
1,5-NDI	221-641-4	1,5-naphthylene diisocyanate	130-132 °C	220-221 °C (40 Torr)	0.06 Pa (25 °C)	8.59
2,2'-MDI	219-799-4	2,2'-methylenediphenyl diisocyanate	43 °C[r]	270 °C[r]	$7.8 \cdot 10^{-4}$ Pa (25 °C)	10.23
m-XDI	222-852-4	1,3-bis(isocyanatomethyl)benzene	-7 °C[r]	126 °C (1 Torr)	0.2 Pa (25 °C)	7.69
m-TMXDI	220-474-4	1,3-bis(1-isocyanato-1-methylethyl)benzene	4 °C[r]	249 °C[r] 106 °C	0.8 Pa (25 °C)	9.99

For the calculation of the corresponding NCO concentration [mass/volume air] the following formula is used:

$$conc_{NCO}\left[\frac{mg}{m^3}\right] = conc_{diisocyanate}\left[\frac{mg}{m^3}\right] \cdot \frac{(number\ of\ NCO\ groups)(molecular\ weight\ of\ isocyanate = 42)\left[\frac{g}{mol}\right]}{(total\ diisocyanate\ molecular\ weight)\left[\frac{g}{mol}\right]}$$

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

There are 11 entries of harmonised classification of diisocyanates in Annex VI of the CLP Regulation 1272/2008. The relevant diisocyanates considered in this proposal, (for which data are available and for which use at a higher tonnages is known), there are nine diisocyanates which have a harmonised classification (Table 3) and two m-XDI (222-852-4) and m-TMXDI (220-474-4) which have no harmonised classification.

The nine diisocyanates with harmonised classification are all are classified as respiratory and eight of these are both respiratory and skin sensitisers. Five of these substances are classified as carcinogenicity category 2- suspected of causing cancer.

Table 3: EU CLP Reg classification: Summary of diisocyanates

Index No	International Chemical Identification	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)	Notes [3]
607-184-00-7	S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate	402-290-8[4]	85702-90-5	Flam. Liq. 3 Resp. Sens. 1 Skin Sens. 1	H226 H334 H317	
615-005-00-9	4,4'-methylenediphenyl diisocyanate; diphenylmethane-4,4'-diisocyanate [1] 2,2'-methylenediphenyl diisocyanate; diphenylmethane-2,2'-diisocyanate [2] o-(p-isocyanatobenzyl)phenyl isocyanate; diphenylmethane-2,4'-diisocyanate [3] methylenediphenyl diisocyanate [4]	202-966-0 [1] 219-799-4 [2] 227-534-9 [3] 247-714-0[4] [4]	101-68-8 [1] 2536-05-2 [2] 5873-54-1 [3] 26447-40-5 [4]	Carc. 2 Acute Tox. 4 * STOT SE 3 STOT RE 2 * Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1	H351 H332 H335: C ≥ 5 % H373 ** H315: C ≥ 5 % H319: C ≥ 5 % H334: C ≥ 0,1 % H317	2 C

[3] Note 2: The concentration of isocyanate stated is the percentage by weight of the free monomer calculated with reference to the total weight of the mixture.

Note C: Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers. , In this case the supplier must state on the label whether the substance is a specific isomer or a mixture of isomers.

[4] Not considered for this proposal due to low tonnage.

Index No	International Chemical Identification	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)	Notes [3]
615-006-00-4	2-methyl-m-phenylene diisocyanate; toluene-2,4-di-isocyanate [1] 4-methyl-m-phenylene diisocyanate; toluene-2,6-di-isocyanate [2] m-tolylidene diisocyanate; toluene-diisocyanate [3]	202-039-0[5] [1] 209-544-5 [2] 247-722-4 [3]	91-08-7 [1] 584-84-9 [2] 26471-62-5 [3]	Carc. 2 Acute Tox. 2 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Chronic 3	H351 H330 H335 H315 H319 H334: C ≥ 0,1 % H317 H412	C
615-007-00-X	1,5-naphthylene diisocyanate	221-641-4	3173-72-6	Acute Tox. 4 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Aquatic Chronic 3	H332 H335 H315 H319 H334 H412	
615-008-00-5	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	223-861-6	4098-71-9	Acute Tox. 3 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Chronic 2	H331 H335 H315 H319 H334: C ≥ 0,5 % H317: C ≥ 0,5 % H411	2
615-009-00-0	4,4'-methylenedi(cyclohexyl isocyanate); dicyclohexylmethane-4,4'-di-isocyanate	225-863-2	5124-30-1	Acute Tox. 3 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1	H331 H335 H315 H319 H334: C ≥ 0,5 % H317: C ≥ 0,5 %	2

Index No	International Chemical Identification	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)	Notes [3]
615-010-00-6	2,2,4-trimethylhexamethylene-1,6-di-isocyanate [1] 2,4,4-trimethylhexamethylene-1,6-di-isocyanate [2]	241-001-8[5] [1] 239-714-4[5] [2]	16938-22-0 [1] 15646-96-5 [2]	Acute Tox. 3 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1	H331 H335 H315 H319 H334: C ≥ 0,5 % H317: C ≥ 0,5 %[6]	2 C
615-011-00-1	hexamethylene-di-isocyanate	212-485-8	822-06-0	Acute Tox. 3 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1	H331 H335 H315 H319 H334: C ≥ 0,5 % H317: C ≥ 0,5 %	2
615-029-00-X	2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane	411-280-2[5]		Acute Tox. 2 * Acute Tox. 4 * Skin Corr. 1B Resp. Sens. 1 Skin Sens. 1 Aquatic Chronic 3	H330 H302 H314 H334 H317 H412	
615-036-00-8	reaction product of diphenylmethanediisocyanate, toluenediisocyanate (reaction mass of isomers: 65 % 2,4- and 35 % 2,6-diisocyanate), octylamine, oleylamine and 4-ethoxyaniline (molar ratio 4:1:7:1:2)	430-940-0[5]	-	Aquatic Chronic 4	H413	
615-038-00-9	reaction product of toluenediisocyanate (reaction mass of isomers: 65 % 2,4- and 35 % 2,6-diisocyanate) and aniline (molarratio 1:2)	430-960-1[5]	-	Aquatic Chronic 4	H413	

[5] Not registered under REACH

[6] There is a known inconsistency between the specific concentration limits for Skin. Sens. and the classification. This is due to be corrected.

3. Chemical Agent and Scope of Legislation - Regulated uses of diisocyanates in the EU

The uses of diisocyanates are currently not covered by an indicative or a binding occupational exposure limit (IOEL, BOEL). However some uses of diisocyanates are covered by legislation as described in sections 3.1-3.8.

3.1 Chemical Agent Directive 98/24/EC

Diisocyanates are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of the legislation.

3.2 REACH Registrations

There are 19 substances for diisocyanates considered registered under REACH[7]. For these substances tonnage information is available as part of a REACH registration. These include, 19 substance with full registrations, and 6 substances also registered as an intermediate. Information on the registrations is available on the ECHA website[8]. Chemical Safety Reports are only available for those with a full registration.

Table 4 gives an overview of the type of registrations with tonnage in the highest quantities, for the eleven registered diisocyanates as referred to in this report. The total tonnage reported for these 11 substances represents 99.9 % of the overall tonnage reported for diisocyanates within registrations; full details are in Appendix 2.

Table 4: REACH registrations and tonnage

Abbrev.	EC Number	NAME	Intermediate registration t/a (count of registrations)	full registration t/a (count of registrations)
TDI	247-722-4	m-tolylidene diisocyanate		>100 000 (32 reg)
4,4'-MDI	202-966-0	4,4'-methylenediphenyl diisocyanate		>100 000 (55 reg)
2,4-TDI	209-544-5	4-methyl-m-phenylene diisocyanate	(<5 reg)	>100 000 (9 reg)
HDI	212-485-8	hexamethylene diisocyanate		10 000-100 000 (19 reg)
2,4'-MDI	227-534-9	o-(p-isocyanatobenzyl)phenyl isocyanate		10 000-100 000 (5 reg)
IPDI	223-861-6	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate		10 000-100 000 (20 reg)

[7] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

[8] ECHA https://echa.europa.eu/information-on-chemicals/registered-substances

Abbrev.	EC Number	NAME	Intermediate registration	full registration
H12-MDI	225-863-2	4,4'-methylenedicyclohexyl diisocyanate		10 000-100 000 (20 reg)
1,5-NDI	221-641-4	1,5-naphthylene diisocyanate		1000-10 000 (<5 reg)
2,2'-MDI	219-799-4	2,2'-methylenediphenyl diisocyanate		1000-10 000 (<5 reg)
m-XDI	222-852-4	1,3-bis(isocyanatomethyl)benzene		1000-10 000 (<5 reg)
m-TMXDI	220-474-4	1,3-bis(1-isocyanato-1-methylethyl)benzene		1000-10 000 (<5 reg)

3.3 Authorised uses under Annex XIV of REACH

Diisocyanates are not listed in Annex XIV of REACH ("Authorisation List"). Therefore there are no authorised uses for diisocyanates.

3.4 Restricted uses under Annex XVII of REACH

The following restriction on MDI is listed in entry 56 of Annex XVII:

> 1. Shall not be placed on the market after 27 December 2010, as a constituent of mixtures in concentrations equal to or greater than 0,1 % by weight of methylenediphenyl diisocyanate (MDI) for supply to the general public, unless suppliers shall ensure before the placing on the market that the packaging:
>
> (a) Contains protective gloves which comply with the requirements of Council Directive 89/686/EEC (*);
>
> (b) Is marked visibly, legibly and indelibly as follows, and without prejudice to other Community legislation concerning the classification, packaging and labelling of substances and mixtures:
>
> '— Persons already sensitised to diisocyanates may develop allergic reactions when using this product.
>
> — Persons suffering from asthma, eczema or skin problems should avoid contact, including dermal contact, with this product.
>
> — This product should not be used under conditions of poor ventilation unless a protective mask with an appropriate gas filter (i.e. type A1 according to standard EN 14387) is used.'
>
> 2. By way of derogation, paragraph 1(a) shall not apply to hot melt adhesives.

In 2016 a REACH Annex XV dossier on the restriction of diisocyanates was submitted to ECHA by Germany[9]. RAC and SEAC adopted in March 2018 its final opinion to restrict the use of diisocyanates at the workplace in support of the restriction proposal by Germany,

[9] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180876053

primarily to manage the use of diisocyanates through training of workers. The main goal of this restriction proposal is to prevent new cases of respiratory sensitisation among all workers and professionals who may be exposed to diisocyanates in the workplace. The final opinion and accompanying documents are published on ECHA's website (ECHA, 2018a)[10].

3.5 Plant Protection Products Regulation (EC) 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009 which are based on or include diisocyanates. Diisocyanates are not listed as active substances in Annex I to Directive 91/414/EEC.

3.6 Biocidal Products Regulation (EC) 528/2012

There have been no biocidal products authorised under Regulation (EU) No 528/2012 which are based on or include diisocyanates, nor has there been an active substance evaluation on diisocyanates. Diisocyanates are not listed as active substances in Annex I of Regulation (EU) No 528/2012.

3.7 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

There are no authorisations for use of diisocyanates in human or veterinary medicines.

3.8 Plastics Regulation (EC) 10/2011

Annex I of Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food as regards information in the supply chain lists the following diisocyanates: mixture of (40 % w/w) 2,2,4-trimethylhexane-1,6-diisocyanate and (60 % w/w) 2,4,4-trimethylhexane-1,6-diisocyanate; 2,6-toluene diisocyanate; diphenylmethane-4,4'-diisocyanate; 2,4-toluene diisocyanate; hexamethylene diisocyanate; 1,5-naphthalene diisocyanate; diphenylether-4,4'-diisocyanate; dicyclohexylmethane-4,4'-diisocyanate; diphenylmethane-2,4'-diisocyanate and 2,4-toluene diisocyanate dimer. For these substances it is required that isocyanate migration from plastic packaging should not be analytically detectable in the food, and that the content of isocyanates in the food plastic material must not exceed 1 mg/kg in the final product expressed as isocyanate moiety.

3.9 Cosmetic Products Regulation (EC) 1223/2009

Toluene 2,6-diisocyanate, toluene 2,4-diisocyanate and toluene diisocyanate are included in the list of substances prohibited in cosmetic products (Annex II) of the Commission Regulation 1223/2009 on cosmetic products.

[10] The Commission Regulation (EU) 2020/1149 amending the Annex XVII to this regulation as regards diisocyanates is published in the Official Journal on 3 August, 2020.

4. Existing Occupational Exposure Limits (OELs)

In various EU Member States as well as outside the EU OEL's for diisocyanates are established at a national level. Some MS have established limit values for the diisocyanates as a group; these are presented in Table 5 but the list should not be considered as exhaustive.

Some member states have also established limit values for individual diisocyanates. Table 6, Table 7 and Table 8 present the OELs for the three diisocyanates having more often a limit value established in EU (4,4' MDI, 2, 4 TDI and HDI). Values for other diisocyanates can be found at: http://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp

Table 5: Existing Occupational Exposure Limits (OELs) for diisocyanates

Country/ Organisation	Diisocyanates TWA -8 hrs		Diisocyanates Short term -15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Finland				0.035 (1)	OEL for Isocyanates, (as -NCO)
Ireland		0.02 (1)		0.07 (1)	As NCO
Norway		0.005		0.01	Sensitiser
Sweden	0.002		0.005		Short-term limit value, 5 minutes average value Sensitiser
Switzerland	0.005	0.02	0.005	0.02	OEL for Isocyanates, (as -NCO)
United Kingdom		0.02		0.07	OEL for Isocyanates, (as -NCO)

(1) 15 minutes reference period

Table 6: Existing Occupational Exposure Limits (OELs) for 4,4'-MDI

Country/ Organisation	4,4'-MDI TWA -8 hrs		4,4'-MDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Austria	0.005	0.05	0.01	0.1	
Belgium	0.005	0.052			
Denmark	0.005	0.05	0.01	0.1	Carcinogenicity notation
France	0.01	0.1	0.02	0.2	
Germany (AGS)		0.05 (1)		0.05 (1)	Inhalable aerosol and vapour
				0.1	Inhalable aerosol and vapour Ceiling limit value

Country/ Organisation	4,4'-MDI TWA -8 hrs		4,4'-MDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Germany (DFG)		0.05 (1)		0.05 (1)	Inhalable aerosol and vapour A momentary value of 0,1 mg/m³ should not be exceeded
Hungary		0.05		0.05	
Ireland		0.02		0.07 (1)	as NCO
Norway	0.005	0.05	0.01		Sensitiser
Poland		0.05		0.2	Ceiling limit value
Romania				0.15 (1)	
Spain	0.005	0.052			Sensitiser
Sweden	0.002	0.03	0.005	0.05	Short-term limit value, 5 minutes average value Sensitiser
USA - NIOSH	0.005	0.05	0.02 (1)	0.2	Ceiling limit value (10 min)
USA - OSHA			0.02	0.2	

(1) 15 minutes average value

Table 7: Existing Occupational Exposure Limits (OELs) for 2,4 TDI

Country/ Organisation	2,4 TDI TWA -8 hrs		2,4 TDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Austria	0.005	0.035	0.02	0.17	
Belgium	0.005	0.037	0.02 (1)	0.14 (1)	
Denmark	0.005	0.035	0.01	0.07	Carcinogenicity notation
France	0.01	0.08	0.02	0.16	
Germany (AGS)	0.005	0.035	0.005 (1)	0.035 (1)	Inhalable aerosol and vapour
			0.02	0.14	Inhalable aerosol and vapour Ceiling limit value
Hungary				0.035	

Country/ Organisation	2,4 TDI TWA -8 hrs		2,4 TDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Ireland		0.001		0.003 (1)	as NCO
Latvia		0.05			
Norway	0.005	0.035	0.01		Sensitiser
Poland		0.007		0.021	
Romania	0.009	0.07	0.02 (1)	0.15 (1)	
Spain	0.005	0.036	0.02	0.14	Sensitiser
Sweden	0.002	0.014	0.005	0.04	Sensitiser Carcinogenicity notation
USA - ACGIH	0.001	0.007	0.005	0.035	Skin and respiratory sensitiser
USA - OSHA			0.02	0.14	

(1) 15 minutes average value

Table 8: Existing Occupational Exposure Limits (OELs) for HDI

Country/ Organisation	HDI TWA -8 hrs		HDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Austria	0.005	0.035	0.005	0.035	
Belgium	0.005	0.034			
Denmark	0.005	0.035	0.01	0.07	
France	0.01	0.075	0.02	0.15	
Germany (AGS)	0.005	0.035	0.005 (1)	0.035 (1)	Inhalable aerosol and vapour
			0.01	0.07	Inhalable aerosol and vapour Ceiling limit value
Germany (DFG)	0.005 (1)	0.035 (1)	0.005 (1)(2)(3)	0.035 (1)(2)(3)	Inhalable aerosol and vapour A momentary value of 0.01 ml/m³ (0.070 mg/m³) should not be exceeded.
Hungary		0.035		0.035	
Ireland	0.005				as NCO
Italy		1			
Latvia		0.05			
Norway	0.005	0.035	0.01		Sensitiser
Poland		0.04		0.08	

Country/ Organisation	HDI TWA -8 hrs		HDI Short term – 15 min		Comments
	ppm	mg/m³	ppm	mg/m³	
Romania	0.007	0.05	0.14 (1)	1 (1)	
Spain	0.005	0.035			Sensitiser
Sweden	0.002	0.02	0.005	0.03	Short-term limit value, 5 minutes average value Sensitiser
USA - NIOSH		0.035		0.14 (1)	Ceiling limit value (10 min)

(1) 15 minutes average value

Biological limit values (BLVs)

Some Member States have also published biological limit values for diisocyanates compounds. The Table 9 (non-exhaustive) shows the list of biological limit values.

Table 9: Biological limit values for diisocyanates and its compounds

Country/ Organisation	Diisocyanate(s)	Biomarker	Limit value	Comments
ACGIH	TDI; 2,4 TDI; 2,6 TDI	2,4 + 2,6- urinary toluenediamine (TDA)	0.4 µg/gcreatinine	Reference value for general population (95th percentile)
ACGIH	TDI; 2,4 TDI; 2,6 TDI	2,4 + 2,6- urinary toluenediamine (TDA)	5 µg/g creatinine	BEI value Sampling end of the shift
Germany	4,4'-MDI	diaminodiphenylmethane (MDA) in urine	10 µg/l	BLW value Sampling time: end of exposure or end of shift
Germany	HDI	hexamethylenediamin (HDA) in urine	15 µg /g creatinine	BAT value
UK	HDI, MDI, TDI, IPDI	isocyanate-derived diamine	1 µmol isocyanate-derived diamine/mol creatinine	BMGV Sampling time: At the end of the period of exposure

Notes:

BEI: Biological exposure index
BLW: BLW ("Biologischer Leit-Wert") is the amount of a chemical substance or its metabolites or the deviation from the norm of biological parameters induced by the substance in exposed humans which serves as an indicator for necessary protective measures. BLWs are assigned only for hazardous materials for which the available toxicological or occupational-medical data are insufficient for the establishment of BAT
BAT: Biological tolerance value for occupational exposures
BMGV: biological monitoring guidance value

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

Diisocyanates are important industrial chemicals including use as raw materials for all polyurethane products which are formed when an isocyanate reacts with a polyol (a compound of more than one hydroxyl group). In addition to their use in manufacturing of polyurethane foam, diisocyanates are used in surface coatings, adhesives, sealants, elastomers and textiles (DECOS, 2018).

Polyurethanes, like all plastics, are polymers. Polyurethane materials are lightweight, strong, and durable and they resist to abrasion and corrosion. This is a reason why the different forms of polyurethanes are widely used in Europe, including insulated building panels, mattresses, upholstered furniture, car seats, domestic refrigerators, freezers, composite wood panels, truck bodies and footwear (ISOPA 2014).

5.2 Production and Use Information

The 11 diisocyanates that are presented in Table 1 account for more than 99.9% of the manufactured and imported isocyanates in Europe. The most common commercial TDI (m-tolylidene diisocyanate) is a mixture of 2,4'-TDI and 2,6'-TDI (80/20 TDI or 65/35 TDI). This TDI presents already 48% of the overall used amount of isocyanates. The second highest volume is for 4,4'-MDI (29%), the third highest for 2,4'-TDI (12%) and the fourth highest for HDI (4.3%). These four substances account together about 94% of the manufactured/imported amount in Europe.

Isocyanates are typically used in the following products:

- polyurethanes foams (flexible and rigid foam)
- assembly foams (e.g. insulation panels)
- foundry cores (casting)
- coating materials (paints, lacquers, varnishes)
- adhesives and sealants
- glues
- elastomers
- pre-polymers in chemical synthesis
- engineering plastics
- polyurethane fibres /composites

There is some variation in use between different diisocyanates. However, the three most produced isocyanates (TDI, 4,4'-MDI and 2,4'-TDI) are all aromatic isocyanates and they have a similar use pattern which consists of for example, flexible and rigid foams, adhesives and sealants. Aliphatic isocyanates (HDI and IPDI) are often present in coatings and paints. However, this cannot be identified through the registration dossiers for HDI. According to the registrations it can be concluded that aliphatic isocyanates are not used in flexible and rigid foams or composites or in cleaning. Based on the registration dossiers the identified uses for different diisocyanates are presented in the Table 10.

Table 10: Identified uses for different diisocyanates from the registration dossiers.

Substance	EC No	Manufacture	Formulation	Use in coatings	Adhesives and sealants	Flexible foam	Rigid foam	Elastomers	Composites	Cleaning	Foundry	Monomer in polymer	Intermediate use
TDI	247-722-4	x	x	x + paints	x	x		x	x				X
4,4'-MDI	202-966-0	x	x	x + paints + c	x + c	x	x	x	x	x	x	x	X
2,4'-TDI	209-544-5	x	x	X	x	x		x	x			x	X
HDI	212-485-8	x	x									x ¤	X
2,4'-MDI	227-534-9	x	x	x + c	x + c	x	x + c	x	x	x	x		
IPDI	223-861-6	x	x	X	x							x	X
H12-MDI	225-863-2	x	x		x			x				x	X
NDI	221-641-4	x	x #					x				x	
2,2'-MDI	219-799-4	x	x	x + c	x + c	x	x + c		x	x	x		X
mXDI	222-852-4	x	x	X	x							x *	X
mTMXDI	220-474-4											x	

oil additives in lubricants

* optical lenses and thermoplastic

¤ thermoplastic

c=also consumer use

Comments were received during the Consultation that MDI is the most common diisocyanate in Europe and MDI market is largely driven by the use of polyurethane rigid foam for thermal insulation in the construction industry. TDI is primarily used in flexible foam production, with mattresses, upholstery and transport seats representing the main end-use applications. Both MDI and TDI are used in C.A.S.E. (Coatings, Adhesives, Sealants, Elastomers) applications, but much smaller quantities. The comments received in Consultation considered that the most workers in Europe are handling MDI containing products (>90%) while less than 5% of the workers are handling HDI and less than 3% TDI containing products. Also the ratio of industrial and professional use is much higher for MDI and HDI compared to TDI.

According to the information the information received during the published Call of Evidence, diisocyanates are used for the production of modern vehicles in a large variety of applications. The use of diisocyanates is widespread throughout the entire supply chain of the automotive industry, from the development via the production to the car workshop. The unique properties of diisocyanates make this substance group indispensable for many areas of the automotive industry. Different diisocyanates with concentrations of monomers higher than 0.1 % by weight, are processed in various applications. The following applications are widely used in the automotive industry:

- Adhesives and primers on the basis of MDI for bonding windshields in automatic and manual processes
- Adhesives and sealing compounds on the basis of MDI and IPDI in the body shop and the assembly
- Adhesives on the basis of MDI for the production of plastic parts
- Casting resins on the basis of MDI in the tool shop
- Hardener for clear coats on the basis of HDI for the manual and series painting of vehicles
- Hardeners for fillers on the basis of HDI for the manual painting of vehicles
- Polyurethane foam on the basis of MDI for acoustic insulation in the assembly

Diisocyanates are applied as well in automatic and encapsulated units as in manual operations by using appropriate technical and/or personal protective equipment.

Other comments received during the call of evidence informed that diisocyanates for production of polyurethanes are used in the European Space Sector for a variety of applications (e. g. cryogenic foams). More specifically diisocyanates are used as follows for satellites and launchers (not exhaustive list):

- Common use in commercial paint to formulate polyurethane black coatings, both electrically conductive and even non-conductive, that are used for thermal finish of equipment on board of satellites. They are largely used because they have moderate cost, good adhesion on different aluminium alloys and metal in general, are easy to apply, have medium to high environmental durability and can be also easily restored in case of local damage.

- 4,4'-Diphenylmethane Diisocyanate (MDI)) is included in low concentrations (below 1%) in a thermal control paint, which is used in a variety of space products; outside of electronic boxes, as well as antennas.

- Methylene Diphenyl Diisocyanate (MDI) is almost exclusively used in production of polyurethane foams. Polyurethane based conformal coatings (to provide electrical isolation and mechanical protection with limited outgassing) and as potting of heavy Electrical and Electronic Equipment (EEE) to provide electrical isolation and mechanical stability in high reliability electronic assemblies. Polyurethanes for the insulation of electrical power units may contain for example Toluene Diisocyanates (TDI) or Hexamethylene Diisocyanates (HDI)).

- Polyurethane insulation is widely used in the partially reusable launcher systems (for cryogenic tanks). The key properties are density before and after curing, thermal conductivity and operational temperature.

- Beside paints, primers, hardeners, polyurethane foams, diisocyanates are also applied in some adhesives and varnishes.

- Diisocyanates are also used in the production of liner and composite propellant used in propulsion.

A summary of different industries where isocyanates are used and where occupational exposure can occur are listed below (DECOS, 2018):

- The automotive industry and the shipbuilding industry (through use in paints, glues, greases, insulation, sealants and fibre bonding)
- The casting industry (through use in foundry cores)
- The building and construction industry (through use in sealants, glues, insulation material, fillers, lacquers, finishes on synthetic floorings and other applications)
- The electricity and electronics industry (through use in cable insulation, polyurethane coated circuit boards)
- The mechanical engineering industry (insulation material)
- The paints industry (lacquers)
- The plastic industry (soft and hard plastics, plastic foam and cellular plastic)
- The printing industry (inks and lacquers)
- The timber and furniture industry (adhesive, lacquers, upholstery stuffing and fabric coatings)
- The white goods industry (insulation materials)
- The textile industry (use in synthetic textile fibres)
- The medical care industry (polyurethane casts)
- The mining industry (sealants and insulating material)
- The food industry (packaging materials and lacquers)

5.3 Occupational exposure

5.3.1 General aspects of occupational exposure to diisocyanates

According the ECHA Restriction background document (ECHA, 2018a), the potential for occupational exposure to isocyanates is determined by several factors:

Volatility: One factor is the volatility of the compounds. Diisocyanates with a low molecular weight have significant vapour pressures already at room temperature. In particular toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) are common diisocyanates which can vaporise easily at ambient temperature thus leading to significant concentrations in the workplace air.

Hot processes: Higher temperatures increase the vapour pressure and thus the tendency of isocyanates to become airborne. Monomers of diisocyanates do not tend to thermally decompose. But some polyurethane material can decompose at temperatures as low as 150- 200 °C (Delebecq et al., 2013). Thermal degradation can give rise to release of the original monomeric diisocyanate but also other low molecular isocyanates or fragments as part of thermal decomposition processes. Therefore hot work activities and processes can lead to significant exposure to isocyanates. Such work may include (but is not limited to):

- welding
- brazing
- soldering
- grinding

- treatment with a heat gun
- cutting with torches or hot wire
- heating of diisocyanate based glues
- flame laminating and bonding
- heating of polyurethane containing materials

Aerosolisation: Isocyanate based paints and varnishes are often used for spray painting. Especially in vehicle body refinish HDI based spray paints are ubiquitously used and lead to significant occupational exposures. Spray foaming, especially when applied to greater surfaces (e. g. insulation of ceilings/walls) can also lead to high aerosol release (Christensen et al., 2014). Inhalation can also occur with dust arising from handling of solid diisocyanate-containing products or articles.

Dermal exposure: Skin contact with products containing isocyanates (e. g. uncured polyurethane foams, paint or glue splashes) is a significant route of exposure (Austin, 2007).

Occupational exposure to diisocyanates is in particular possible during heating and spraying of isocyanates, during production of polyurethanes (e.g. slab-stock foam), handling of partly uncured polyurethane products (e.g. cutting, demoulding, spray-application of foam), when isocyanates/PUs are heated (e.g. hot lamination, foundry applications/casting forms) and C.A.S.E. applications (Coatings, Adhesives, Sealants, Elastomers).

Table 12 in section 5.3.4, summarises most of the recently performed diisocyanate exposure assessment studies in Europe and in the USA (the list is not comprehensive) for giving a view of the current exposure levels in Europe. The studies have been performed mainly in polyurethane industry. Studies contain often both air and biomonitoring and in some cases also dermal exposure assessment. The ECHA Restriction background document of diisocyanates includes very comprehensive review of occupational exposure of diisocyanates (ECHA, 2018a) and some of that information is referred in this section.

5.3.2 Manufacture of diisocyanates

The main process to produce diisocyanates is the phosgenation of corresponding diamines. Since phosgene (carbonyl dichloride) is very hazardous, the entire process is operated in closed system. Therefore it is generally considered that the manufacture of diisocyanates creates low occupational exposure. However, the manufacturing process may also include for example loading which is not performed in closed system and may though create exposure as it can be seen from the US study (Middendorf et al., 2017). Middendorf et al (2017) collected TDI exposure data over nearly 7-year period from three different TDI plants from the USA. The arithmetic mean TWA exposure to TDI was 0.65 ppb (4.7 $\mu g/m^3$) and the range was 0.01 to 92 ppb (0.072 – 655 $\mu g/m^3$). The highest exposures were in loading (92 ppb = 655 $\mu g/m^3$), among field operator (90 ppb = 640 $\mu g/m^3$) and in drumming (33 ppb = 234 $\mu g/m^3$).

Some diisocyanates are not manufactured in EU area for example mTMXDI. The following ranges of the exposure estimates for MDI, TDI, HDI, IPDI, NDI and XDI are taken from the CSRs. The ranges cover the exposure estimates of the contributing scenarios within the scenarios "Manufacturing" of the respective diisocyanate. All of the exposure estimates are based on data from occupational hygiene measurements and represent the 90th percentiles of the respective datasets (Table 11).

Table 11: Diisocyanate concentration (mg/m³) during manufacturing of the diisocyanate. Literature data covers also other task (e.g. loading) than manufacturing process in the production plant.

	MDI	TDI	HDI	IPDI	NDI	XDI
CSR	0.0056 –	0.005 – 0.032	0.003 – 0.024	0.013-0.04	0.005-	RA to HDI
Middendorf 2017		0.001-0.67				

5.3.3 Use in polyurethane industry

Polyurethane industry covers almost all the uses of isocyanates. Manufacture of polyurethanes is the major use of diisocyanates and in a certain sense almost all of the other uses can be subsumed as special uses / applications of polyurethanes (such as polyurethanes in foam applications, coatings, adhesives, sealants etc.).

To produce polyurethanes, the diisocyanates are reacted with macropolyols and/or other polynucleophiles and usually optional additives like catalysts, surfactants, stabilisers, flame retardants and the like. The polyaddition of isocyanates with the nucleophiles is a highly exothermic reaction. Depending on the reaction quantities and conditions, the temperature can increase considerably during the process.

Usually the reaction is largely completed within seconds but can be up to 30 minutes, whereby the isocyanate groups form urethane bonds with the polyol in the polymer backbone. However, the final curing and post-curing of polyurethanes where exposure to unreacted isocyanates is still possible, may take up to 72 h.

As mentioned above, the reaction of isocyanates with polyols or amines is a highly exothermic process. Therefore, especially when high volumes of diisocyanates are reacted to produce polyurethanes, a significant increase in temperature of the reaction mass can be assumed. This also affects the potential for exposure since the vapour pressure may rise significantly. (ECHA, 2018a)

Exposure data from air and dermal monitoring

Exposure to diisocyanates (MDI, TDI and HDI) and their corresponding diamines was assessed in seven different workplaces in the UK by using air, skin and biomonitoring. The deliberate addition of water and ambient humidity produces diamines as seen *during spray painting* which generated the highest air concentration of HDI (measured as NCO 421-423 $\mu g/m^3$) and also diamines (16-24 $\mu g/m^3$). Foam blowing generated also diamines. However, TDI in air and on glove liners were significant factors in determining the urinary TDA level. Measurements indicated also that exposure through the skin is the most likely route of exposure for MDI and TDI (Jones et al., 2017).

Occupational exposure (air and biomonitoring) to diisocyanates was investigated in polyurethane foam factory workers in Poland. Air concentrations ranged from 0.2 to 58.9 $\mu g/m^3$ for TDI isomers. Maintenance and folding paper tasks created the highest airborne diisocyanate concentrations (Swierczynska-Machura et al., 2015).

Isocyanate exposures (MDI, TDI, HDI and IPDI) were assessed in polyurethane industry sector in the UK by using air monitoring and biomonitoring methods. The study included 22 companies using isocyanates for moulding polyurethane products, insulation material as well as industrial painting. Only those companies that used good working practices were included in the survey. A total of 70 air samples were collected from 11 different tasks 50 of the 70 samples were below the limit of quantification (LOQ; 1 $\mu g/m^3$) and they were assigned as half of the LOQ. The geometric mean of the samples was 0.9 $\mu g/m^3$ and the 90th percentile was 6.2 $\mu g/m^3$ (range 0.5-65.8 $\mu g/m^3$) expressed as NCO. The highest inhalation exposures occurred during spray painting activities in a truck manufacturing company (66 $\mu g/m^3$) and during spray application of polyurethane foam insulation (23 $\mu g/m^3$). Semi-automatic moulding and polyurethane spraying tasks had the highest geometric mean values of 2.1 and 2.0 $\mu g/m^3$, respectively (Creely et al., 2006).

Occupational exposure to different diisocyanates (MDI, TDI, IPDI and NDI) during moulding, continuous foaming, flame lamination and low or no heating processes was assessed in Sweden. 111 personal samples were collected and the total isocyanate concentration ranged from 0.004 to 5.2 ppb. The current Swedish OEL of 5 ppb was exceeded only once in the study. Highest exposures were measured in continuous foaming, where the median concentration was 4.1 ppb. The average personal exposure levels for the different types of manufacturing processes were in decreasing order: continuous foaming>flame lamination>moulding>>low or no heating processes. Maintenance workers were not studied. The use of MDI and NDI in moulding resulted to the highest exposures, median air concentrations of 0.36 and 0.39 ppb (Sennbro et al., 2004a). The ppb concentrations were calculated to $\mu g/m^3$ for some studied plants in the ECHA Restriction Background Document (ECHA 2018) and the following exposure levels were presented: Plant M1 which used MDI in manufacture of polyurethane and polyurethane materials, the measured 8 h TWA levels of MDI ranged between 0.042 $\mu g/m^3$ to 7.8 $\mu g/m^3$; Plant M3 which manufactured rigid polyurethane based on TDI by moulding, the personal 8 h TWA TDI levels ranged between 1.30 $\mu g/m^3$ to 6.67 $\mu g/m^3$ in case of 2,4-TDI and between 0.038 $\mu g/m^3$ to 3.53 $\mu g/m^3$ for 2,6-TDI; the total isocyanate exposure was in the range between 1.69 $\mu g/m^3$ to 9.97 $\mu g/m^3$; and Plants (M4 – M7) which manufactured TDI based polyurethane components by foam moulding, the respective exposure levels ranged from 0.23 $\mu g/m^3$ to 4.75 $\mu g/m^3$ for 2,4-TDI and from 0.15 $\mu g/m^3$ to 3.91 $\mu g/m^3$ for 2,6-TDI; the corresponding total isocyanate exposures ranged from 0.08 $\mu g/m^3$ to 14.60 $\mu g/m^3$.

A comparative air and biological monitoring study was conducted at three Finnish factories where MDI was used in moulding rigid polyurethane foam as parts for insulation of refrigerators. Exposure to MDI was measured for 57 workers by overall 205 personal air measurements and 70 stationary samples. 131 of the personal air samples (64 %) and 49 of the stationary (70 %) air samples were below the limit of detection of 0.03 $\mu g/m^3$. The overall measured levels of airborne MDI were low, ranging, as far as quantifiable, from 0.3 to 3.3 $\mu g/m^3$. No further analysis of the stationary air samples was presented in the study, besides that the measured stationary concentrations were less than 0.5 % of the Finnish OEL of 35 $\mu g/m^3$ for isocyanates (expressed as NCO groups) (Kääriä et al., 2001b). The results of the biological monitoring will be discussed later in the respective section of this section.

Inhalation and dermal exposure to MDI during spray polyurethane foam (SPF) insulation was studied in the USA during 2015 and 2016. Breathing zone exposures to 4,4' MDI ranged from 0.9 to 123.0 $\mu g/m^3$, geometric mean being 13.8 $\mu g/m^3$. Area samples showed higher exposure levels than personal samples. Dermal exposure was measured with glove dosimeters and the GM was 11.4 μg/glove pair/min (range 2-152 μg/glove pair/min, or 59-4575 ng/cm^2) suggesting high potential for dermal exposure (Bello et al., 2019).

Data from biomonitoring

Occupational exposure (air and biomonitoring) to diisocyanates was investigated in polyurethane foam factory workers in Poland. Concentrations of TDI metabolites in post-shift urine samples were significantly higher than in pre-shift urine samples. However, no correlation was found between air concentrations and urinary concentrations. TDA concentration in post-shift urine samples varied from LOQ to 3.9 μmol/mol creatinine. Highest concentrations were among maintenance workers (Swierczynska-Machura et al., 2015).

A biological monitoring study among workers exposed to MDI was conducted in 19 French PU industries, ranging from medium sized enterprises to large factories (Robert et al., 2007). The study covers various industrial processes and uses of MDI like moulding, but also spraying and continuous foaming. All of the workers investigated were classified according to the potential for exposure into three job categories (high (I), medium (II) and low (III)) by assessment via questionnaires. The types of processes run in the

workplaces were also classified into enclosed, open and specialty processes. Urinary levels of MDA were measured for 169 exposed workers as well as for 120 not exposed workers as a control group. Detectable levels of MDA were found in 73 % of all of the post shift samples, ranging from <0.10 µg/L (LOD) to 23.60 µg/L (<0.5 – 12 µmol/mol creatinine), while the levels of MDA in the control group ranges from below the detection limit to 0.08 µg/L. The highest amounts of MDA in urine were found in the spraying or in the hot processes. The level of automation of the mixing operation and the job category had an effect on the urinary MDA concentrations. (Robert et al., 2007)

TDI and urine TDA levels were studied in handlers and non-handlers in production of flexible polyurethane foam in the UK. The air concentrations of TDI were similar in both groups (2.6 and 2.7 µg/m^3 NCO), but the mean urine TDA after shift was higher among handlers (2.21 µmol/mol creatinine) compared to non-handlers (0.11 µmol/mol creatinine). The results suggest that skin protection in handling uncured polyurethane foam may not receive sufficient consideration and dermal exposure is a potential route of exposure (Austin, 2007).

Isocyanate exposures (MDI, TDI, HDI and IPDI) were assessed in polyurethane industry sector in the UK by using biomonitoring and air monitoring methods as is reported above. The geometric mean total isocyanate metabolite level was 0.29 µmol/mol creatinine and the 90th percentile was 3.94 µmol/mol creatinine (range 0.05-12.64 µmol/mol creatinine). The highest geometric means were measured in mixing and casting (median 5.24 µmol/mol creatinine), where the highest measured values were in semiautomatic moulding (median 1.85 µmol/mol creatinine), in resin application (3.91 µmol/mol creatinine; one sample) and in glazing (median 0.91 µmol/mol creatinine). Isocyanate metabolites were present in several samples of workers using control measures (respiratory protective equipment, ventilated work areas and gloves). In particular the effectiveness of protective gloves in providing adequate protection was found to be questionable since when dermal exposure was evident many companies used unsuitable gloves that were a compromise between chemical protection and minimal limitation of dexterity (Creely et al., 2006).

Biological monitoring of NDA and MDA was performed for workers at four different plants (three moulding plants and one plant with low heating process) in Sweden. Urinary levels on the day of air monitoring after shift ranged 0.4-38 µg/l (0.2-19 µmol/mol creatinine) for MDA and 0.7-81 µg/l (0.4-51 µmol/mol creatinine) for NDA. Urinary levels were similar also in another day, 0.3-78 and 3-81 µg/l (0.1-39 and 1.9-51 µmol/mol creatinine), respectively (Sennbro et al., 2006).

Biological monitoring of TDA was studied at nine plants where polyurethane was manufactured in Sweden. A strong association between personal air and biomarker levels were found in the study. The biomarker levels ranged <0.1-162 µg/l (<0.1-133 µmol/mol creatinine) for total TDA (Sennbro et al., 2004b).

A comparative study of MDI inhalation exposure and urinary biomarkers (MDA) was conducted among 57 workers in Finland who were manufacturing rigid polyurethane foam parts by moulding. Despite that the measured levels of MDI in the air were generally very low and below the detection limit for 64 % of the personal samples, MDA was detected in 97 % of the urinary samples, ranging from 0.015 to 1.38 µmol/mol creatinine. The mean concentrations ranged between 0.12 to 0.20 µmol/mol creatinine and the median concentrations between 0.04 to 0.12 µmol/mol creatinine. As a control, the urinary MDA levels of eleven non- exposed workers were also measured and ranged from 0.012 to 0.022 µmol/mol creatinine (Kääriä et al., 2001b).

Occupational exposure to MDI during spray polyurethane foam (SPF) insulation was studied in the USA during 2015 and 2016. Inhalation and dermal monitoring results are described already above. Urinary MDA ranged from nd (not detected) to 14.5 µmol/mol creatinine and geometric mean being 0.7 µmol/mol creatinine (Bello et al., 2019).

5.3.4 Use in other industries

Construction and building industry

Occupational exposure to MDI among construction and boat building workers who manually handled MDI-urethanes was studied in Finland between 2010 and 2012. The measured amounts of MDI on the workers hands ranged from below 0.1 to 17 μg/10 cm². Nearly all workers had dermal exposure below 2 μg/10 cm^2 measured with the tape-strip technique from hands and arms. The MDA concentrations in urine were 0.1 to 0.2 μmol/mol creatinine during working days and the air concentrations were at the same level as in another Finnish study among moulders (Kääriä et al 2001). The air concentrations of MDI, 0.08-0.8 μg/m^3, were measured from the breathing zone of the workers. The use of a powered hood with appropriate filter reduced inhalable exposure by 60% and in the foaming process with a spray gun the use of appropriate RPE reduced exposure 98% (Henriks-Eckerman et al., 2015).

Autobody shop

Dermal, inhalation and internal exposure to 1,6-HDI and its oligomers was assessed in car body repair shop workers and industrial spray painters in the Netherlands. Inhalation exposure was assessed by using a midget impinger containing a reagent (DBA) sampling and dermal sampling was performed by using nitrile gloves without a reagent. Also urine samples during 24 hours were collected from the workers. Air concentrations were higher in industrial painting (ranged 0.01- 29 μg NCO/m^3 for HDI) than in car body repair shops (ranged 0.2-6.5 μg NCO/m^3 for HDI) for both HDI and its oligomers. Oligomers of HDI dominated over the monomer during all tasks in the study. Dermal sampling method worked well and it described that dermal exposure was relevant in car body repair shops, where the association between inhalation and dermal exposure suggests aerosol deposition. Inhalation exposure was strongly associated with tasks during which aerosolisation occurred and dermal exposure occurred during tasks that involve direct handling of paint. Spray painting workers have the highest inhalation and dermal exposure, but also by-standers of spray painting received a considerable dose of HDI and its oligomers (Pronk et al., 2006b).

Dermal exposure to IPDI monomer, HDI monomer, IPDI polyisocyanate and three polyisocyanate forms of HDI was assessed among spray painters in the USA. The measurements were performed during spray painting, mixing and other paint related tasks for example sanding and compounding. Some samples were collected under PPE. The geometric mean (GM) for unprotected skin was 1.9 and range 0.0-64.4 ng NCO/cm^2. The major contributor to the total NCO content were HDI polyisocyanates. The highest exposures were measured for clear coating and paint mixing tasks. Isocyanates were commonly detected also under PPE. The study demonstrated skin exposure to aliphatic polyisocyanates during painting, mixing and paint related other tasks in auto body shop workers is common and also common to detect under routine personal protective equipment (PPE) (Bello et al., 2008).

Dermal and inhalation exposure assessments of monomeric and polymeric HDI among *automotive spray painters* were conducted in the USA. HDI levels in air ranged from 0.003 to 179 μg/m^3 in the breathing zone samples. The geometric mean of dermal exposure varied from 0.01 to 0.16 ng/cm^2 between different sampled body parts and use of protective clothing. The highest exposure, 0.16 ng/cm^2, was measured from the lower legs area. A link between the concentration in the breathing zone area and dermal concentration was established (Fent et al., 2009).

Spray painters (N=33) were studied for occupational exposure to IPDI monomer, HDI monomer, IPDI polyisocyanate and three polyisocyanate forms of HDI at *the autobody shops* in the USA. The air concentrations were compared with the short term exposure limits (STELs). 98% of the samples exceeded the UK HSE STEL which is 70 μg NCO/m^3 for all isocyanates (Reeb-Whitaker et al., 2012). In another study, the exposure levels were investigated when the paint is applied with a paint brush and roller instead of a spray gun.

All isocyanate samples were below analytical detection. The finding is attributed to the use of a paint brush which minimize aerosolisation and the paint formulation which contained <1% of volatile HDI monomer (Reeb-Whitaker and Schoonover, 2016).

Plastic industry

NDI is used as a curing agent in the plastic industry. Occupational exposure to NDI was studied by measuring biomarkers and air concentrations during different tasks at the workplace. Air levels for NDI were from 1 to 82 $\mu g/m^3$, the highest air concentration were measured from the breathing zones of operators of casting machine and stoker. Urinary metabolite levels ranged from 0.4 to 55 pmol NDA/ml urine (4-550 μmol/mol creatinine) (Sepai and Sabbioni, 2017).

Foundry

Liljelind et al (2010) have quantified the occupational exposure to MDI in iron foundry workers in Sweden. Inhalation and dermal exposure by using impregnated filters and tape-strip technique during mechanized moulding and production of cores was measured from 19 workers. The average MDI concentration was 0.55 $\mu g/m^3$ (range 0.044-3.5 $\mu g/m^3$) and the highest concentrations were measured from the breathing zones of core makers being 0.77 $\mu g/m^3$ for arithmetic mean and 0.35 $\mu m/m^3$ for median concentration. The core makers mean dermal exposure varied from 0.13 to 0.34 μg/skin site (10 cm^2).

Table 12: Diisocyanate exposure assessment studies (the list is not comprehensive) including exposure data from air, dermal or/and biomonitoring performed in Europe and in the USA during recent years.

Task/occupation	Country	Year	Diisocyanate/ NCO	Air conc µg/m³	Dermal µg/glove pair	Biomonitoring µmol/mol creat	Reference
Manufacture of diisocyanates							
Production plant 1, total	USA	7-year period	TDI	0.14-655	-	-	Middendorf et al 2017
Field operator				0.2-135			
Loading				0.2-655			
Laboratory				0.2-85			
Production plant 2, total	USA	7-year period	TDI	0.1-65	-	-	Middendorf et al 2017
Field operator				0.1-65			
Loading				0.1-17			
Laboratory				0.1-1.1			
Drumming				0.2-26			
Production plant 3, total	USA	7-year period	TDI	0.1-640	-	-	Middendorf et al 2017
Field operator				0.1-640			
Loading				0.2-107			
Laboratory				0.1-16			
Drumming				0.2-235			
Polyurethane production and use							
Spray polyurethane foam (SPF); sprayers (N=24) and helpers (N=7)	USA	2015-2016	4,4'-MDI and Total NCO (isomers of MDI)	0.80-123, <0.09-254	2.0-153 µg/glove pair/min 1.0-73 µg/glove pair/min	ND-14.5 MDA	Bello et al 2019
Handling NDI powder and manufacturing polyurethane parts for automobile industry (e.g. casting) (N=20)	Germany		NDI	1-82	-	4-550	Sepai and Sabbioni 2017

Task/occupation	Country	Year	Diisocyanate/ NCO	Air conc µg/m³	Dermal µg/glove pair	Biomonitoring µmol/mol creat	Reference
Polyurethane foam production; TDI-based flexible PUR foam in continuous foam blocks	Poland		TDI	0.2-59	-	<LOQ-3.9	Swierczynska-Machura et al 2015
-Foaming head operator (N=10)				0.6-11	-	<LOQ-1.9	
-Cutting machine operator (N=3)				0.2-6.5	-	0.6-2.1	
-Maintenance workers (N=2)				9.9-42	-	1.7-3.9	
-Folding paper (N=5)				0.3-59	-	0.2-2.9	
-Foam production (low volume)			MDI	<0.6			
Spray painting	UK		Total NCO (MDI)	0.06-8.1	<0.05	ND-0.4	Jones et al 2017
Spray painting	UK		Total NCO (HDI)	421-423	3-11	ND-1.0	Jones et al 2017
Casting/grouting	UK		Total NCO (MDI)	<0.05-0.08	<0.05-20.5	ND	Jones et al 2017
Casting	UK		Total NCO (MDI)	0.49	230	ND-0.8	Jones et al 2017
Floor screeding	UK		Total NCO (MDI)	0.1-0.47	<0.05-1091	0.5-6.0	Jones et al 2017
Foam blowing	UK		Total NCO (TDI)	0.03-3.1	256-2488	ND-5.4	Jones et al 2017
Foam blowing	UK		Total NCO (TDI/MDI)	0.07-0.85	<0.05-54	ND-8.5	Jones et al 2017
Foam blowing	UK		Total NCO (TDI/MDI)	0.07-2.47	<0.05-56	ND-6.3	Jones et al 2017
Continuous foaming plant (N=6)	Sweden	2000, 2005	TDI	63 median, 13 median	-	<LOQ	Tinnerberg et al 2008
PUR industry (N=169)	France	1998-2004	MDI	-	-	<0.10-12	Robert et al 2007
PU foam production (N=26)	UK		NCO (TDI)	<3.5-8.4 (AM 2.7 for handlers; (AM 2.6 non-handlers		2.21 for handlers, 0.11 for non-handlers	Austin 2007
PUR industry (N=70)	UK		Total NCO	0.5-66	-	0.05-13	Creely et al 2006

Task/occupation	Country	Year	Diisocyanate/ NCO	Air conc µg/m³	Dermal µg/glove pair	Biomonitoring µmol/mol creat	Reference
-Coating and spreading				0.5-12	-	0.05-1.49	
-Semiautomatic moulding				0.5-10	-	0.05-4.80	
-PUR spraying				0.5-23	-	0.05-1.81	
-Painting (spray)				0.5-66	-	0.05-1.71	
-Mixing and casting				0.5-4.7	-	0.05-13	
PUR industry; moulding and heating processes, manu-facturing rigid PUR products by moulding (N=30)	Sweden		MDI, NDI,	0.03-7.8** for MDI; 0.2-15 ** for NDI	-	0.2-19** and 0.1-39 for MDA; 0.4-51** and 1.9-51 for NDA	Sennbro et al 2006
PUR industry (N=81)	Sweden	2000-2001?	TDI	<LOQ-44**	-	4.5 (median)**, 5.4 (median)	Sennbro, Lindh, Tinnerberg et al 2004
PUR industry (N=111)	Sweden	2000-2001	NCO (TDI, MDI, NDI, PI and IPDI)	0.004-5.2 ppb; MDI 0.042-7.8; TDI 1.7-10; and total isocyanate conc. 0.08-15	-	-	Sennbro, Lindh, Östin et al 2004
-moulding			MDI	0.004-0.75			
-moulding			NDI	<LOQ-1.8			
-moulding			IPDI	0.01-0.10			
-low or no heating process			MDI	0.01-0.06			
Moulding of rigid PUR foam (N=57)	Finland	1996-1997	MDI	0.03-3.3	-	0.015-1.38	Kääriä et al 2001
Construction and boat building							
Manual handling of MDI (foaming, moulding, gluing,	Finland	2010-2012	MDI	0.08-27	0.1-17 µg/10 cm²	0.1-0.2	Henriks-Eckerman et al 2015

Task/occupation	Country	Year	Diisocyanate/ NCO	Air conc µg/m³	Dermal µg/glove pair	Biomonitoring µmol/mol creat	Reference
laminating and coating with polyurethane) (N=24)							
Motor vehicle repair trade							
Car body repair shops:	Netherlands	2004	NCO (HDI)/ NCO (oligomers)				Pronk et al 2006
-Mixing PU lacquer (N=15)				0.2-2.7/0.3-33	0.3-20/20-2849		
-Spraying PU lacquer (N=31)				0.2-6.5/2.5-728	0.3-10/6.5-1507		
-Cleaning spray gun (N=19)				-/1.6-45	0.3-2.0/16-316		
-Welding (N=3)				0.04/0.1	-		
Industrial painting company	Netherlands	2004	NCO (HDI)/ NCO (oligomers)				
-Spraying PU lacquer (N=10)				0.03-29/6.4-2614	0.5/3.8-210		
-Rolling/brushing PU lacquer (N=11)				0.01-0.1/0.1-5.3	-/3.5-154		
-Mixing PU lacquer (N=3)				0.01-1.0/1.6-20	-/3.5-95		
-Assisting spray painting (N=3)				0.09-4.4/6.3-348	-/0.7		
Polyurethane paints; paint brush and roller	USA	2012, 2013, 2014	HDI	<LOD (0.2)	-	-	Reeb-Whitaker and Schoonover 2016
Spray painting (N=228)	USA	2006-2007	NCO (HDI monomer, IPDI monomer+ corresponding polyisocyanates)	98% >70 µg NCO/m³	-	-	Reeb-Whitaker et al 2012
Sprays painters and technicians -spraying (N=49)	USA		NCO (HDI monomer, IPDI monomer+ corresponding polyisocyanates)	-	0-64.4 ng NCO/cm²		Bello et al 2008

Task/occupation	Country	Year	Diisocyanate/ NCO	Air conc µg/m³	Dermal µg/glove pair	Biomonitoring µmol/mol creat	Reference
-mixing (N=13)					0.1-59.8 ng NCO/cm²		
-paint related wet sanding (N=10)					0-67.3 ng NCO/cm²		
Spray painting	USA		HDI	-	Positive (qualitative assessment)	-	Liu et al 2009
Automotive spray painters (N=47)	USA		HDI, polymeric HDI	0.003-179 HDI	-	-	Fent et al 2009b
Automotive spray painters (N=47)	USA		HDI, polymeric HDI		GM 0.01-0.16 ng/cm² for different part of the body (lower arms, hands, neck, wrists, face and lower legs)		Fent et al 2009a
Foundry							
Core makers, installers and core sand preparers (N=19)	Sweden	2006, 2007	MDI	0.044-3.5			Liljelind et al 2010
** air and biological monitoring performed at the same day							

5.3.5 Occupational exposure to isocyanates as recorded in National databases

Occupational exposure data from the Finnish Industrial hygiene measurement registry in FIOH

The main part of the workplace air measurements for isocyanates (92%) were below the Finnish OEL (0.035 mg/m^3) performed during 2008-2016 in Finland. The arithmetic mean concentration was 5 µg/m^3, the median was 0.03 µg/m^3, the 95th percentile concentration was 10 µg/m^3 and the maximum concentration was 1003 µg/m^3. The highest concentrations were measured for a prepolymer, HDI-trimer, from the breathing zone of painters or from the room where the painting was performed. Also welding operations created high exposures to HDI. The highest TDI concentrations were measured during production of prepolymers and foaming, and also in manufacturing of medicinal products (but not the medicinal product itself). The air concentrations for MDI were mainly well below the Finnish OEL. The range of the measurements are presented in the Table 13Table 13. (FIOH, 2019)

During the period 2008-2016, a total of 178 urine samples were monitored for the isocyanate exposure in Finland. The main portion of the samples (71%) were below the detection limit for the method. The arithmetic mean value was 1.6 µmol/mol, the median was 0.1 µmol/mol, the 95th percentile was 2.3 µmol/mol and the maximum value was 121 µmol/mol. 29% of the results were at the level of non-occupational exposed reference value (0.2 µmol/mol) or above it. The workers in construction, in foundry and in welding had the highest exposures to isocyanates. (FIOH, 2019)

Table 13: Workplace air monitoring results (µg/m^3) for isocyanates from different industry sectors during the period 2008-2016 in Finland.

Finland (2008-2016)	N	TDI	MDI, MDI-trimer	HDI, HDI-trimer
Sector of use		Range (µg/m^3)	Range (µg/m^3)	Range (µg/m^3)
Rubber- and other plastic products	382	0.0025 - 18.9	0.005 - 2.53	0.005 - 0.25
Other machines and equipment production	171	0.005 - 0.8	0.005 - 67.6	0.005 - 478
Other non-metallic mineral products production	95	0.02 - 17	0.005 - 2.96	0.01 - 0.32
Metal products production	82	0.005 - 0.04	0.005 - 1.54	0.005 - 16.5
Production of medicine and medicinal products	73	0.003 - 342	0.01 - 0.025	0.025
Production of chemicals and chemical products	58	0.01 - 176	0.005 – 0.43	0 – 9.2
Furniture production	60	0.01 - 106	0.005 - 0.11	0.04 - 1.65
Textiles production	57	0.005 - 171	0.005 - 0.51	0.01 - 0.05
Production of leather and leather products	53	0.02 - 0.81	0.005 - 5.59	-
Other vehicles production	47	0.03 - 0.055	0.025 - 23.7	0.025 - 466
Motor vehicles retail and repair	44	-	0.01 - 0.015	0.005 - 89.9
Electronic and optical devices	43	0.21 - 341	0.0025 - 1.18	0.02 - 0.44
Repair, maintenance and assembly of machines	41	0.005 - 0.37	0.005 - 0.32	0.005 - 1003
Wood and wood-based products	36	-	0.0025 - 0.66	0.025
Electric devices production	33	-	0.005 -1.06	0.005 - 208
Special construction	16	0.14	0.025	0.02 - 36.9

The bolded industry sector has had exposures above the Finnish OEL (35 µg NCO/m^3 for a short term exposure).

Data are from the Finnish Industrial hygiene measurement registry in FIOH, Finland. (FIOH 2019) (Link to the data: https://www.ttl.fi/kemikaalit-ja-tyo/isosyanaatit/ Last accessed 10.07.2019)

Occupational exposure data from the German Social Accident Insurance (IFA)

Measured workplace exposure data (MEGA database) from Germany have been evaluated in a study by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2010) (see Table 14). The data have been gathered from 2000 to 2009. Overall, a total of 10 541 measurement data for MDI (4484 for 4,4'-MDI and 1810 for 2,4'-MDI) and TDI (2113 for 2,6'-TDI and 2134 for 2,4'-TDI) have been evaluated according to industry groups as well as work area groups. Most of the air monitoring samples (over 86%) have been below the analytical quantification limit (AQL). The German workplace limit value was exceeded in 9 to 49 cases, being 0.5-2.3% of the measurements.

According to industry groups the occupational exposure to MDI and TDI has most often been above German workplace limit value (8-hour values 5 ppb for TDI and 0.05 mg/m^3 for MDI) in plastic industry, leather and textile industry, processing metals and mechanical engineering and wood and paper industry. The foam-filling, foaming, casting, gluing and flaming/singeing/burning are the activities that have created highest exposures to workers. Generally the 95th percentile values ranges from AQL to 76 μg/m^3 (0.076 mg/m^3) for separate isocyanates.(IFA, 2010)

Table 14: MDI and TDI exposure data from German MEGA database 2000-2009 (IFA 2012)

Work area group	LEV	4,4'-MDI			2,4'-MDI			2,6'-TDI			2,4'-TDI		
		N	AM µg/m³	95th µg/m³	N	AM µg/m³	95th µg/m³	N	AM µg/m³	95th µg/m³	N	AM µg/m³	95th µg/m³
All areas	Yes	1110	3.0	9	426	1.4	2	557	4.8	22	570	3.0	14
	No	658	3.4	7	288	1.6	AQL	236	1.3	2	239	1.3	2
Processing, subsequent treatment	Yes	52	1.4	2.4	17	1.1	2	29	15.3	96	30	3.5	17
	No	35	4.8	3	13	1	AQL	12	1.1	AQL	12	1.1	AQL
Moulding	Yes	22	4.8	23	13	1.3	3						
	No	11	3.6	15									
Flaming, singeing, burning	Yes							10	21.6	41	10	11.5	24
Casting	Yes	82	2.9	11	39	1.1	AQL	29	3.6	18	29	5.2	26
	No	54	1.1	AQL	26	1.1	AQL	13	1.1	AQL	13	1.1	AQL
Gluing	Yes	165	6	14	60	1	AQL	77	2.3	5	74	1.6	2
	No	196	2.6	6	112	1.1	AQL	85	1.4	2	83	1.4	AQL
Storing, conveying, filling, weighing	Yes	37	4.0	13	19	1.5	2				11	2.3	7
	No	34	2	5	14	4.5	16						
Mixing, stirring	Yes	19	1.1	2				10	1	AQL	10	1	AQL
Surface coating processes, miscellaneous	Yes	64	6.3	37	29	1.3	2	43	2.3	5.9	45	2.7	6
	No	21	1.6	AQL							18	1.1	AQL
Pressing, extrusion	Yes	38	7.2	28	17	3.2	10	10	30	76	10	18.1	50
	No	11	1.4	3									
Foaming (all kind of)	Yes	250	1.4	3	93	1.1	AQL	63	10.5	36	64	6.8	34
	No	180	2.6	8	63	1.4	3	44	1.1	AQL	44	1.2	2
Spraying (all kind of)	Yes	210	2.2	3	81	2.3	AQL	201	1.2	AQL	212	1.1	2
	No	21	3.6	9				20	1.1	AQL	21	1.1	AQL

AQL = number of measured values below analytical quantification limit is greater than the number of measured values represented by the cumulative frequency value

5.3.6 Summary of the occupational exposure

In recent years, the average and the 95th percentile airborne concentrations (calculated as NCO) for TDI and MDI are below 5 μg/m^3 and 12 μg/m^3, respectively, according to German and Finnish databases of workplace monitoring. From the collected literature data, diisocyanate exposure in Europe is generally below 30 μg NCO/m^3 and very often even much lower, except for spraying applications. The highest airborne concentrations are measured for HDI during spray painting (>400 µg/m^3 measured as NCO; (Jones et al., 2017). High airborne levels during spray painting were also measured in other studies (Creely et al., 2006, Fent et al., 2009). Generally, it can be summarised that inhalation exposure is strongly associated with tasks where aerosolisation occurs.

However, air monitoring/measurement data do not necessarily support the assumption that the exposure is adequately controlled even though the measured air levels are low as highlighted in the ECHA Restriction Background Document (2018). Since isocyanates are highly reactive and very unstable, even in the same air samples several different chemical species may be present. Also there has been a trend in the industry to reduce the content of free monomers in formulations and replace the monomers with prepolymers and polyisocyanates. However, most of the sampling and analytical methods address only diisocyanate monomers and quantification of polyisocyanates (oligomers) is much more complex (Bello et al., 2004). Also some tasks/activities last only short time and the exposure to diisocyanates is so-called short-term exposure/peak exposure. Also spillages or incidents may create peak exposures. This kind of exposure can be monitored with short sampling time (≤15 minutes) or with direct reading equipment.

When complemented with biomonitoring data there is often clear evidence for occupational exposure to isocyanates of workers, even in cases where air monitoring suggests that the exposure situation might be well controlled. For example, Kääriä et al. (2001b) assessed worker exposure to MDI at three factories in Finland during moulding of rigid polyurethane foam. While MDI concentrations were below the limit of detection in 64 % of the breathing zone air samples they found MDA (as a MDI metabolite) in 97 % of the urine samples of the workers (Kääriä et al., 2001b). These findings are especially important since there is an increasing body of literature highlighting the relevance of the dermal route for causing occupational asthma by isocyanate. (ECHA, 2018a).

Dermal exposure often occurs during tasks that involve direct handling of paint, contact with uncured polyurethane or deposition of aerosols. Skin contamination can be detected with semiquantitative methods, such as direct reading indicators in the form of wipes (e.g. colorimetric SWYPE™ indicators) or visual scoring system for dermal exposure assessment (WHO, 2014). Different quantitative techniques have been applied in workers occupationally exposed to isocyanates (e.g. skin surface wipe sampling, skin tape stripping, sampling of inner gloves and pads under PPE) (Heederik et al., 2012). Even though there are studies where the dermal exposure to isocyanates has been studied, the quantification of dermal exposure is particularly difficult because of lack of standardised and validated methods for measuring (Lockey et al., 2015) (Bello et al 2007). For these reasons, dermal exposure to isocyanates is often assessed indirectly by comparison of personal air samples with corresponding biomonitoring data.

Exposure to diisocyanates occurs in various industrial sectors for example automobile industry, plastic industry, leather and textile industry, processing metals and mechanical engineering and wood and paper industry as can be seen from the literature review and National databases. However, the main use is different polyurethane applications. The activities such as spraying, loading in manufacturing, mixing and casting, surface coating, pressing and extrusion, are the activities that have created highest exposures. Since diisocyanates are sensitising compounds, effective risk management measures should be implemented in operational conditions. There are a couple studies where the effect of risk management measures was studied before and after implementation (Tinnerberg and

Mattsson, 2008, Clayton and Baxter, 2015, Jones et al., 2013)) showing that the exposure can be reduced remarkably by training workers. This is also the purpose of the Restriction proposal of diisocyanates that was submitted to ECHA by Germany[11].

5.4 Routes of exposure

Both inhalation and dermal routes are the most likely routes for occupational exposure to isocyanates. Isocyanates can become airborne as aerosols (e. g. spray painting, blow foaming) or as fumes and vapours in hot processes (e. g. hot melt adhesives and sealants) and can also be released by thermal degradation of polyurethanes. Also potential for dermal exposure has been demonstrated in many studies (Bello et al., 2019, Henriks-Eckerman et al., 2015, Jones et al., 2017, Kääriä et al., 2001b). The form (and volatility) of the diisocyanates and the processes involved affect the significance of dermal exposure (Cocker, 2011). For example, uncured or not fully cured polyurethane products pose a source of skin exposure to isocyanates and the fully curing can last days or even weeks (Bello et al., 2007).

6. Monitoring Exposure

6.1 External exposure

6.1.1 Challenges in monitoring

Depending on diisocyanates and the on-going activity, airborne diisocyanates can be associated with both vapours and aerosols, the latter with a wide range of particle sizes. Aromatic diisocyanates in the gas phase tend to condense to aerosols (particles < 1µm), while monoisocyanates and aliphatic diisocyanates in the gas phase were not found to form particles in a similar way (Dahlin et al., 2008). Since diisocyanates are highly reactive, the total isocyanate content and the physical form varies with time (Dahlin et al 2008). To reduce volatility of the lower molecular weight diisocyanates, prepolymer and polyisocyanate forms of these diisocyanates have been developed and they have replaced the monomers in many product formulations (Streicher et al., 2000). For instance, HDI products may contain less than 1% free HDI monomers and the rest is polyisocyanates. The quantification of polyisocyanates (oligomers) is much more complex than monomers (Bello et al., 2004). Since there are no standards for polyisocyanates, the identification of the peaks in the chromatogram is performed different ways by using e.g. bulk material, the ratio of two different detectors (UV/EC), diode array detection or mass spectrometry library. Because of the above mentioned reasons the quantification of oligomers is often not as accurate as is the quantification of monomers.

Air sampling and analytical methods for isocyanates require reaction with derivatising reagents during sampling to stabilise the functional group. Most of the sampling methods use either an impregnated filter with a derivatisation reagent or impingers, where the derivatisation reagent is dissolved in an organic solvent and the analyte air is bubbled through, or a combination of both. While impingers provide better results for measurement of fast curing systems, they are more laborious to use for personal sampling (and may pose a risk of leakage, evaporation of volatile organic solvents etc.) (Lockey et al., 2015, Puscasu et al., 2015). However, non-spill impingers are commercially available. Impingers are efficient to sample aromatic isocyanate aerosols with particles larger than 2 µm, but particles less than 2 µm can pass through them. The fibre filters impregnated with derivatising reagent can be used to sample vapours, slow-reacting aerosols (typically

[11] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180876053

aliphatic isocyanate systems) and isocyanate aerosols with particles less than 2 µm (DECOS 2018).

The aromatic diisocyanates can be detected at the lower levels than the aliphatic ones. The median quantification levels (8 h TWA) for aromatic diisocyanates (isomers of TDI and MDI and NDI) were from 0.42 to 1.22 µg/m^3 according nine laboratories among industry member companies and IFA (Information that was sent during Consultation). For aliphatic diisocyanates (HDI, IPDI and H_{12}MDI) the median quantification levels (8 h TWA) varied from 0.67 to 2.38 µg/m^3 in the same laboratories. The used analytical methods were mainly LC-UV(/FLD).

6.1.2 Available air monitoring methods

Available standard methods for monitoring the most common diisocyanates in workplace air which are mainly according to the criteria set out in the standard EN 482 "Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents" are described in Table 15. However, there can be some shortcomings in validation data (e.g. sampling and recovery efficiencies, storage condition, expanded uncertainty) with the methods. For example, for ISO 16702:2007 expanded uncertainty is 54% and for ISO 17735:2019 it is 36%. According the criteria in the standard EN 482, the expanded uncertainty should be below 50%. For all of the methods, the analysis are performed with liquid chromatography connected to UV, fluorescence, electrochemical nitrogen or mass detection. Often two detectors are needed for the identification of peaks in the chromatogram. With the LC-MS/(MS/MS) method the lowest quantification limits are achieved. ANSES recommends the methods of ISO 17735 (2009) and NIOSH 5525 (2003) as indicative for the regulatory control of 15 min STEL for TDI (draft ANSES report March 2019 under Public Consultation)[12].

In many workplaces the exposure to diisocyanates is an integration of short and event-based peak exposure. Current practice in many industrial sectors is to use direct monitoring equipment to warn workers about excessive and peak exposures and ensure safe use of isocyanates (information sent during Consultation). Direct reading devices are available for the most common diisocyanates (e.g. TDI, MDI, HDI). The methods can be based on drawing air through a paper tape that has been treated with an isocyanate-specific colorimetric reagent; the colour density on the tape is then read spectrophotometrically. The direct reading devices are mainly an isocyanate specific meaning that they detect one di-isocyanate at a time and they are not specific for prepolymers or oligomers. The lowest detection limit can be around 0.5 ppb for diisocyanate and typically it is around 1 ppb (corresponds to 7 µg TDI/m^3 and 3.4 µg NCO/m^3) with a resolution of 1 ppb.

[12] Document for public consultation:
https://www.anses.fr/fr/system/files/REC_NEC_VLEP_TDI_pourconsult_paraphV3.pdf

Table 15: Air monitoring methods for the most common diisocyanate monomers and for their polymeric isocyanates

Method	Suitable for	Sampler	Derivatising agent	Analytical technique	Sampling flow rate, volume, time	LOD/LOQ/range 15 l (corresponds to STEL)	LOD/LOQ/range 240 l (corresponds to 8-h OEL)
ISO 17734-1: 2013*	Gas and vapour phase isocyanates; monomers, prepolymers and oligomers	Impinger/filter or tube/filter (solvent-free sampling)	DBA	HPLC-MS/CLND	1 l/min and 30 min or 0.2 l/min and even > 8 h	LOD: 0.02 ng/m^3 for TDI and 0.6 ng/m^3 for HDI; Range: 0.001-200 000 µg/m^3 for TDI (5 l)	LOD: 0.001 ng/m^3 for TDI and 0.04 ng/m^3 for HDI
ISO 17735: 2019	Vapours and aerosols; monomers, prepolymers	Reagent impregnated filters and/or impinger samples	MAP	HPLC-UV/FL (LC-MS-MS)	1 -960 l; 1 or 2 l/min	LOD: 0.7 – 1.4 µg monomer/m^3 for filters and 2.0-5.3 monomer µg/m^3 for impingers	LOD: 0.04 – 0.08 µg monomer /m^3 for filters; 0.13 – 0.3 µg monomer /m^3 for impingers
ISO 17736: 2010 **	Vapours and aerosols; monomers, prepolymers and oligomers	Douple filters	MAMA	HPLC-UV/FL/ DAD	1 l/min; for short-term exposure, but if only vapour form the sampling can be extended to 8 hour;	Range: 0.67 – 140 µg NCO/m^3	
ISO 16702 2007	Vapours and aerosols; Any product containing free isocyanate groups. Primarily MDI, HDI and TDI both monomers and their oligomers and polymers	Chemically treated filters or impinger/ filters	1,2-MP	LC-UV/EC/ (DAD)	0.5 min to 8 hour	LOD: 0.07 µg NCO/m^3 LOQ: 0.3 µg NCO/m^3 Range: 0.1 – 140 µg/m^3	LOD: 0.004 µg NCO/m^3 LOQ: 0.019 µg NCO/m^3

Method	Suitable for	Sampler	Derivatising agent	Analytical technique	Sampling flow rate, volume, time	LOD/LOQ/range 15 l (corresponds to STEL)	LOD/LOQ/range 240 l (corresponds to 8-h OEL)
MDHS 25/4	Vapours and aerosols; monomers and prepolymers	Glass fibre filters (vapours); impinger + glass fibre filters (aerosols)	1,2-MP	HPLC-UV/ EC/ (MS/MS)	Vapours 2 l/min and 20 -900 l; Aerosols 1 l/min and 15-480 l	LOD: 0.07 µg NCO/m^3 (EC) LOQ: 0.27 µg NCO/m^3 (EC)	LOD: 0.004 µg NCO/m^3 (EC) LOQ: 0.017 µg NCO/m^3 (EC)
NIOSH 5522 (1998)	Vapours and aerosols; only for area samples; monomer (TDI, MDI HDI) and estimate oligomer; not for mixtures of different isocyanates	Impinger	Tryptamine/DMSO	HPLC-FL/EC	15-360 l; 1-2 l/min	Range: 10 – 250 µg/m^3 for TDI (50 l);	
NIOSH 5525 (2003)	Vapour, aerosols and condensation aerosols; monomeric and oligomeric isocyanates	Glass fibre filters; impinger; impinger + glass fibre filters	MAP	HPLC-UV/ FL	1-500 l; 1-2 l/min	Range: 1.4 – 840 µg NCO /m^3; LOD: 1.1 µg/m^3 for HDI	Range: 0.1 – 52 µg NCO/m^3; LOD: 0.18 µg/m^3 for HDI

*reviewed and confirmed in 2019

** reviewed and confirmed in 2016

DBA = dibutylamine; 1,2-MP = 1-(2-methyoxyphenyl)piperazine; MAMA = 9-(methylaminomethyl)anthracene; DMSO = Dimethyl sulfoxide; MAP = 1-(9-anthracenylmethyl)piperazine

LOD limit of detection; LOQ limit of quantification

LC liquid chromatography; HPLC high pressure liquid chromatography; MS mass spectrometry; CLND = chemiluminescent nitrogen detection; UV ultraviolet detection; FL fluorescence detection; EC electrochemical detection; DAD diode array detector

6.2 Biomonitoring of exposure (internal exposure)

Biological monitoring of diisocyanates is normally based on the analysis of diisocyanate-adducts with haemoglobin or albumin in the blood or the determination of corresponding diamines in plasma or in urine. The amines are not specific markers for diisocyanates and exposure to the corresponding diamines has to be ruled out since, otherwise, the results can be biased. (Cocker, 2011).

Biological monitoring is most commonly undertaken using urine samples. The elimination half lives of the derived diamines in urine are relatively short (2-5 h), which means that the urine samples need to be collected at the end of the exposure and results mostly reflect the exposure of the data collection (Cocker, 2011) (see Table 20).

It has also been proposed to carry out biomonitoring based on immunologic [immunoglobulin G (IgG)] responses to exposure. Isocyanate-specific IgG are not normally found in human serum (the chemicals are man-made and do not exist naturally), but are present with a relatively high prevalence among exposed workers. See for instance (Wisnewski et al., 2012).

Currently, the quantitative analysis of diamines in urine after hydrolysis is the best established approach in human biomonitoring of diisocyanates and assessment values for occupational examinations have been derived.

6.2.1 Background levels

Non-occupational exposures may occur since polyurethane foams are a component of many household materials including bedding, upholstered furniture, urethane-containing adhesives, and insulation (ACGIH, 2016). The ACGIH has established a reference value for the general population (95th percentile) for TDI of 0.4 µg of TDA/g creatinine.
Others (Sennbro et al., 2005) have also studied levels of diisocyanates in the general population (non- exposed workers). The study showed detectable levels of MDI in 97% of the sample population and for other isocyanates only in 0-15 % of the population (none or few individuals presented levels above the limit of detection). The study also calculated 95th percentiles values for the non-exposed population. Results are reported in Table 16.

Table 16: Levels of diisocyanate metabolites in urine or blood of non-occupationally exposed workers (Sennbro et al., 2005)

Biomarker	Range (µg/L)	Median (µg/L)	95th Percentile (µg/L)
U-2,4-TDA	<0.1–0.4	<0.1	0.1
P-2,4-TDA	<0.1–0.1	<0.1	0.1
U-2,6-TDA	<0.1–0.2	<0.1	0.1
P-2,6-TDA	<0.1–0.1	<0.1	0.1
U-NDA	<0.1–0.2	<0.1	<0.1
P-NDA	<0.1	<0.1	<0.1
U-MDA	<0.05–3	0.2	0.4
P-MDA	<0.05–0.4	0.2	0.3

U urinary samples, P plasma samples

The background levels of the general population are in most cases non detectable. It is proposed to establish a BGV at the level of the analytical limit of quantification for the corresponding revived diamine in urine**.**

Current limits of detection for diisocyanates are available Table 20 in section 6.2.3 below. Since the biological half-life of the urinary metabolites is very short, it is recommended that the sampling is taken at the end of the exposure period.

6.2.2 Exposure correlations

Several studies support the correlation between the concentrations of diisocyanates in air and the corresponding diamines in urine. The German BAT value for HDI, BLW for MDI and the ACGIH BEI value for TDI are based on correlation between air and urine concentrations. However, exposure to the diamine (Jones et al., 2017) or combined exposure with polymeric diisocyanates (Cocker, 2011), confounding factors need to be considered .The biological monitoring guidance value (BMGV) established in the UK follows a different approach. It is based on the 90th percentile of biological monitoring data from workplaces with exposure to HDI, IPDI, TDI, or MDI. It is also not a health-based guidance value but one based on exposure control. Any results exceeding the BMGV should simply trigger an examination of exposure controls and work practice with the intent of reducing exposure.

Budnik et al (2011) studied the differences in excretion kinetics for different isocyanates and established the elimination patterns for all major diisocyanates at different exposure concentrations. When looking closer at different isocyanates, it became clear that the aliphatic isocyanate 1,6-HDI has a shorter excretion time than aromatic isocyanates (4,4'-MDI, 2,4-/2,6-TDI).[13] Notably, aromatic MDA, NDA and cycloaliphatic IPDA were not completely eliminated after 24 h. After pulmonary absorption of 2,4- and 2,6-TDI, the majority had been excreted in urine 6 h after the end of exposure.

The different excretion kinetics of different diisocyanates together with the inter-individual differences and the contribution of dermal uptake, make it difficult to find a correlation between air monitoring data and biomarker concentration. Most correlations between air and urine concentrations (diisocyanates vs related diamine) found in the literature are for the specific diisocyanates compounds and not for the concentrations of diisocyanates as a group.

Due to the limitations stated above, no biological limit value is proposed.

The subsections below summarise the correlations found in reports/ reviews for individual diisocyanates and the corresponding diamine.

6.2.2.1 HDI

For the derivation of the BAT value (DFG, 2012) the correlations found in the studies in Table 17 were taken into account.

[13] After the onset of inhalation challenge test with diisocyanates (at 0.5 and 30 ppb for 0 to 120 minutes), (major) excretion peaks for respective metabolites were observed at: 2 h for 1,6-hexamethylene diamine (1,6-HDA); around 4-5 h for 2,4-TDI and 2,6-TDI; around 6 h for 1,5-naphthalene diamine (1,5-NDA) and isophorone diamines (IPDA); 14 h for 4,4'-diphenylmethane diamine (4,4'-MDA). Half-lives reported in this study were 2.5 h for 1,6-HDA, 4-5.5 h for IPDA, and 6 h for 2,4-TDI and 2,6-TDI (Budnik et al., 2011).

Table 17: HDA levels in urine against HDI exposed persons (DFG, 2012)

N	HDI in air **Median ± SD [µg/m³] (Range)**	**HDA in urine** **Median ± SD**	**Reference**
5 people (chamber test)	n.a (25–29)	n.a (0.01–0.03 mmol/mol creatinine ≅ 10–30 µg/g creatinine)	(Brorson et al., 1990)
19 (workers of the HDI industry)	14.3 ± 26 (AM) (0.3–97.7)	8.52 µg/g creatinine ± 7.46 (AM) (1.36–27.7 µg/g creatinine)	(Maître et al., 1996)
50 (workers from the PU industry- 100 air samples)	78.5 (AM) (61–96)	3.39 µmol/mol creatinine ± 0.6 (AM)	(Mirmohammadi et al., 2010)

The correlation found by (Maître et al., 1996) was used to derive the BAT value (calculating the corresponding HDA value from the air limit value established for HDI):

$$\log(HDA) = 0.4396 * \log(HDI) + 0.4612$$

6.2.2.2 MDI

The German DGF established a BAT value for MDI (DFG, 2000). The value was based on a correlation between the concentration of MDI in air and the concentration of MDA in urine. The value was based on field studies by a working group (Lewalter, 1994) which are not completely documented (see Table 18).

Table 18: MDA levels in urine against MDI exposed persons

N	MDI in air **Median [µg/m³] (Range)**	MDA in urine **Median (Range)**	Reference
43	3.9 (0.1–5.4)	0.87 (0.6–2.0) µg /g creatinine	(Lewalter, 1994)
154	12.7 (1.8–15.3)	2.58 (0.3–3.7) µg /g creatinine	(Lewalter, 1994)
64	10 (1-21)	2.1 µg/l	(Lewalter J, 2002)

From these data a value of 10 µg 4,4'-dMDA (after hydrolysis)/g creatinine (for a MAK value of 0.05 mg/m3) was established. When the value was revised in 2006 (DFG, 2007), the correlation was confirmed by later studies (Lewalter J, 2002). However, the correlation is based on excretion data and is not protein related, so the BLW was established in terms of MDA per/l of Urine as: 10 µg 4,4'-diaminodiphenylmethane (MDA) (after hydrolysis)/l urine (for a MAK value of 0.05mg/m^3).

6.2.2.3 TDI

The ACGIH proposed a Biological Exposure Index (BEI) that is based on the levels of the metabolites expected with an exposure equivalent to the TWA of 1 ppb (ACGIH, 2016). The value was based on the results from field studies comparing the TDI air values with the urine TDA. Results from those studies are summarised in Table 19:

Table 19: TDI in air and urinary TDA levels reported in the public scientific literature (ACGIH, 2016)

N	TDI in air **Median ± SD [ppb] (Range)**	TDA in urine **Median (µg/g creatinine)**	Correlation coefficient (r)	Regression equation	Reference
16	(0.25-3.25)		0.9 0.64	2,4 TDI: y=3.2x +0.39 2,6 TDI: y=6.6x-1.48	(Sakai et al., 2005)
84/91	0.4 (median)	5.6 (median)			(Sennbro et al., 2005)
6	0.25 (estimated)	0.49			(Rosenberg et al., 2002)
14	(0.56-4.5)		0.63	Y=9.7x-5.5	(Kääriä et al., 2001a)
9	3 (estimated)			Log(y)= 0.579log(x) +0328	(Maître et al., 1993)

6.2.3 Biomonitoring analytical methods

The analytical methods for biomonitoring of diisocyanates are based on the determination of corresponding diamines released after acid hydrolysis the released amines that are then extracted from urine and separated via gas chromatography on a capillary column and detected by a mass sensitive detector.

Table 20: Methods for biomonitoring

Standard method	Biomarker (Diisocyanate)	Analytical technique	LOQ	Reference
MAK method (*)	HDA in urine (HDI)	GC/MS (gas chromatography with mass spectrometry	0.7 µg/l urine	(DFG, 2017)
	2,4 TDA in urine (2,4 TDI)		0.4 µg/l urine	
	2,6 TDA in urine (2,6 TDI)		0.4 µg/l urine	
	IPDA in urine (IPDI)		0.5 µg/l urine	
	MDA in urine (MDI)		0.4 µg/l urine	
BMGV method	Isocyanate-derived Diamine (HDI, MDI, TDI, IPDI)	GC/MS	5 nmol/l (approx 0.5 µmol/ mol creatinine)	(HSL)

Notes:

(*) The method allow the simultaneous determination of the diamines

HDI :hexamethylene diisocyanate /HDA: hexamethylenediamine
TDI: toluene diisocyanate / TDA: toluenediamine
IPDI: isophorone diisocyanate / IPDA: isophoronediamine
MDI: methylene diphenyl diisocyanate / MDA: methylenedianiline

7. Health Effects

In this section on health effects, the inhalation exposure concentrations are expressed in the units used in the original papers (normally ppm or mg/m^3), but with a conversion to the other unit in brackets. As the NCO group has been identified as playing an important role in the hazardous effects, the corresponding NCO concentrations have also been calculated, making it easier to compare effects of different diisocyanates, especially as regards studies on respiratory sensitisation. For conversion factors and calculation formulas, see Table 1 and Appendix 1.

7.1 Toxicokinetics

7.1.1 Human data

Absorption

Exposure to 25, 50 or 70 µg/m^3 TDI (2,6-TDI:2,4-TDI mixture 70:30) (0.0035, 0.007, 0.010 ppm, corresponding to 0.012, 0.024, 0.034 mg/m^3 NCO) for four hours in an exposure chamber, showed excretion of 2,6-TDA and 2,4-TDA in hydrolysed plasma samples of two male volunteers. 2,6-TDA was detected at the two highest dose levels and 2,4-TDA only at the highest dose (Skarping et al., 1991).

Three volunteers inhaled HDI in an exposure chamber (11.9. 20.5 or 22.1 µg/m^3, respectively; 0.0017, 0.0030, 0.0032 ppm, corresponding to 0.0059, 0.010, 0.011 mg/m^3 NCO) 2 h/day every second day during one week after which hydrolysed plasma samples were analysed. No metabolites of HDA were detected (Tinnerberg et al., 1995).

Hamada et al. dermally exposed four volunteers to 10, 25, 49 or 50 mg 4,4'-MDI (as 2.0% MDI in petrolatum) for 8 hours. Based on sum of plasma and urine MDA, systemic absorption of applied MDI dose ranged from <0.01% to 0.2%. The authors concluded that 4,4'-MDI absorbed by the skin probably remained bound in the upper layers of the skin. (Hamada et al., 2018)

Distribution

As reported in DECOS (2018), TDI is primarily bound to albumin in plasma of exposed workers. In addition, there have been observations of binding to macromolecules in the blood and to haemoglobin. Furthermore, according to DECOS (2018), HDI can bind to keratin-18 in the bronchial epithelium and to albumin in the fluid that lines the airway epithelium.

Metabolism

Diisocyanates are reactive molecules (due to the NCO group) which easily form adducts with nucleophilic biological macromolecules, specifically albumin or haemoglobin. Also glutathione conjugates are considered relevant. The reaction products can be found in high concentrations at the site of entry and the distribution into the body may continue for longer times. In urine, the corresponding amines can be detected. (ATSDR, 2018, Montelius, 2001, OEHHA, 2019).

Excretion

In the study of Brorson et al. (1991) (see above), TDA was found in hydrolysed urine samples of exposed persons, estimated to represent 17-23% of the inhaled 2,6-TDI dose and 14-19% of the 2,4-TDI dose.

Urinary levels of 2,4-TDA and 2,6-TDA, estimated to represent 8-14% of the inhaled 2,4-TDI dose and with 14-18% of the 2,6-TDI dose, were observed when analysing hydrolysed urine samples (representing the first 24-28 h of excretion) of five men who had been exposed to a TDI mixture (52:48 2,6-TDI:2,4-TDI) at concentrations of 36-43 µg/m^3

(0.0051-0.0060 ppm, corresponding to 0.017-0.021 mg/m^3 NCO) for 7.5 hours (Skarping et al., 1991).

In workers chronically exposed to 2,4-TDI and 2,6-TDI (0.4-4 µg/m^3 (0.000056-0.00056 ppm, corresponding to 0.00019-0.0019 mg/m^3 NCO), the plasma elimination rate was estimated to be 21 days on average (Lind et al., 1996).

HDA metabolites were analysed from urine samples of the exposed volunteers in the study by Tinnerberg et al. (1995). The average urinary excretion was 39%, but the individual variation was notable, ranging from 9% to 94%. The average half-time for excretion was 2.5 h.

The average urine excretion of HDA was 16% of the estimated inhaled dose, when five volunteers had been exposed to 25 µg/m^3 (0.0036 ppm, corresponding to 0.12 mg/m^3 NCO) of HDI for 7.5 hours. >90% of the urinary excretion occurred within 4 hours after exposure and the average half-time for excretion was 1.1-1.4 h (Brorson et al., 1990).

Controlled exposure of workers for 120 minutes in exposure chambers at 0.5-30 ppb of TDI, MDI, HDI, NDI or IPDI was performed by Budnik et al. (2011) . The number of exposed persons varied between three (1,5-NDI) and 55 (1,6-GDI). The study subjects were divided into two groups and the calculated isocyanate load was 496 ± 103 ppb-min for the low dose group and 1569 ± 420 ppb-min for the high-dose group. Urinary excretion of metabolites (isocyanate-diamines) was measured in samples collected during 24 hours. The estimated excretion half-times were calculated as 2.5 h for HDA (peak level in urine at 2 h after exposure) and 6 h for TDA (2,4-TDA peak at 4.1 h and 2,6-TDA at 4.8 h). Urinary excretion of 4,4'-MDA and IPDA peaked at 14 h and 5.6 h after exposure, respectively. A complete elimination of 4,4'-MDA or IPDA was not detected within the 24 h sampling period. In the case of 4,4'-MDA and IPDA, higher urinary peaks were observed in the high-dose group compared to the results of the low-dose group. Such an effect was not observed for 2,4-TDA or 2,6-TDA.

7.1.2 Animal data

Absorption

The information on absorption upon oral administration is limited. At least 12% of the 2,4-TDI-dose (60 mg/kg bw) was reported to be absorbed following oral gavage in rats (Timchalk et al., 1994). It was discussed that most likely, the absorbed radioactive substance was the corresponding amine (2,4-TDA) and not TDI.

Significant absorption of inhaled diisocyanates has been shown in the nasal and alveolar region of experimental animals. In rats, the absorption of inhaled TDI (2 ppm; 14.2 mg/m^3, corresponding to 6,8 mg/m^3 NCO) has been estimated to be 61-90% (Timchalk et al., 1994) and that of MDI (2 mg/m^3) 32% (Gledhill et al., 2005). The nasal uptake of HDI in rats was reported to be >90% (Schroeter et al., 2013). A linear uptake of TDI was observed in guinea pigs exposed by inhalation to doses of 0.0005 ppm to 0.146 ppm (0.0036-1.0 mg/m^3), corresponding to 0.0017-0,48 mg/m^3 NCO) (Kennedy et al., 1989).

Dermal absorption of TDI in male rats was presented in the studies by Yeh et al. (2008) and Hoffman et al. (2010). The absorbed fraction was estimated to be <1% when the applied dose was 350 mg/kg bw (Hoffmann et al., 2010).

Similarly, the absorbed amounts were estimated to be low (0.21-0.88%, 8-120 h after exposure) upon topical application of MDI (15 or 165 mg/kg bw) on rat skin (Hoffmann et al., 2010). In contrast, 29-30% of the dermally administered MDI dose was recovered in the faeces of female rats 48 h after treatment (~30 mg/kg bw) (Vock and Lutz, 1997). Unintentional oral exposure cannot be excluded in the study by Vock and Lutz (1997).

Distribution

Oral administration of a single dose of radiolabelled TDI to male rats showed a high proportion of the dose in the gastrointestinal tract 2 and 48 h after exposure. Low radioactivity levels were also seen in the skin, lung, liver and kidney (Timchalk et al., 1994).

Inhalation of 2 ppm (14.2 mg/m^3) radiolabelled 2,4-TDI (corresponding to 6.8 mg/m^3 NCO) for 4 h resulted in distribution to the carcass, skin, gastrointestinal tract and gastrointestinal contents of the exposed male rats directly after exposure. 48 h later, the highest recovered dose was observed in the gastrointestinal contents (17%) (Timchalk et al., 1994).

Another study (Kennedy et al., 1994), showed highest absolute doses in the trachea and lung, followed by the oesophagus and stomach, and the systemic circulation (blood, liver, kidney, spleen and heart) of rats exposed to 0.026-0.821 ppm (0.19-5.8 mg/m^3) 2,4-TDI corresponding to 0.092-2.8 mg/m^3 NCO) by inhalation for 4 h. Similarly, in guinea pigs exposed to 0.00005-0.146 ppm (0.0036-1.0 mg/m^3) 2,4-TDI (corresponding to 0.0017-0.48 mg/m^3 NCO) for 1, 4 or 5 h, the highest levels were detected in the trachea and lung, followed by the kidney, heart, spleen and liver (Kennedy et al., 1989). A gradual decline in TDI in the blood of guinea pigs exposed by inhalation to 0.004-0.336 ppm (0.028-2.4 mg/m^3) of radiolabelled 2,4-TDI (corresponding to 0.014-1,2 mg/m^3 NCO) was reported. Radioactivity was observed in the blood 72 h after exposure, and persisted at that level for a week, indicating saturation of the molecules to which TDI was bound. In the study by Kennedy et al. (1994), the vast majority of the radioactivity was related to binding with large proteins, most likely albumin.

Haemoglobin adducts of TDI were observed in the blood of guinea pigs exposed by inhalation 3 h/day, 5 days, 1 ppm (7.12 mg/m^3), corresponding to 3,4 mg/m^3 NCO), demonstrating the transport from the lungs to blood (Day et al., 1996).

Exposure of male rats to 2 mg/m^3 (0.20 ppm) of radiolabelled 4,4'-MDI (corresponding to 0.67 mg/m^3 NCO) for 6 h resulted in distribution to several tissues, the concentrations being highest in the respiratory and gastrointestinal tract (Gledhill et al., 2005). The authors were not able to exclude the possibility of additional exposure by the oral route during the study.

Very low concentrations (max 0.52% of the applied dose) were detected in the carcasses of male rats after single dermal application of radiolabelled 2,4-TDI (330 mg/kg bw). No radioactivity was detected in the tissues when radiolabelled 4,4'-MDI was used (8, 24 or 120 h after the exposure) (Hoffmann et al., 2010).

Less than 1% of the applied radioactivity was detected in total in the lungs, liver, kidney and muscles of female rats upon topical application of radiolabelled 4,4'-MDI for 24 h (11-15 mg/kg bw) or 48 h (29-30 mg/kg bw) (Vock and Lutz, 1997).

Metabolism

Diisocyanates are readily hydrolysed in the acidic environment of the gastrointestinal tract to the corresponding amines, which may then be metabolized further. Timchalk et al.(1994) proposed that orally administered TDI is first hydrolysed to TDA, which is then acetylated, conjugated or forming aminophenolic or aminobenzoic acid compounds. In addition, TDA may also form polyuria polymers upon reaction with unhydrolysed TDI. Kennedy et al. (1994) reported conjugation to macromolecules for 95% of the TDI in the plasma of orally exposed rats. Under neutral pH conditions, like in the mouth, TDI is expected to form polyurea polymers when reacting with other TDI molecules, and not to hydrolyse (Sielken et al., 2012).

Inhalation of diisocyanates is mainly expected to result in conjugation reactions. Inhaled diisocyanates may deposit in the lungs and react with glutathione, and the formed conjugates may then be absorbed and detected in the blood as albumin or haemoglobin adducts (ATSDR, 2018, DFG, 2008). Acetylated TDA represented only 10% of the

metabolites detected in rats after inhalation of TDI. No free TDA was found in the urine (Timchalk et al., 1994).

A decrease in CYP2B1 mRNA and protein levels was observed in the lungs of rats exposed to TDI (80:20 mixture 2,4-TDI:2,6-TDI) by inhalation (Pons et al., 2000). No effects on CYP1A1, CYP2E1, CYP3A1 or glutathione-S-transferase were observed.

N-acetylated and N-acetylated hydroxylated MDI-metabolites were identified in the urine, faeces and bile of male rats after inhalation exposure to MDI (Gledhill et al., 2005). Free MDA was not detected. Mixed polyureas formed in spontaneous reactions of MDI were the primary products detected in the faeces.

Excretion

Diisocyanates are mainly excreted in the faeces (DECOS, 2018, Montelius, 2001, IARC, 1999). Orally administered radiolabelled TDI was reported to be eliminated primarily (81%) in the faeces of exposed rats. Small amounts (8%) were also detected in the urine (Timchalk et al., 1994). Biliary excretion of TDI was suggested as significant amounts of radioactivity were observed in the gastrointestinal contents.

Exposure to TDI by inhalation seems to result in a smaller proportion excreted in the faeces (47%, 48 h after administration) compared to oral exposure (Timchalk et al., 1994).

Less than 1% of the dermally applied dose (330 mg/kg bw) of radiolabelled TDI was detected in the urine of rats after up to 8 h of exposure. No radioactivity was detected in the faeces (Hoffmann et al., 2010). The half-life for urinary elimination of 2,4-TDA and 2,6-TDA in male rats after topical application was reported as 18.4-26.6 h. Urine samples were collected at 12-h intervals during 6 days. The maximum concentration in the urine was reached in the first 12-h interval (Yeh et al., 2008).

Very low levels of radioactivity were detected in the faeces and urine of male rats 8, 24 or 120 h after dermal exposure (8 h) to 4,4'-MDI (Hoffmann et al., 2010). Another study (Vock and Lutz, 1997), however, reported detection of 29-30% of the radioactivity in the faeces during 48 h dermal exposure to 4,4'-MDI. The recovery in the urine was <1%. No measures were taken to prevent oral exposure (e.g. via grooming).

7.1.3 In vitro data

No relevant data available.

7.1.4 Biological monitoring

For human biomonitoring, diisocyanate metabolites (diamines) can be measured in urine (for instance, MDA for biomonitoring of MDI, and similarly TDA for TDI). After the hydrolysis of urine, the released amines can be analyzed using different methods.

The elimination half lives of the derived diamines in urine are relatively short (2-5 h), which means that the urine samples need to be collected at the end of the exposure and results mostly reflect the exposure of the data collection (Cocker, 2011).

Further information on this topic, including relationships found between airborne and urine concentrations, is available in section 6.2.

7.1.5 Summary

Diisocyanates are reactive molecules which easily form adducts with nucleophilic biological macromolecules, specifically albumin or haemoglobin. Also glutathione conjugates are considered relevant. The reaction products can be found in high concentrations at the site of entry and the distribution into the body may continue for longer times. The

corresponding amines have been detected in human and animal urine samples after exposure to different diisocyanates, mainly by the inhalation route.

7.2 Acute effects

7.2.1 Human data

Acute human exposure to diisocyanates is in particular related to irritation and sensitisation, as reported in sections 7.4.1. and 7.5.1. Some rare cases of human fatalities attributed to TDI-induced chemical pneumonitis have been published, but there was no information on exposure (NRC, 2004).

7.2.2 Animal data

Acute oral toxicity

Low to moderate acute toxicity has been observed following oral exposure. Oral LD50 values are summarised in the Table 21.

Table 21: Oral LD50 values

Substance	Oral LD_{50} (mg/kg bw)	References
TDI	>2000	(ECHA, 2019)
Mixture of 2,4-TDI and 2,6 TDI (80:20)	5110 (M), 5620 (F)	(NTP, 1986)
TDI (mixed isomers)	5840	(ECHA, 2019)
HDI	959	(ECHA, 2019)
HDI	746-959	(OECD, 2001)
MDI	>2000	(ECHA, 2019)
MDI	>7616	(ECHA, 2019)
MDI	>10000	(ECHA, 2019)
NDI	>5000	(ECHA, 2019)
IPDI	4814	(ECHA, 2019)
IPDI	5490	(ECHA, 2019)

Acute dermal toxicity

Exposure to diisocyanates via the dermal route has not been shown to result in deaths of test animals (see Table 22)

Table 22: Dermal LD50 values

Substance	Dermal LD_{50} (mg/kg bw)	References
TDI	>9400	(ECHA, 2019)
HDI	>7000	(ECHA, 2019)
Polymethylene Polyphenylisocyanate (PAPI)	>9400	(ECHA, 2019)
IPDI	>7000	(ECHA, 2019)

Acute inhalation toxicity

Acute exposure to diisocyanates by inhalation can cause pulmonary haemorrhage, emphysema, pneumonia and death. At lower doses, the symptoms include mouth-breathing, lacrimation, salivation and restlessness. (ATSDR, 2018, OEHHA, 2019, Montelius, 2001).

Concentration-dependent signs of respiratory distress, including irregular and laboured breathing, reduced breathing rate and red encrusted nostrils, were reported in rats exposed to PMDI for six hours (doses 0.7-20 mg/m^3) (Pauluhn, 2000a). Acute exposure of rats to PMDI at 15.8 and 38.7 mg/m^3 during 150 minutes resulted in an increase in respiratory rate (Pauluhn et al., 1999).

In a 4-hour inhalation study with HDI monomer vapour or HDI isocyanurate prepolymer aerosol in rats, the main findings included nasal discharge, laboured respiration and spasms of the eyelid muscles. The HDI monomer showed a higher potency and longer-lasting signs of respiratory distress than the aerosol (Pauluhn, 2000b). Lee et al. (2003) compared the effects of HDI monomer vapour (3 h; 1 or 10 mg/m^3) with HDI biuret aerosol (5 h; 1 or 10 mg/m^3) in mice. The HDI monomer vapour seemed to react in the upper airways, showing no lung pathology or influx of macrophages or neutrophils. The HDI biuret, on the other hand, seemed to deposit in alveolar ducts and terminal bronchioles.

LC50 values are summarised in Table 23.

Table 23: Inhalation LC50 values (rats, 4 h exposure)

Substance	Inhalation LC_{50}	References
TDI	13.9 ppm (99 mg/m^3)	(Duncan et al., 1962)
Mixture of 2,4-TDI and 2,6 TDI (80:20)	66 ppm (470 mg/m^3) (1 h exposure)	(ECHA, 2019)
HDI (monomer)	124 mg/m3 (18 ppm)	(Pauluhn, 2000b)
HDI (isocyanurate)	462 mg/m3	(Pauluhn, 2000b)
MDI	490 mg/m3 (48 ppm)	(ECHA, 2019)
MDI	415 mg/m3 (41 ppm)	(ECHA, 2019)
NDI	270 mg/m3 (31 ppm)	(ECHA, 2019)
IPDI	40 mg/m3 (4.4 ppm)	(ECHA, 2019)
IPDI	31 mg/m3 (3.4 ppm)	(ECHA, 2019)

7.2.3 In vitro data

No relevant data available.

7.2.4 Summary

The main diisocyanate-induced acute effects reported are related to symptoms occurring after exposure by inhalation. Diisocyanates can cause pulmonary haemorrhage, emphysema, pneumonia and death. Some of the diisocyanates have a harmonised classification as Acute Tox 2, 3 or 4 (see Section 0).

7.3 Specific target organ toxicity / Repeated dose toxicity

7.3.1 Human data

Case reports and case series have been published concerning suspected central and peripheral nerve toxicity following heavy exposure to TDI efor example during a fire at a

polyurethane foam factory (Axford et al., 1976, Le Quesne et al., 1976) or dockworkers exposed to liquid TDI from a punctured storage drum (Singer and Scott, 1987).

Hughes et al. (2014) recently evaluated the available data on the neurotoxicity of diisocyanates to determine whether a causal association could be established between diisocyanate exposure (the studies involved exposure to TDI, MDI, HDI, or unspecified diisocyanates) and neurotoxicity. Using the Hill criteria for causality, Hughes et al. (2014) concluded that there was limited evidence for strength of association and consistency, and the data were inadequate to establish a causal association between diisocyanates and neurotoxicity. The investigators noted several limitations of the studies included in their systematic review such as limited exposure information (including the lack of objective exposure measures and no dose-response assessment), co-exposure to known neurotoxicants, and lack of objective measures of neurotoxicity. Additionally, they noted that no plausible mechanisms of toxicity were identified.

7.3.2 Animal data

Oral studies

Repeated dose effects were studied in rats (0, 7 (only in the first study group), 15, 30, 60, 120, 240mg/kg bw; mice (first study group 0, 6, 12, 25, 50, 100 mg/kg bw, and second group 0, 15, 30, 60 and 120 mg/kg bw) exposed to TDI by oral gavage during 13 weeks. The exposure resulted in mucoid bronchopneumonia in male and female rats at 240 mg/kg bw. In male rats a depressed mean body weight was seen at 120 and 240 mg/kg bw. 2/10 female mice of the 240 mg/kg bw dose group and one of the 120 mg/kg bw group died as a result of exposure. No effects were seen in male mice. (NTP, 1986)

Inhalation studies

No studies indicating systemic effects in specific target organs were found. The upper airways are the target organ for local effects upon inhalation exposure, which has been shown in several studies performed with different diisocyanates. The effects seem to be more related to concentration than to duration of exposure. (ATSDR, 2018, DECOS, 2018).

Focal inflammatory lesions and accumulation of foreign material in alveolar macrophages were observed in rats exposed to PMDI (3.3 and 13.7 mg/m^3) 6 h/day during two weeks. At 3.3 mg/m^3, the respiratory rate increased slightly, whereas at 13.7 mg/m^3 serious nasal discharge, laboured breathing, breathlessness and an increase in inflammatory cells in BAL fluid was observed. (Pauluhn et al., 1999)

Three-week exposure of rats with monomeric HDI (0.03, 0.12, 1.03 mg/m^3 (0.004, 0.017, 0.15 ppm); corresponding to (0.015, 0.06, 0.51 mg/m^3 NCO); 5 h/day, 5 days/week) resulted in lesions (squamous metaplasia, epithelial hyperplasia and globlet cell hyperplasia) in different nasal regions even at the lowest dose. These effects were considered reversible. Chronic inflammation was observed at the two highest doses and degeneration of the olfactory epithelium occurred at the highest dose. The changes in the olfactory epithelium persisted two weeks after exposure and were regarded as critical, adverse effects. (Shiotsuka et al., 2006)

Whole-body exposure of rats to HDI monomer vapour for 13 weeks (6 h/day, 5 days/week; 0.07, 0.3, 0.96 mg/m^3, (0.010, 0.043, 0.14 ppm; corresponding to 0.035, 0.15, 0.48 mg/m^3 NCO), resulted in nasal lesions, including hyperplasia, squamous metaplasia and mucous cell hyperplasia of the respiratory epithelium, and infiltration of inflammatory cells mainly in subepithelial tissues. Effects were seen at all dose levels, but were minor at the lowest dose. Degenerative changes in olfactory epithelium were observed only in two male rats at the highest dose. No effects were observed in the larynx, trachea or lungs. (OECD, 2001, OEHHA, 2019)

Also in a chronic study where rats were exposed to monomeric HDI at concentrations up to 1.13 mg/m^3 (0.16 ppm, corresponding to 0.56 mg/m^3 NCO) for two years, the nasal cavity was the principal target organ, with chronic inflammation and olfactory epithelium degeneration reported as the main findings (Shiotsuka et al., 2010).

Adverse effects in the respiratory system were observed in rats exposed three weeks to HDI isocyanurate or biuret (3, 15, 75 mg/m^3, 6h/day, 5 days/week). Histopathological findings covered focal hyperplasia in the larynx and trachea. Inflammation, fibrosis, septum thickening and an increase in alveolar macrophages in the bronchioalveolar region were also observed. The findings occurred at the highest dose level in the groups exposed to HDI isocyanurate or biuret, and to a lesser extent at the mid-dose level of the HDI biuret group. (Pauluhn and Mohr, 2001). A sub-chronic (13-week) study was performed with rats exposed to HDI isocyanurate or biuret (0.4, 3, 25 mg/m^3, 6h/day, 5 days/week) (Pauluhn and Mohr, 2001). At the highest dose-level, both tested chemicals caused bronchioalveolar lesions (increase in alveolar macrophages, thickening of septa, fibrosis and bronchioalveolar proliferation). No changes in lung functions were observed.

7.3.3 In vitro data

No relevant data available.

7.3.4 Summary

A few studies indicate a potential for neurotoxic effects in humans exposed to diisocyanates. The data are however inadequate to establish a causal association between diisocyanates and neurotoxicity. No indications of neurotoxicity have been observed in animal studies.

The main specific target organ effects reported in several animal studies are varying levels of lesions in the respiratory tract occurring upon inhalation of diisocyanates. Minor, reversible, nasal lesions have been observed already at low doses (0.03-0.07 mg/m^3; corresponding to 0.004-0.01 mg/m^3 NCO), repeated exposure three or thirteen weeks) and at higher concentrations, the lesions were more severe.

7.4 Irritancy and corrosivity

7.4.1 Human data

In humans, exposure to (di)isocyanates can result in irritation of the skin, mucous membranes, eyes, and respiratory tract. The IPCS (1987) concluded from their review of volunteer studies that short term exposure to TDI causes eye and nose irritation with a threshold of 0.35 - 0.92 mg/m^3 (0.17-0.44 mg/m^3 NCO) with skin irritation generally arising at higher concentrations. As there is clear evidence that respiratory sensitisation occurs at much lower exposure levels, these effects are not further discussed in this report. However, one human voluntary study (Vandenplass et al., 1999) studying more subtle airway injury and cellular inflammation effects of short-term TDI exposure is described in Chapter 7.5.1

7.4.2 Animal data

Skin irritation

MDI caused skin irritations in acute dermal irritation/corrosion guideline tests performed in rabbits. In addition, the results obtained with TDI, HDI and IPDI indicate that the substances are corrosive. NDI did not cause skin irritation. (ECHA, 2019)

Eye irritation

Application of TDI, HDI and IPDI to the eyes of rabbits resulted in serious eye irritation. MDI was slightly irritating, whereas NDI did not cause eye irritation. (ECHA, 2019)

Respiratory irritation

Inhalation of TDI has been shown to cause histological alterations (inflammation, hyperplasia, degeneration, ulceration and metaplasia) in the nasal cavity, trachea and lungs of the exposed animals (Arts et al., 2008, Buckley et al., 1984, Johnson et al., 2007, Loeser, 1983, Matheson et al., 2005, Sangha and Alarie, 1979, Zissu, 1995, Gordon et al., 1985, Wong et al., 1985). A NOAEL of 0.031 ppm (0.22 mg/m^3, corresponding to 0.11 mg/m^3 NCO) for histopathological nasal changes was identified in the study by Sangha and Alarie (1979).

For the 2,4-TDI isomer, RD_{50} values (expressing 50% decrease in respiratory frequency) of 0.813, 0.498, 0.386, 0.249, 0.199 and 0.199 ppm (5.8, 3.5, 2.7, 1.8, 1.4 and 1.4 mg/m^3, corresponding to 2.8, 1.7, 1.3, 0.87, 0.68 and 0.68 mg/m^3 NCO) were obtained in mice following exposure durations of 10, 30, 60, 120, 180, and 240 minutes (Sangha and Alarie, 1979). The RD_{50} value for the 2,6-isomer was 0.26 ppm (1.9 mg/m^3, corresponding to 0.92 mg/m^3 NCO) (180 minutes exposure) (Weyel et al., 1982). Additional studies presented RD_{50} values of 0.24 ppm (1.7 mg/m^3, corresponding to 0.82 mg/m^3 NCO) (Barrow et al., 1978), 0.39 ppm (2.8 mg/m^3, corresponding to 1.4 mg/m^3 NCO) (de Ceaurriz et al., 1981) and 0.67 ppm (4.8 mg/m^3, corresponding to 2.3 mg/m^3 NCO) (Schaper, 1993).

In the study of Weyel and Schaffer (1985), an RD_{50} value of 32 mg/m^3 (3.1 ppm) was obtained when mice were exposed to 4,4'-MDI for 4 hours (corresponding to 11 mg/m^3 NCO). At 7 mg/m^3 (0.68 ppm, corresponding to 2.3 mg/m^3 NCO) an increased respiratory rate followed by a gradually declining respiratory rate was observed, indicating that the substance caused pulmonary irritation rather than sensory irritation.

The RD_{50} values for HDI monomer were determined in mice as 0.35 ppm (2.4 mg/m^3, corresponding to 1.2 mg/m^3 NCO) at 60 minutes and 0.17 ppm (1.2 mg/m^3, corresponding to 0.60 mg/m^3 NCO) at 180 minutes (Sangha et al., 1981).

In a three-week rat study, the animals were exposed to monomeric HDI 5 h/day. Sneezing was observed at the first study week among animals of the high-dose group (0.300 ppm; 2.06 mg/m^3, corresponding to 1.0 mg/m^3 NCO) and at the second week in rats exposed to 0.150 ppm (1.03 mg/m^3, corresponding to 0.51 mg/m^3 NCO). (OECD, 2001, OEHHA, 2019)

An immediate decrease in minute volume occurred in rats exposed to HDI monomer 30 minutes at 4 mg/m^3 (0.58 ppm, corresponding to 2.0 mg/m^3 NCO) or higher doses, showing a clear dose-response. The maximum depression of minute volume was calculated to occur at exposure levels higher than 70 mg/m^3 (Pauluhn, 2015).

In the study by Pauluhn (2004) the effects of different polyisocyanates on lung weight and total protein and lactate dehydrogenase in the BALF were measured and interpreted as indicators of pulmonary irritation. The results did not show a clear correlation between the NOAECs and the free isocyanate moieties, and the author concluded that the content of free NCO seems to be a poor predictor of the potency of polyisocyanates to cause pulmonary irritation.

In Pauluhn (2000a) the BAL protein level increased by approximately 50% at 0.7 mg/m^3 (LOAEC) following 6-hour exposure of rats to MDI/polymeric MDI mix aerosol (approximately 54% monomeric MDI, 34% 3-oligomeric MDI and 9% 4-oligomeric MDI).

In a study in rats, 6-hour exposure to HDI-based polyisocyanate mixture at the level of 2.7 mg/m^3 (mainly as aerosol) statistically significantly increased BAL protein concentration (by approximately 2.5 times). NOAEL was 0.5 mg/m^3. Sensory irritation-related decrease in respiration rate and minute volume was not assessed. (Ma-Hock et al., 2007)

7.4.3 In vitro data

No relevant data available.

7.4.4 Summary

Diisocyanates are well-known to cause skin and eye irritation, and have harmonised classifications as skin and eye irritating substances. Some diisocyanates (TDI, HDI and IPDI) are also corrosive. Diisocyanates are also causing respiratory irritation, and studies investigating RD_{50} values have been published. A NOAEL of 0.031 ppm (0.22 mg/m^3, corresponding to 0.015 ppm/0.11 mg/m^3 as NCO) has been reported for nasal effects of TDI.

7.5 Sensitisation

7.5.1 Human data

The most common adverse health effect of diisocyanate exposure is respiratory allergy of which asthma is the most disabling effect. Less prevalent are other forms of sensitisation, like allergic contact dermatitis. The below paragraphs concentrate on describing human data concerning asthma and its relation to peak, cumulative and average inhalation exposure, dermal exposure as well as timing of exposure. The most relevant studies and findings are then summarised together with animal data in Section 7.5.3.

When interpreting the human data on diisocyanate-induced asthma it is important to note that methods to assess both the exposure and the outcome have developed over the time and consequently it is not straightforward to compare older and more recent studies.

Isocyanates may be in the form of vapours or aerosols, they are highly reactive and therefore very unstable. Even in the same air sample several different chemical species may be present. Also there has been a trend in the industry to reduce the content of free monomers in formulations and replace the monomers with prepolymers and polyisocyanates (Streicher et al., 2000). Most of the sampling and analytical methods address only diisocyanate monomers and quantification of polyisocyanates (oligomers) is much more complex (Bello et al., 2004). Studies using such methods would not give comparable information of the overall exposure in current and historical situations with different share of monomers vs prepolymers or polyisocyanates.

Asthma is characterised by a variable airway obstruction. Modern guidelines define asthma as follows: *Asthma is a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (GINA, 2019)*. Occupational asthma (OA), in turn, is defined as follows: *Occupational asthma is a disease characterised by variable airflow limitation and/or hyperresponsiveness associated with inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace* (Baur et al. (2012), Bernstein et al. (2013)).

The diagnosis of asthma is a clinical one, based on typical symptoms and evidence of variable airway obstruction. For the latter the diagnostic methods include peak expiratory flow monitoring, spirometry and measurement of bronchial hyperresponsiveness. The latter diagnostic tool was not used in the studies before early 1990s. Bronchial hyperresponsiveness is non-specific and may be caused by a number of factors. This would, however, not cause a bias in an epidemiologic study provided that the exposure to those other factors is not dependent of the exposure to the factor that one studies.

The diagnosis of occupational asthma is usually done by tests that separate asthma cases from normality or other lung diseases, tests that identify the workplace as the cause of the respiratory symptoms, and tests that identify the agent causing the occupational asthma; procedures are extensively discussed in a European Respiratory Society working group report (Baur et al., 2012). Workers with confirmed sensitisation-induced occupational asthma may not fulfil the criteria for compensation in a particular country. Criteria for legal compensation vary between different administrations. In epidemiological studies, a complete clinical workup is often not feasible and because of the complex etiology of diisocyanate asthma, as well as the different phenotypes of asthma, proxies of occupational di-isocyante asthma are often being used for practical reasons such as combinations of (work related) asthma symptoms and bronchial-hyperresponsiveness (assessed by metacholine challenge), and/or peak expiratory flow records over longer periods of time. Indicators of specific sensitization, of which a specific inhalation challenge test with the suspected causative under controlled conditions in an inhalation chamber is the most sophisticated one, are more often used in workers compensation purposed rather than in research projects.

As explained above occupational asthma as a recognised occupational disease on the other hand is based on national compensation criteria which typically include rules concerning the asthma diagnosis itself, evidence of causality between the factor at work as well as a requirement of a certain level of severity of disease. Data from such systems is briefly discussed, but not considered useful for risk assessment purposed for various reasons.

7.5.1.1 Respiratory sensitisation

Case reports and case studies

ECHA (2018a) summarised 86 human case reports or case studies that had been published between 1955 and 2013. These reports primarily provide overwhelming proof that humans exposed to diisocyanates may suffer from a broad spectrum of respiratory effects including asthma and pathological remodelling of the airways. Also a number of fatal cases have been reported, albeit not in recent years. On the other hand very few of these studies include reliable exposure (let alone exposure-response) information and they feature only a small number of patients. For all of these reasons, these reports are therefore principally unsuited for use in quantitative hazard assessment.

Some of the case reports describe OA cases also in non-industrial occupations like among hospital personnel applying orthopaedic plaster casts containing diisocyanates (Sommer et al., 2000, Donnelly et al., 2004). More recently, Suojalehto et al. (2011) reported two such OA cases in nurses, confirmed with a placebo controlled inhalation chamber challenge test with MDI. Based on a casting simulation with 15 minute sampling, exposures were estimated for breathing zone (0.11 µg NCO/m^3), near casting spot (0.55 µg NCO/m^3) and removing plaster cast, near sawing spot (2.5 µg NCO/m^3). During actual hospital work the exposures were lower due to the 60 minute sampling period including phases without casting work. No estimates of past peak exposures were given and the total NCO, instead of specific isocyanate types, was measured.

Epidemiological studies

This paragraph as well as the summary description of the epidemiological studies in Appendix 3 is based on the work reported by ECHA (2018a). However, some details from the original studies have been added that are relevant for exposure-response considerations. Also, some studies published only more recently have been added.

As the NCO group is considered to be responsible for the sensitising properties of isocyanates, several different diisocyanates (and sometimes also their oligomers) are presented together (see also Bello et al. (2004)). In case an eligible study for dose-response assessment would be found, transfer of this to the whole group of diisocyanates could be considered (see also Mode of Action considerations in Chapter 7.9).

The tables in Appendix 3 comprise three reviews on TDI from the early 2000s (Diller, 2002, Ott, 2002b, Ott et al., 2003a), one more recently (Daniels, 2018), two case-control studies on asthma due to TDI, MDI or HDI (Meredith et al., 2000, Tarlo et al., 1997) and many longitudinal as well as cross sectional studies. The longitudinal studies are of different length, ranging from 1 year to 19 years (Cassidy et al., 2010). Most of the studies were performed with workers exposed to TDI.

In what follows, the most relevant studies are described. The studies are grouped in reviews, longitudinal, case-control and cross-sectional studies. The focus is on studies that may provide quantitative information on exposure and exposure-response relationships. Also human voluntary studies and data from occupational disease statistics are briefly described.

Reviews

In the early 2000s, three reviews on respiratory effects due to TDI were published (Diller (2002), Ott (2002) and Ott et al (2003)). Diller (2002) reviewed studies on OA due to TDI to calculate prevalence and incidence of TDI-induced asthma. The author states that the reviewed studies are heterogeneous (regarding population, validity of diagnosis of TDI asthma, industry, exposure levels), of limited validity, and difficult to interpret.

The prevalence of asthma due to TDI was estimated from ten cross-sectional studies conducted in TDI manufacturing, foam production, applications of varnish or paint, and other uses. The studies included 788 individuals and covered the 38-year period from 1954 to 1992. The reported prevalence of OA in the exposed populations varied widely (from 0 to 85 %) and ranged from 0 to 10 % since the late 1980s at workplaces with mean TDI exposure levels < 15 ppb (108 µg TDI/m³, 52 µg NCO/m3) and was higher in workplaces with higher exposures. Later reviews have reported a prevalence of work-related allergic respiratory disorders due to TDI was estimated to be 1-10 % and prevalence due to MDI 13-27 % by the Health Council of the Netherlands (Gezondheidsraad, 2008). In a study by Pronk et al prevalence of bronchial hyperreactivity was as high as 20 % in spray painters, who were mainly exposed to HDI oligomers (Pronk et al., 2009).

It should be noted that cross-sectional studies are likely to look at survivor populations and therefore disease frequency may be underestimated.

Incidence of OA due to TDI was estimated by Diller (2002) from nine longitudinal studies conducted in TDI manufacturing, research and development, and flexible foam production. The studies included 2751 workers under risk and cover the 38-year period from 1954 to 1992. Annual incidence of TDI asthma has been up to more than 5 % before 1980 and was reported to be between 0 and 0.7 % thereafter. The downward trend is attributed to a downward trend in TDI exposure. The review reports sparse and mostly qualitative information on the exposure levels and the incidence of TDI-induced asthma is not discussed with regard to particular exposure levels.

The reviews of Ott (2002) and Ott et al. (2003) however focus on exposure-response relationships (Ott 2002; Ott et al. 2003)(Ott, 2002a, Ott et al., 2003b). Appendix 3 gives an overview of the exposure levels and the incidence of OA in the studies reviewed by Ott (2002). It shows that annual OA incidence rates were reported as 5-6 % in earlier times (1950s-1970s) both in TDI manufacture and in TDI using industries and that incidence declined to < 1 % with reduction of TDI concentrations to < 5 ppb (= 36 µg TDI/m³, 17 µg NCO/m^3) (8 h personal samples). The second review by Ott et al. (2003) also reports annual asthma incidences between 0.7 to 1.1 % from four newer studies (1970s to 1990s) with TWA concentrations mostly < 5 ppb (= 36 µg TDI/m³, 17 µg NCO/m^3). However, short-term TDI concentrations were > 20 ppb (= 145 µg TDI/m³, 70 µg NCO/m^3) and occasionally > 80 ppb (= 570 µg TDI/m³, 275 µg NCO/m^3). The author of the two reviews assumes that the majority of asthma cases may arise from TDI short-term concentrations > 20 ppb (= 145 µg TDI/m³, 70 µg NCO/m^3). For example, in one of the longest studies in a TDI manufacturing facility, 7 of 19 cases had reported previous incidents of exposure

to TDI, 2 of them related to rashes that had developed while handling TDI or waste products containing TDI (Ott et al., 2000). Likewise, in a cross-sectional study in a urethane mould plant designed to minimise exposure to MDI and where continuous monitoring of MDI area levels showed concentrations below 5 ppb (= 51 µg MDI/m³, 17 µg NCO/m^3), asthma cases were considered to be due to intermittent higher than normal exposures to MDI during non-routine working activities (Bernstein et al., 1993) . However, when trying to establish a threshold or exposure-response relationship for sensitisation, one has to keep in mind that very high exposure concentrations, for example during accidental spills, might also lead to irritant induced asthma (Reactive Airways Dysfunction Syndrome, RADS).

After analysing the levels and roles of average and peak exposures in the reviewed studies Ott (2002) and Ott et al. (2003) draw two main conclusions. Firstly that under conditions with TDI exposures below 8h TWA of 5ppb and peak exposures below 20 ppb the annual incidence of occupational asthma has dropped below 1%, as compared to annual incidences from 1% to as high as 5-6% under earlier higher exposures. Secondly, that while studies of lung function have indicated that continued exposure after development of work-related respiratory symptoms can lead to transient or accelerated fixed declines in FEV_1, under conditions with TDI exposures below 8h TWA of 5ppb longitudinal studies in settings with ongoing medical surveillance have provided no consistent evidence of accelerated FEV_1 loss. The conclusions of Ott et al. were debated by others (Högberg et al., 2005).Regarding the two conclusions of Ott et al., It is noted that an annual incidence of less than 1% does not mean absence of occupational asthma or exclusion of an important cumulative incidence in a working population over several years. Secondly, asthma is a disease characterised by a variable airflow obstruction (varying in severity and frequency) (see section 7.5.1 above). Accelerated FEV_1 loss is not part of modern definitions of asthma or occupational asthma, while it is possible that later in the course of disease airway obstruction becomes permanent and may also get worse. However, absence of subjects with accelerated FEV_1 loss in a working population cannot be taken as a proof of absence of cases with occupational asthma.

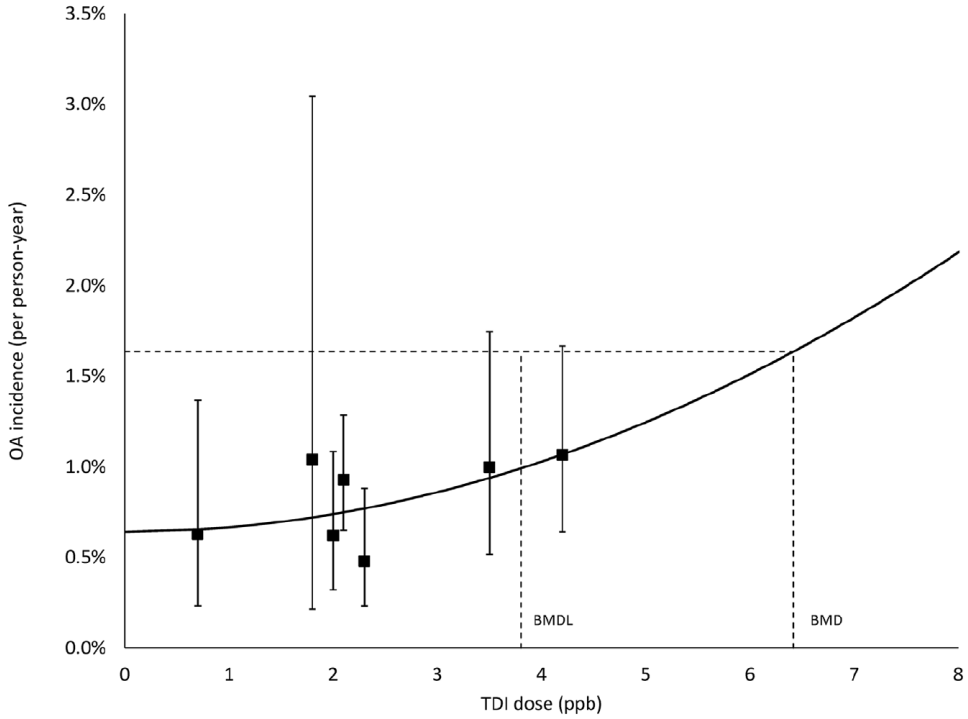
More recently, Daniels (2018) reviewed studies on occupational asthma risk from exposure to TDI, performed a meta-regression analysis of the suitable studies, calculated BMD_{01} and $BMDL_{01}$ values, and applied a low dose extrapolation to calculate a risk-based OEL corresponding to a 45 year working life extra risk of 1/1000. Studies judged suitable for dose-response analyses were those reporting data sufficient to estimate three key variables for dose-response modelling: i) the number of potential OA incidence cases; ii) the average TDI airborne exposure level over the observation period; and iii) the number of person-years at risk. Data sources were limited to study populations exposed to average TDI concentrations below 20 ppb. Data on eight TDI-exposed populations were suitable for analysis. There were 118 OA cases in a population contributing 13 590 person-years. The quadratic model showed the best fit resulting in a $BMDL_{01}$ of 4.32 ppb of TDI. Given the severity of disease and in the absence of specific information on human toxicokinetics and toxicodynamics an uncertainty factor of 10 was applied resulting in an OEL of 0.4 ppb. Also a low-dose extrapolation using either linear no threshold (LNT) or quadratic rate function was performed to estimate an OEL corresponding to a working lifetime extra risk of 1/1000. The quadratic model had the best fit and resulted in an OEL of 0.3 ppb of TDI corresponding to 1/1000 extra risk. It is noted that the above ppb values of 0.4 and 0.3 for TDI would correspond to NCO concentrations of 1.4 and 1.0 µg NCO/m^3. It is to be noted that with LNT rate function the exposure concentration corresponding to a 1/1000 excess was lower (0.018 ppb of TDI). An extra risk of 1/100 corresponded to an exposure of 1 ppb (quadratic rate function) or 0.2 ppb (linear rate function), i.e. 3.4 and 0.7 µg NCO/m^3 respectively. The two dose-responses are presented in Table 24.

Table 24: Excess risk of TDI-induced OA from continuous TDI exposure over a 45-year working lifetime (Daniels, 2018).

Average TDI exposure (ppb)	Extra risk (cases per 1000 persons)	
	Quadratic rate function	Linear rate function
5	238	245
1	10	55
0.3	1	-
0.1	<1	6
0.02	-	1
0.01	<1	<1

The role of peak exposures was not assessed. Moreover Daniels (2018) acknowledged that "*Data on the appropriate exposure index for dose-response modelling are uncertain. It remains unclear whether TDI-induced asthma is a consequence of low cumulative exposure, exposure intensity, or some combination that also accounts for time ordering of intermittent exposure.*" and "*For this study, it is assumed that the risk of TDI sensitization is related to average exposure, which may also be a correlate of peak exposures.*" The extra risk per average exposure was calculated per 1000 workers who are continuously exposed to that average level of TDI over a 45-year working lifetime. The case definition varied between the studies and was based either on work-related symptoms compatible with OA, a diagnosis by a physician or review of medical files. It is also noteworthy that the best fitting models of Daniels (2018) showed a significant non-zero incidence at zero cumulative exposure. This indicates that factors other than average TDI air concentration played a role. Lynch et al. (2018) recently additionally pointed out that Daniels (2018) did not consider underlying study quality and used aggregated data over decades of plant operation within studies (i.e., combined data on OA incidence across several decades during which airborne concentrations declined). Lynch et al. (2018) also questioned the need for an additional uncertainty factor of 10 for human sensitivity used by Daniels.

It is to be noted that studies with exposure to HDI (e.g. Pronk et al. (2007) and Pronk et al. (2009) see below) were not included. Also the study of Collins et al. (2017) (see below) was not included as it was published after the literature search for the review was performed.



Meta-exposure response relation across 7 epidemiological studies (3 cross-sectional studies and 4 longitudinal studies) as derived by Daniels et al. (2018) for the estimated incidence of TDI induced asthma and cohort average TDI exposure. The curve is based on a Benmarck Dose-analysis resulting in a (statistically non-significant) quadratic model, which had the highest fit. The closed squares are point estimates of exposure and asthma incidence per study, the whiskers are confidence intervals for each individual study.

Concerning the studies and analyses of Daniels (2008):

Daniels et al. specifically reviewed the literature for studies suitable for exposure-response analyses and identified 8 studies which could potentially be used for secondary exposure-response analyses.(Daniels, 2018) These studies were identified on the basis that they should give information about the number of potential occupational asthma cases, the average TDI airborne exposure level for the study and the number of person-years at risk. Also cross-sectional studies were included and the number of person years at risk were estimated from the available information in the respective publications. In the figure below the meta-exposure response relation is shown across 7 studies. The study by Daftarian et al. (2000), was removed because it was argued that this study was an "outlier" because of the unexpected high asthma incidence rate.

It is noted that some key methodological issues complicate a straightforward analysis:

- Person time has been reconstructed for the cross-sectional studies. Because individuals eligible for inclusion in the cross-sectional study may have died or disappeared before establishment of the cross-sectional sample, this approach likely leads to biased estimates of the person time at risk and thus biased incidence rates. This approach is not an accepted epidemiological practice and not commonly applied in case of meta-analyses.

- the Daniels et al. (2018) study is a meta-regression study in which each study contributes one point to the exposure response analysis presented in figure 1 of the paper. The position on the exposure axis for each study depends strongly on the allocation of exposure measurements across the cohort. In most cases, sampling effort was highest for occupational titles with higher exposures, biasing a simple estimate of cohort average exposure. The location on the asthma incidence axis is, in particular when lung function or symptom data has been used, potentially also influenced by confounding variables such as smoking, age, and potentially atopy. Thus, considerable uncertainties exist which are not reflected by the confidence intervals.
- The five longitudinal studies, which represent almost 11 000 person years of follow-up and 89 asthma cases, point to an overall incidence rate of 0.82 per 100 person years at exposure levels between 2 and 4 ppm of TDI. The populations in these studies were exposed between 1967 and 1997 and likely accumulated most person years during the early decades. Differences in average exposure between cohort studies were a little higher than a factor two. It is likely that such a small difference in exposure can be the result of differences in exposure assessment approaches between studies. Similarly, disease rates also differ little more than a factor two and these differences can also easily be explained by differences in endpoint characterization.
- Studies allowed to a meta-analysis should in essence have a similar methodology. That was not the case for the disease endpoint and exposure information.

It is considered that the above-mentioned aspects make indicate that the results of the Daniels study could not be used for a quantitative risk assessment and that a meta-regression analysis should preferably use exposure response relations from individual studies, adjusted for confounding variables, which are combined into one meta-exposure response relation. It was therefore evaluated whether the studies included in the review by Daniels (2018) could supply individual exposure-response which could be of use in an alternative exposure-response analysis.

Three cross-sectional studies were included in the review (Daftarian et al. (2000), Belin et al. (1983), Omae (1984)). Only one of the three cross-sectional studies included in the review did perform an internal exposure response type of analysis (Daftarian et al. (2000)). This study involved 114 workers (participation rate 39%) (numbers differ for different variables) who underwent a medical evaluation (symptoms, serology, serial peak flow measurements). In addition, an extensive exposure survey was completed to characeterize exposure to diisocyanates. Because of the relatively small size of the study, a meaningful epidemiological analysis was not possible. Generally, more symptoms and serological responses and a higher peak flow variabilty were seen among the high exposed (>0.43 $\mu g/m^3$ TDI (or ~1ppb)) although differences were generally not statistically significant because of the limited power of the study. The low response rate might have introduced selection bias.

The longitudinal studies included in the Daniels study had an estimated asthma incidence between 0.48 and 1.07 cases per 100 person years of observation and an estimated average TDI exposure between 2.0 and 4.2 ppm over eight hours TWA and are evaluated below:

- UK 12 factory cohort study. A large study among more than 1000 workers by Bugler et al. (1991), has only been published in a report and has not been made available as a peer review publication. The report could not be found through an internet search. Two papers on the same population focus on longitudinal lung function changes, but not asthma specifically (Clark et al. (1998), Clark et al. (2003)). These papers did not produce any information that could be used for the purpose of this evaluation.

- US Cohort. Jones et al. (1992) studied 386 workers (88.7% of target population) with exposure to toluene diisocyanate (TDI) for effects on respiratory health in two plants manufacturing polyurethane foams. Personal monitoring was used to characterize job exposures and 4,845 12-min personal samples were available of which 9% exceeded 5 ppb and 1% exceeded 20 ppb. Logistic regression showed that chronic bronchitis was more prevalent among those with higher cumulative exposures, after controlling for smoking, age, and sex. Methacholine reactivity was associated with reduced airway function. Daniels et al. (2018) reconstructed the person time exposed crudely on the basis of the size of the population and the average duration of follow-up. 12 cases occurred during follow up, leading to an incidence rate of 0.62 per 100 person years, but cases might have been missed because of loss of medical services at some point during surveillance. The case definitions were unclear. Half of the cases were confirmed by a TDI challenge test. No internal exposure response relations was presented for these asthma cases.
- NIOSH US Southwestern Louisiana new plant study. The study described by Weill et al. (1981) and Diem et al. (1982) included 168 naïve subjects followed for 5,5 years in a TDI production plant. In years 2, 3, 4 and 5 approximately 25 subject were added bringing the total population size to 277 individuals. The study subjects included during follow-up had less than 11 person-months prior TDI exposure. 12 asthma cases developed during follow-up with an accumulated 1200 exposure years of follow-up leading to an incidence rate of 1 per 100 person years. Approximately 2000 personal samples had been collected and the median 8-hour time-weighted average exposure was 0.002 ppm. The 25th and 75th percentiles were 0.0011 and 0.0036 ppm respectively. No internal exposure response analysis was conducted.
- BASF manufacturing complex in Geismar, Louisiana plant. Ott et al. (2000) gives an average annual incidence of 1.1% over the period of 1967-1996 for 297 TDI workers. Exposure was characterized using the paper tape method. The cumulative occupational asthma incidence for workers in the TDI unit over a 20 year period was estimated to be 11%. Occupational isocyanate asthma was not explicitly defined, but the authors concluded that the occurrence of a single episode of asthma-like symptoms was not considered sufficient to classify the person as having occupational asthma. Although several exposure reponse type of analyses were considered, these were not informative for or presented in ways that they could be used for a quantitative risk assessment.
- Dow Chemicals cohorts. Bodner et al. (2001) studied a cohort created from epidemiological surveillance data system. Workers whom were employed for at least three consecutive months in TDI-related departments from January 1, 1971 (beginning of production), through September 18, 1997 were selected and compared to a group of control workers from a hydrocarbon production plant. Workers included had an average follow-up was 7.8 years. Of 305 eligible isocyanate workers, 267 (87.5%) completed at least one medical examination within the observation period. Duration of follow-up for individual participants ranged from 0 to 22 years and data on 4892 examinations were available, conducted between 1971 and 1997 on 886 subjects. These data allowed for an analysis of symptom incidence during follow-up but only a comparison of baseline and last examination is included. The paper describes an internal exposure-response analysis, but data and results are not sufficiently transparently described to allow an adequate interpretation of the results. Daniels et al. (2018) reconstructed the person time experience of this cohort and was able to calculate an incidence rate of for asthma of 0,48 per 100 person years at an average exposure of 2.3 ppb. The definition of asthma is unclear from the original paper but was based on a review of medical records, details on the reconstruction of the person time information was not presented.

The above review of the studies included by Daniels et al. (2018), indicates that no individual studies were included that would allow a robust evaluation of an (internal) quantitative exposure-response relation to be used in further analyses.

Longitudinal studies

Gui et al. (2014) published a study on health effects due to TDI which indicates that even keeping 8-h TWA below 5 ppb (= 36 µg TDI/m³, 17 µg NCO/m^3) and peak exposures below 20 ppb (= 145 µg TDI/m³, 70 µg NCO/m^3) may not prevent sensitisation, and dermal exposure may contribute to the induction of the effect. This inception cohort study was conducted in a newly built factory in Europe, which is reported to apply TDI-based state-of-the-art polyurethane foam production technology. Newly hired workers (n = 49) were evaluated pre-employment, after 6 months and after 12 months. Over the first year of employment, 7 workers (14 %) had findings that could indicate TDI-related health effects (new asthma symptoms: n = 3, TDI-specific Immunoglobin G (IgG): n = 1, new airflow obstruction: n = 1, decline in forced expiratory volume in one second (FEV_1) ≥ 15 %: n = 3). Yet more thorough medical evaluation, such as bronchodilator testing or serial peak flow monitoring at and off work was not possible and there were thus no clinically confirmed cases of OA. Baseline spirometry was available only for 49% or the workers and was done at a different site than the follow-up testing, thus hampering the possibility to detect a > 15% decline in FEV_1 at follow-up. Twelve workers (25 %) were lost to follow-up. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up. Exposure to TDI measured by continuous fixed-point air sampling was below the LOD (0.1 ppb) in 90 % of the samples. The maximum recorded was 10.0 ppb (72 µg TDI/m³, 34 µg NCO/m^3). No air sampling period exceeded an 8-h TWA of 5 ppb and peak exposures recorded were below 20 ppb. However, fixed area samples may underestimate personal exposures, especially those near the source when fulfilling cleaning or maintenance tasks. Personal sampling performed on seven workers showed TDI levels < LOD. Skin exposure probably has occurred, because TDI was detected in 27% of the surface samples taken on surfaces such as handrails and tables, which workers touch without gloves. In addition, 28 % of the workers reported potential skin contact and during site visits, unprotected hand contact with uncured or just cured foam was noted.

Cassidy et al. (2017) reported a surveillance study, for which the exposure assessment was published by Middendorf et al. (2017). Based on these, Collins et al. (2017) reported asthma incidence among 197 workers in US facilities producing TDI. The workers were followed from 2007 to 2012. New asthma cases were identified from the medical monitoring program by application of standardised annual medical assessment, including spirometry and questionnaires on symptoms and exposure. Workers could also report symptoms consistent with asthma at any time. If symptoms or spirometry indicated possible asthma, further medical evaluation was performed. TDI air concentrations and questionnaires were used to estimate exposure for different exposure groups. Seven cases were identified as consistent with TDI-induced asthma (0.009 per person-years). Two more cases were considered consistent with asthma but indeterminate regarding work-relatedness (total asthma incidence rate of 0.012 per person-years). Increased risk of cases consistent with TDI asthma was observed for cumulative exposure (OR = 2.08, CI 1.07-4.05, per unit increase in log ppb-years) and peak TDI exposures (OR = 1.18, 95% CI 1.06-1.32, per unit increase in parts per billion). The ORs were adjusted for age. When comparing the predicted probability of being a TDI-induced asthma case by exposure the probability increased by 153% when cumulative exposure increased from 5 to 20 ppb-years (Table 25) while by estimated peak exposure it increased 962% from 5 to 20 ppb (Table 26). Further alternative outcome definitions included a FEV_1 decline of 350 ml or 10% or more in any 12-month period (which also triggered medical examinations) as well as respiratory symptoms qualifying for clinical examination for possible work-related asthma (also reported in Table 25 and Table 26).

Table 25: Predicted probability for being a case for median age of 42 by cumulative exposure (Collins et al., 2017).

Outcome	N	Cumulative exposure (ppb-years)			
		5	10	15	20
TDI-induced asthma	7	0.053	0.085	0.111	0.134
TDI-induced or indeterminate asthma	9	0.061	0.081	0.096	0.107
FEV_1 decline	19	0.147	0.177	0.198	0.213
Symptoms of work-related asthma	23	0.143	0.160	0.170	0.178

Table 26: Predicted probability for being a case for median age of 42 by estimated peak exposure (= Estimated highest 95th percentile for the worker's highest TWA potential exposure) (Collins et al., 2017).

Outcome	N	Peak exposure (ppb)			
		5	10	15	20
TDI-induced asthma	7	0.051	0.029	0.065	0.138
TDI-induced or indeterminate asthma	9	0.025	0.045	0.081	0.140
FEV_1 decline	19	0.090	0.118	0.153	0.196
Symptoms of work-related asthma	23	0.109	0.132	0.159	0.190

Of the seven cases with findings consistent with TDI-induced asthma, four had less than 1 year of job tenure (range 1 to 7 months), one had worked for 2 years when beginning participation, and the other two had worked at the job for 7 and 8 years. Tenure at the time of an event that met criteria for further evaluation for asthma ranged from 3 months to 8 years. Two of the seven had less than 1 year tenure at the time of event and one less than 2 years. Of the two participants with more than 7 years of job tenure, one had a triggering event at the time of intake and the other 4 months from the start of the study. It is noted that these findings of relatively quick onset of symptoms after employment are similar to those observed by Meredith et al. (2000). However, the findings by Collins et al. (2017) are descriptive in nature without specific risk calculations regarding the time windows.

Collins et al. (2017) did not try discerning the effect of cumulative and peak exposure in their analyses. Both exposure metrics include some methodological uncertainty. Firstly, the peak exposures were not based on measurements but each worker was assigned a peak exposure value corresponding to the highest 95th percentile 8h TWA of all the plant and task specific 8h TWAs that applied to that worker's task history. Middendorf et al. (2017) reported that in the overall data set collected for the short term high exposure potential tasks, the short term exposure measurement results ranged from below the LOQ of about 0.1 ppb to as high as 19 ppb (65 µg NCO/m^3), 200 ppb (1400 µg NCO/m^3) and 1726 ppb (6000 µg NCO/m^3) in the three plants, respectively. Collins and colleagues, however, did not use these measured data as they were not collected in sufficient number to allow estimating peak exposures at individual level. As the range of TWA percentile based peak exposure estimates was 0.01 to 19.2 ppb, it seems that these peak estimates may underestimate the real maximum peaks experienced by the workers. As the magnitude of peak exposure was based on the highest 95th percentile 8h TWA and not

measures peaks as such, it is not clear how the numbers of all peaks were estimated and taken into account when generating the cumulative exposure estimates. Secondly, as regards cumulative exposure it is to be noted that at the onset of the study the mean duration of job tenure was 11.8 years. However, the cumulative exposures used in the study were calculated using the self-reported date of first TDI exposure for those about 25% participants who reported that date, but for the remaining 75% the exposure was assumed to commence only at the start of the study when the hire-date preceded the start of the study, or was assumed to begin at their hire date when this occurred after the start of the study. This convention of calculating the cumulative exposure fails to capture altogether the cumulative exposure that preceded the start of the study for those participants that did not self-report the start date of their exposure. Given that 75% of participants did not report such a date and as the mean job tenure at onset of the study was 11.8 years (compared to study duration of 5 years), this indicates potential for quite an important underestimation of the real cumulative exposures. Finally, according to Middendorf et al. (2017), no attempt was made to characterize dermal exposure and biomonitoring was considered but not included. Finally, alternative models (e.g. threshold, or influence of time of exposure) were not explored and the onset of many cases during the first years of exposure seems not fully compatible with a cumulative exposure approach based on average exposure.

In a separate paper Wang et al. (2017) used spirometry to investigate lung function changes among the same 197 TDI production workers and potential links with cumulative or peak exposure levels. There were on average of 5.1 spirometry measurements per worker. The cohort's mean FEV_1 and forced vital capacity (FVC) (as percent of the population reference values) although greater than 90%, were significantly lower and the prevalence of abnormal spirometry (predominantly restrictive pattern) was significantly higher than in the U.S. population. Differences in lung function among workers with higher cumulative TDI exposure were in the direction of an exposure effect, but not significant. There was no statistically significant correlation between the annual FEV_1 decline and cumulative exposure to TDI. It is noted that a restrictive instead of obstructive pattern of lung function abnormality is not compatible with asthma. As regards the observation concerning annual FEV_1 decline, It is noted that asthma is characterised by a variable expiratory airway limitation, while an annual decline of FEV_1 is not part of modern definitions of asthma (or occupational asthma) (see beginning of Chapter 7.5.1).

Case-control studies

The two case-control studies also indicate a dose-response relationship for OA. Meredith et al. (2000) conducted a case-control study on asthma in two UK companies. For company A, 27 OA cases were matched to 51 controls by sex and work area. In company B seven cases were identified and all non-cases (n = 12) served as controls, because matching was not possible (moving between work areas, few workers). Data from the two sites were analysed separately.

In company A, 24 cases were attributed to TDI (n = 22 in the manufacture of moulded and block flexible poly urethane foam, n = 2 in factories involved in flame bonding and surface coating of fabrics) and three cases were attributed to MDI (batch moulding of rigid PU components (vehicle roof liners) at 200 °C). Personal exposure measurements by job category, which were performed for a separate study (1979-1986), as well as data collected after 1986 by occupational hygiene consultants were used to estimate the 8-h TWA and peak exposure for each subject based on job title and date. Peak exposures were between 1 - 50 ppb (= 7 - 361 µg TDI/m³, 3 – 174 µg NCO/m^3), and in 31 subjects (44%) peak exposure was > 20 ppb (= 145 µg TDI/m³, 70 µg NCO/m^3). There was no difference between cases and controls in the means of estimated peak exposures. Mean 8-h TWA was 1.5 ppb (= 11 µg TDI/m³, 5 µg NCO/m^3) for cases and 1.2 ppb (= 9 µg TDI/m³, 4 µg NCO/m^3) for controls. With a conditional logistic regression analysis an odds ratio (OR) for exposure above the median of the control group (1.125 ppb TDI, i.e. 4 µg NCO/m^3) was

calculated as 3.2 (95% CI 0.96 – 10.6; p = 0.06). The OR for each 0.1 ppb increase in exposure (as 8-h TWA) was 1.07 (95 % CI 0.99 – 1.16; adjusted for smoking and atopic diseases, p = 0.10). The adjusted OR was higher for smoking (2.4) as well as for history of atopic disease (3.4), but not statistically significant. In 11 (41%) of the cases, symptoms began in the first year of employment at the plant and in nine they occurred within 3 months. The OR for each 0.1 ppb increase in current 8-h TWA was higher for cases with symptoms occurring within a year from start of employment (1.5, 95% CI 0.82 – 2.7, p = 0.18) than among those with a later onset of symptoms (1.04, 95% CI 0.95 – 1.13, p = 0.41). Although this analysis was based on relatively small numbers of cases and referents in each of the time windows, the authors concluded that there seemed to be no association between current exposure to isocyanates and the development of asthma more than 1 year from employment. The authors analysed also the role of exposure metrics other than current 8-hour TWA (TWA for all jobs since employment, TWA in the first job, the highest estimated TWA and the highest estimated peak exposure). None of these measures of exposure was associated with disease which developed after 1 year of employment.

Cases of company B (n = 7) were attributed to MDI from a chemical plant in which MDI and polymeric MDI mixtures were processed and poured into drums. Some processes involved heating the mixtures. Personal monitoring results from 1988 were available (Marcali method to the middle of 1990 (Marcali, 1957), HPLC thereafter). For each subject, the proportion of measurements ≥ LOD of the Marcali method (2 ppb = 21 µg MDI/m³, 7 µg NCO/m^3) and > 5 ppb (= 52 µg MDI/m³, 17 µg NCO/m^3) were calculated. Measurements < 2 ppb were treated as being zero. Ninety percent of the 269 TWA samples were < 2 ppb. For the two groups this meant that 169/185 TWA samples for controls and 74/84 for cases were < 2 ppb. Mean and median exposures were < LOD for cases and controls. Median of the highest concentration recorded for each subject was 3 ppb (= 31 µg MDI/m³, 10 µg NCO/m^3) for both groups. The proportion of measurements ≥ 2 ppb was 0.09 for controls and 0.18 for cases. The proportion of measurements > 5 ppb was 0.004 for controls and 0.09 for cases. 3/7 cases and 1/11 controls had at least one 8 h TWA exposure measurement > 5 ppb (OR 7.5; p = 0.09). The authors conclude: *"Asthma can occur at low concentrations of isocyanates, but even at low concentrations, the higher the exposure the greater the risk."*

Tarlo et al. (1997) used a case-control study design, treating 20 companies with compensated isocyanate asthma claims as cases and 203 companies without claims as controls, to investigate the association between isocyanate exposure level and asthma claims. OA cases with identified isocyanate exposure during the 4-year period from mid-1984 to mid-1988 were identified in the Ontario Workers' Compensation Board. Exposure data were taken from a database of the Ontario Ministry of Labour which is based on company's regulatory monitoring obligation if a worker is likely to inhale or to come into contact with isocyanates: air samples collected during the same 4-year period during which the OA claims arose. For the study, exposure in the companies was determined as a binary variable on the basis of the highest level identified (always < 5 ppb vs. ever ≥ 5 ppb). The estimated incidence of OA in the 4-year study period was 2.7 % for high exposure companies with claims, 2.2 % for low exposure companies with claims and 0.9 % overall in the total 223 companies surveyed (56 out of 6 308 workers). Combined across isocyanate types, 10/20 (50 %) companies with claims were in the high exposure category and 50/203 (25 %) companies without claims were in the high exposure category (OR = 3.1; 95 %; CI: 1.1–8.5; p = 0.03). The study included cases with exposure to HDI, MDI or TDI.

Cross-sectional studies

In two publications, Pronk and colleagues reported on exposure-response relationships of respiratory symptoms and sensitisation in cross-sectional studies among large populations occupationally exposed to isocyanate oligomers during spray painting (Pronk et al., 2009, Pronk et al., 2007).

The participants were involved in spray painting in various industries ranging from car spray painting, spray painting of air planes, ships and other objects. Exposure to di-isocyanates was first studied in great detail using liquid chromatography and mass spectrometry for isocyanate monomers, oligomers and products of thermal degradation (Pronk et al. (2006a) and Pronk et al. (2006b)). The sampling strategy was based on short term measurements on task level, which were integrated into a personal exposure estimate for each study participant over a period of a month, based on average time activity patterns. From the 23 analysed compounds, 20 were detected. Exploratory factor analysis (to identify clusters of compounds that occurred regularly in combination with each other during personal exposure) resulted in a HDI factor, TDI factor and MDI factor with the thermal degradation products divided over the TDI and MDI factors. The HDI factor mainly consisted of HDI oligomers and was dominant in frequency and exposure levels in both industries. Spray painting of PU lacquers resulted in highest exposures for the HDI factor (<LOD to 2640 µg/m^3 NCO), with no significant difference between industries. Exposure variability during PU spray painting was large with variability over time being approximately 5.5 times higher than variability between workers. Low level exposure to the HDI factor was found during other painting-related tasks and even tasks without direct exposure to paint. Exposure to the TDI factor was found more regularly in car body repair shops than in industrial painting companies. Exposure levels were generally considered low (<LOD-5 µg /m^3 NCO) compared with the HDI factor and no clear contrast in levels between the tasks was observed. Exposure to the MDI factor was found incidentally during spraying and welding in car body repair shops (<LOD-0.5 µg/m^3 NCO). The results indicate that paint was the most important source and major contributor of isocyanate exposure in both industries with highest exposures during PU spraying.

In the first study (Pronk et al, 2007) the included companies were mainly car body refinish shops, but also furniture paint shops and industrial paint shops. In total, 581 workers from 128 companies took part in the study, including 50 office workers (no tasks outside the office), 241 spray painters (workers involved in spray painting) and 290 others (mostly mechanics and metal workers. Asthmatic and COPD-like symptoms were assessed using questionnaires. Also, HDI-specific IgE and IgG serology was performed.

Individual cumulative exposure estimates were obtained by combining personal task-based inhalational measurements for 23 isocyanate compounds (monomers and oligomers) and time-activity information.

Exposure = $\sum_{n=1}^{6}(Time)_n \times (\% > LOD)_n \times (Median\ NCO\ Concentration)_n$

- The personal exposure is expressed in µg NCO/m^3 x hours/month.
- n describes the task (spray painting, mixing, cleaning paint equipment, assisting a spray painter, sanding, welding).
- $(\text{Time})_n$ is the time task n was performed expressed in hours per month. On average, 82 h [SD, 89] out of a 161 h [SD, 26] working month were spent on exposed tasks.
- $(\% > \text{LOD})_n$ is the percentage of samples above the limit of detection (LOD) for task n.
- $(\text{Median NCO concentration})_n$ is the median inhalational isocyanate concentration during task n expressed in µg NCO/m^3.

Cumulative exposure in spray painters ranged from 4 to 66,464 µg NCO/m3*h/months (median 3,682 µg NCO/m3*h/month). Statistically significant associations were found for an interquartile range (IQR) increase in cumulative exposure (about 2000-fold increase) and prevalence ratio of asthmatic symptoms, COPD-like symptoms, work-related chest tightness, and work-related conjunctivitis, while not for work-related rhinitis (Table 27).

Table 27: Association between respiratory symptoms and cumulative isocyanate (NCO) exposure (Pronk et al., 2007)

Symptom	PR * (95% CI)
Asthma-like symptoms	1.2 (1.0 – 1.5)
COPD-like symptoms	1.3 (1.0 – 1.7)
Work-related chest tightness	2.0 (1.0 – 3.9)
Work-related rhinitis	1.3 (0.9 – 1.7)
Work-related conjunctivitis	1.5 (1.0 – 2.1)

* PR = prevalence ratio for an interquartile range increase of cumulative exposure (from 1.7 to 3382 µg NCO/m3*h/months) adjusted for age, sex, smoking and atopy.

In a second cross-sectional study (Pronk et al 2009) in a subsample of 229 workers (participation rate 66% of the invited), associations between isocyanate exposure and more objective respiratory effect measures (BHR, baseline spirometry, exhaled nitric oxide (eNO)) were assessed. BHR_{20} was used, i.e. a fall of 20 % in forced expiratory volume in one second (FEV_1) during a methacholine challenge test with methacholine of 2.5 mg (~10 µmol) or less indicates bronchial hyperresponsiveness (Sterk et al., 1993, Pronk et al., 2009). The same exposure estimation was used as in the first study and median exposure in spray painters was 4,530 µg NCO/m3*h/months (range 15.4-66,464 µg NCO/m3*h/month). Workers with higher isocyanate exposure were more often hyperresponsive. The IQR increase in cumulative exposure (about 9000-fold increase) was associated with a BHR prevalence ratio of 2.0 and a prevalence ratio of 2.7 when outcome was defined as BHR combined with asthma-like symptoms (see Table 28).

Table 28: Association between health end-points and cumulative isocyanate (NCO) exposure (Pronk et al., 2009).

Health outcome	N	PR* (95% CI)
BHR_{20}	33	2.0 (1.1 – 3.8)
$FEV_1/FVC < 70\%$	18	2.7 (1.1 – 6.8)
eNO ppb $\geq 90^{th}$ percentile	22	0.8 (0.4 – 1.6)
Combined parameters		
BHR_{20} + $FEV_1/FVC < 70\%$	10	6.1 (1.2 – 32)
BHR_{20} + eNO ppb $\geq 90^{th}$ percentile	6	7.0 (0.7 – 72)
BHR_{20} + asthma-like symptoms	19	2.7 (1.0 – 6.8)
BHR_{20} + COPD-like symptoms	15	1.5 (0.6 – 3.9)
BHR_{20} + work-related chest tightness	3	0.9 (0.1 – 8.3)
BHR_{20} + work-related rhinitis	10	2.2 (0.6 – 8.0)
BHR_{20} + work-related conjunctivitis	7	4.3 (0.7 – 28)

* PR = prevalence ratio for an interquartile range increase of cumulative exposure (from 0.3 to 2799 µg NCO/m3*h/months) adjusted for age, sex, smoking and atopy

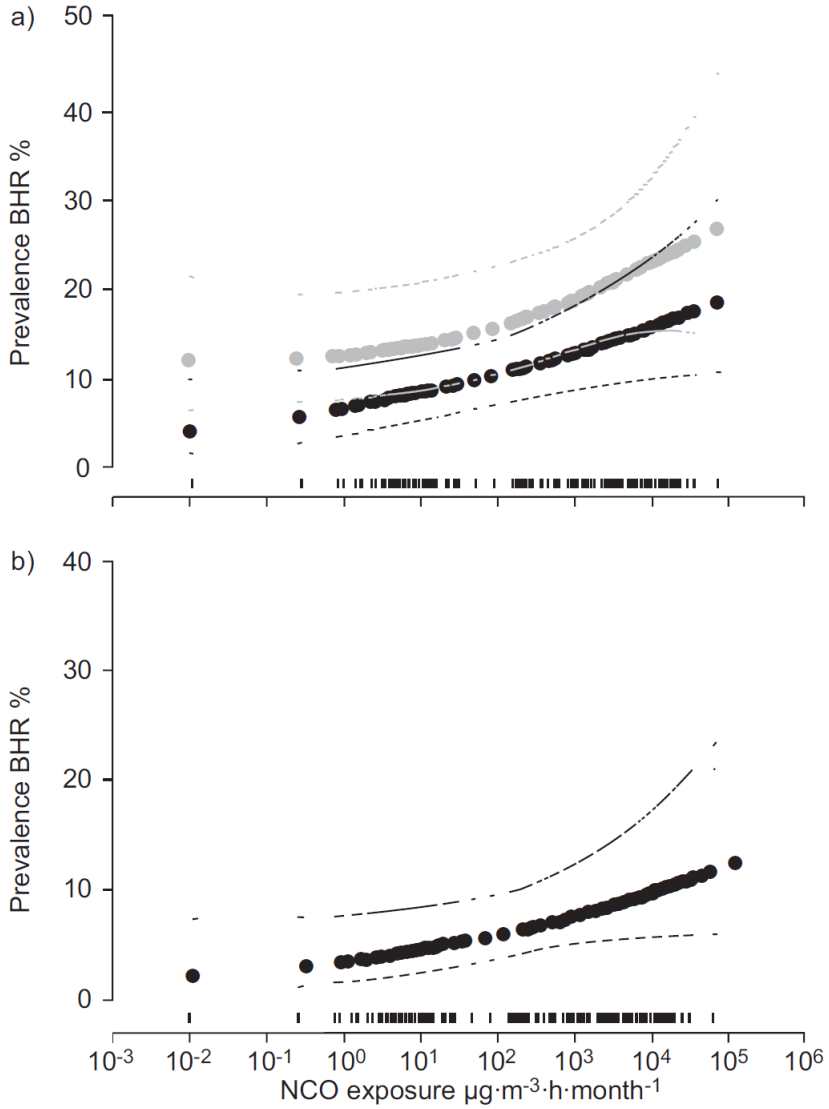
Asthma-like symptoms were more often reported in workers with higher exposure, but the association was not statistically significant: adjusted PR per IQR increase in exposure was 1.3 (95 % CI 0.9 - 1.7). Both in Pronk et al 2007 and Pronk et al 2009, HDI-specific IgE serology was positive only in about 1-4% of the exposed and did not show consistent statistically significant associations with asthma-like symptoms or BHR_{20}.

The prevalence of atopy was significantly lower in the two exposed groups, spray painters and other exposed (about 39% in each) as compared to office workers (55%), which the authors considered indicating healthy worker selection among those exposed groups.

The exposure was mainly for HDI oligomers and according to Pronk et al. (2007), the exposure was estimated from measurements quantifying diisocyanates, several monoisocyanates, aminoisocyanates and oligomers of HDI and MDI. Exposure was then expressed in µg reactive isocyanate group (NCO) to be able to add up exposure to different isocyanate compounds. Widespread exposure to especially HDI oligomers was found with highest exposures during spray painting. Thus the NCO group concentrations used in the study reflect not only exposure to diisocyanates, but a combination of compounds including also monoisocyanates and oligomers of diisocyanates which may have different potencies as regards respiratory sensitisation. Pronk et al. (2009) reported that among spray painters the median (range) exposure (as µg NCO/m3*h/months) to total isocyanate was 4530 (15.4–66464) while for HDI it was two orders of magnitude less 36.2 (1.3–472). Among other exposed workers similar differences were reported (Total isocyanate 5.6 (0–3785), HDI 0.7 (0–354)). Pronk et al. (2007) state that *animal studies indicate that relative potencies of different isocyanate compounds are variable. Theoretically, this kind of information might be used to calculate a weighted total NCO concentration. However, for many of the measured isocyanate compounds, this information is not available, which limits the possibilities to use the information on oligomer levels for calculation of overall NCO levels weighted by toxic properties. Moreover, because exposure to HDI and its individual oligomers correlated highly, this would practically only have led to a rescaling of the exposure variable.*

The statistically significant exposure response relations for BHR and BHR and asthma symptoms, as obtained through a smoothing spline are shown below.[14]

[14] To explore the shape of the associations, nonparametric regression modelling (smoothing), using generalised additive models, was applied. In nonparametric regression no assumption about the shape of the exposure response relation. It is a flexible technique to explore deviations from linearity or other models.



Association between log(exposure to isocyanates) (expressed as NCO) and health endpoints. Penalised smoothed spline plots with 95% confidence interval. a) Bronchial hyperresponsiveness (BHR20 black dots) and BHR15 (grey dots) and b) asthma (BHR20 and wheezing). BHR20, BHR15: bronchial hyperresponsiveness characterized by a respective 20% or 15% reduction in FEV1 as a cut-off level.

Hyperresponsiveness was clearly associated with exposure expressed as total NCO. Exposure–response relationships explored using smoothed spline plots confirmed this and showed similar log-linear associations for both BHR_{20} and BHR_{15}. The occurrence of hyperresponsiveness increased gradually with increasing exposure without a clear indication for an exposure threshold. The spline factors were not statistically significant. The association between exposure and BHR remained, but became statistically borderline significant and slightly weaker, when COPD cases were excluded. These splines did not differ statistically significantly from a logistic regression results using BHR and BHR and asthma symptoms as endpoints and adjusting for smoking, atopic status and gender (spline factor not statistically significant).

The role of peak exposures was not assessed and the exposure assessment does not consider the effect of respirator use. According to Pronk et al. (2007) *a working day of a spray painter consists of cycles of short tasks, and even exposure during spray painting is highly variable for all workers. Therefore, isocyanate exposure in this study consists of a series of peaks, which is highly correlated with average exposure through the duration of the tasks. Consequently, it is not possible to differentiate between cumulative and peak exposure*.

Dermal exposure was not considered in the analysis of the exposure response relationship by Pronk et al. (2009).

Finally, the outcome analysed was not specifically OA, nor diagnosed asthma in general but BHR_{20} (or BHR_{20} + asthma symptoms). However, such a case definition is widely used in asthma epidemiology.

Human volunteer studies

Most cases of diisocyanate-induced OA described above have occurred under conditions of repeated exposures over a period of days, months or years. However, it seems also possible to develop airway effects suggestive of asthma after a single exposure. Vandenplas et al. (1999) studied seventeen subjects without previous respiratory symptoms and without occupational exposure to diisocyanates. The subjects were randomly exposed to ambient air and TDI (5 ppb for 6 h followed by 20 ppb for 20 min) in a single-blind crossover design. At least 4 weeks separated the two exposure events. None of the subjects experienced significant respiratory symptoms in response to the exposures. Exposure to TDI produced a modest decrease in specific airway conductance (sGaw, $p = 0.05$) and maximal expiratory flow at 25% of FVC (MEF25%, $p = 0.02$) when compared to ambient air exposure. The rest of the lung function parameters were not affected (including airway parameters like FEV1, FEV1/FVC ratio and maximal expiratory flow at 50% (MEF50%)). Multivariate regression analysis of the time-point differences in sGaw showed that the mean concentration of TDI was a significant determinant of the response ($p=0.044$), while the level of nonspecific responsiveness to histamine had a significant effect on changes in MEF25% induced by TDI exposure ($p=0.022$). A slight but statistically significant increase in albumin in bronchioalveolar lavage fluid (BAL) was seen following the TDI exposure when compared with that recovered after exposure to ambient air (26.4 vs 21.8 µg/ml, $p = 0.04$) . The concentration of a2-macroglobulin in bronchial lavage (BL) was higher after exposure to TDI than after exposure to ambient air (0.07 vs. 0.05 µg/ml, $p= 0.021$). When the results of biochemical constituents were normalized to albumin concentration in lavage fluids, the a2-macroglobulin/albumin ratio in BL remained higher after TDI exposure than after air exposure (0.0019 vs 0.0012, $p=0.036$). No changes in white blood cells or in blood protein levels were observed in response to TDI exposure. A quite high proportion of these asymptomatic subjects showed a mild to moderate level of nonspecific bronchial hyperresponsiveness (histamine PC_{20} value <8 mg/ml at baseline). All eight current smokers and four of the nine life-time non-smokers showed a histamine PC_{20} value <8 mg/ml.

The results suggest that single exposure to TDI is associated with minimal but detectable changes in airway calibre and in epithelial barrier permeability. It remained uncertain, however, why the detected effect of TDI was limited to sGaw and MEF25% which are assumed to reflect changes in different portions of the airways (both small and large airways) while other airway parameters were not affected. The concentrations of potential indicators of epithelial cell dysfunction (secretory component and CC16) and pro-inflammatory cytokines (TNF-a, IL-4, IL-5, IL-6, and IL-8) in BL and BAL were not significantly altered by TDI exposure. Nor did cellular studies provide evidence of an influx of inflammatory cells into the airway compartment in response to TDI. The authors admitted that an inflammatory response of the airways to TDI exposure could have been missed, since the BAL procedure was performed at a short interval after the end of the exposure. They concluded however, that the results suggest that the observed changes in

pulmonary function tests were not directly related to airway inflammation or injury. The concentrations of 5 and 20 ppb of TDI correspond to 17 and 70 µg NCO/m^3, respectively.

Lemiere et al. (2002) studied whether a re-challenge with low diisocyanate concentration (1ppb) could provoke asthmatic reactions with subjects earlier diagnosed with MDI, HDI or TDI induced OA confirmed with a specific inhalation challenge (SIC) test. The individuals had not been exposed to diisocyanates after the diagnosis of OA. For each individual the dose of occupational agent necessary to induce an asthmatic reaction had been determined at the time of the original SIC and the individuals had not experienced severe asthmatic reactions after their diagnosis, had a well-controlled asthma and no significant co-morbidity. The study comprised two parts. In the first part eight individuals were exposed to 1 ppb of diisocyanate with a dose 10% of the total dose (concentration x time) that induced an asthmatic reaction at the time of the diagnosis. Three of them developed an asthmatic reaction (one MDI, one HDI, and one TDI case). The five that did not, were exposed next day at 15 ppb either until a reaction occurred or for a maximum duration of 2 hours. All of them developed an asthmatic reaction. The second part of the study was set to verify whether low concentrations of isocyanates (1 ppb) could induce asthmatic reactions and airway inflammation in the same proportion of subjects as exposure to a higher isocyanate concentration (15 ppb) for the same total dose of isocyanates delivered. Two SICs were performed 1 month apart, first with 1ppb (until an asthmatic reaction or a maximum of 2 hours) and then with 15 ppb (until the total dose of the 1 ppb SIC of that individual). Seven individuals took part in this phase, of them three had also participated in the first phase. Four developed an asthmatic reaction in the 1 ppb challenge and one in the 15 ppb challenge (this individual had no reaction in the 1 ppb SIC) and two did not react in either experiment. It is noted that the numbers of cases are low and that additionally to asthmatic reactions regarded as positive, an FEV_1 reduction of 20%, some developed FEV_1 reductions that did not reach this threshold set for an asthmatic reaction. The concentration of 1 ppb of HDI, MDI or TDI corresponds to an NCO concentration 3.4 µg NCO/m^3.

Pisati et al. (2007) studied 25 individuals with previously diagnosed OA confirmed with a SIC in order to assess whether the airway hyper-responsiveness to TDI persisted for a long time after cessation of exposure (mean 58, range 46–73 months), whether evolution of specific hyper-responsiveness and asthma were coincident and to identify the determinants of patients' outcome at the time of diagnosis. During a follow-up visit a new SIC test and clinical examination took place and questionnaire data on symptom and asthma history were collected. Seven subjects were still TDI-reactors and 18 had lost reactivity to it. All persistent reactors had still asthma and their symptom score, medication score, FEV_1, PD20 and serum IgE were unchanged between assessments. In the 18 subjects no longer responsive to TDI, 8 had still features of asthma: their symptom and medication score had improved significantly, but FEV_1, PD20 and serum IgE had not significantly changed; the other ten patients no longer reactors to TDI were also asymptomatic and their PD20 had become normal. The duration of symptomatic exposure to TDI preceding OA diagnosis was the only feature at diagnosis that differed statistically significantly between patients with persistent TDI airway hyper-responsiveness and asthma and those who were no longer responsive to TDI but still asthmatic and those who were no longer responsive to TDI and no longer asthmatic (mean and SD: 4 ± 1.6; 2.1 ± 0.8; 0.6 ± 0.3 years, respectively; $p < 0.001$). I.e., the longer the symptomatic exposure before removal from exposure, the more persistent the features of OA at follow-up.

Occupational disease register data

OA from isocyanates is a well-known occupational disease. Information on such diseases is compiled in numerous national reporting systems. These are either relying on cases claimed/recognised/compensated to/by the social security/worker compensation scheme or on voluntary reporting systems most often based on physician reports. Such data for diisocyanates were recently reviewed and collected (ECHA, 2018a). Studies based on such

data indicate a decline in isocyanate OA, for example in Belgium (Vandenplas et al., 2011), France (Paris et al., 2012) and Ontario (Buyantseva et al., 2011), likely reflecting an effect of improved exposure control. However, due to various shortcomings, for example underreporting, level of detail available for the health outcome (diagnosis), causative agent and exposure intensity and lack of information on population at risk, such data are not useful for setting an OEL or establishing a dose-response for diisocyanates.

Challenges of exposure-response considerations of human data

The above studies indicate that asthma incidence decreases when exposure levels decrease. However, despite modern standards and air levels below current OELs, risks for workers may exist and no definitive minimum level of exposure to diisocyanates for humans is known, below which sensitisation and asthma will not occur in susceptible individuals. Beside this limitation in knowledge, all tabulated studies (Appendix 3) also show limitations that cause uncertainty for the derivation of an exposure-response relationship for diisocyanates regarding sensitisation.

Markers of effect

First of all, when describing an exposure-response relationship, the relevant outcome has to be defined. The endpoint of interest here is respiratory sensitisation, which finally leads to the clinical picture of allergic asthma in humans.

OA can be defined as "a disease characterised by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to exposure to a particular occupational environment and not to stimuli encountered outside the workplace." Allergic or immunological OA includes both OA caused by agents with an allergic IgE-mediated mechanism as well as OA induced by specific occupational agents in which the responsible allergic or immune mechanisms have not yet been identified or fully characterised ((Bernstein et al., 2013), p.3).

A critical event in the development of occupational respiratory allergy is the induction of sensitisation. If sensitisation is prevented, elicitation of asthma (and other clinical manifestations of respiratory allergy) will also be prevented. There seems to be high variability in individual susceptibility in already sensitised subjects, and it will be difficult to estimate a "safe" exposure level for this group. Therefore, sensitisation of naïve individuals rather than elicitation in already sensitised persons is suggested to be a more suitable endpoint to serve as the basis for an OEL (Dotson et al., 2015). A possible marker for the induction of sensitisation in IgE mediated allergy is the IgE specific for the antigen. However, unlike in the case of high molecular weight OA causing substances, in the case of diisocyanates, the diisocyanate-specific IgE have been detected only in a fraction and in some studies only a small fraction of symptomatic subjects(Kimber et al., 2014) and other mechanisms maybe involved (see Section 7.9). Consequently there is no universal reliable marker of induction of diisocyanate sensitisation that could be used as a basis for derivation of an OEL or risk-based values from epidemiological studies. Therefore, markers of the elicitation phase of the sensitisation need to be considered. Adverse effects of diisocyanates on the respiratory tract investigated in epidemiological studies include respiratory symptoms, accelerated lung function decline and bronchial hyperresponsiveness their combination or clinically verified asthma (Appendix 3).

Respiratory symptoms are often assessed by self-reporting and therefore do not constitute an objective measure. In addition, respiratory symptoms do not have to be specific for asthma, but may also include for example COPD-like symptoms. However, work-related respiratory symptoms assessed by validated questionnaires, often combined with more objective measures, like bronchial hyperresponsiveness, are often used as outcome measure in epidemiological studies of OA.

Accelerated lung function decline as another outcome was examined in longitudinal epidemiological studies in diisocyanate-exposed workers and reviewed by Ott and co-

workers (Ott, 2002b, Ott et al., 2003a). In these reviews, the effect of TDI on accelerated lung function decline was investigated. Eleven longitudinal studies (five in TDI production units and six in sites using TDI) as well as three cross-sectional studies in units using TDI were included. Decline in FEV_1 was seen in earlier studies and in follow-up studies of workers who continued to work after their diagnosis of OA. However, no consistent evidence of accelerated loss in FEV_1 was found in more recent longitudinal studies with 8-h TWA exposure mostly < 5 ppb (= 36 µg TDI/m³, 17 µg NCO/m³) and even with short-term TDI concentrations > 20 ppb (= 145 µg TDI/m³, 70 µg NCO/m³). However, accelerated lung function decline is not a sensitive outcome measure of asthma, as asthma is characterised by variable airflow obstruction, and lung function may not be decreased permanently. The time of day at spirometry may therefore have a large impact on lung function. There is a diurnal variation, which also may be influenced by shift work. Before to after shift changes in lung function can have high specificity, but have low sensitivity for the validation of occupational asthma (Nicholson et al., 2010). They are not reliable for separating subjects with and without OA (Vandenplas et al., 2013). Further, there is a large intrinsic variability. Thus, it is concluded that accelerated lung function decline does not serve as a suitable predictive marker for dose-response considerations of elicitation of diisocyanate asthma.

It is considered that reasonably relevant markers for asthma examined in the available studies are: clinically verified asthma; work-related symptoms compatible with asthma assessed with a validated method; and non-specific bronchial hyperresponsiveness (BHR), assessed by a methacholine or histamine challenge. For the latter, lung function (FEV_1) of the subjects is measured before the challenge and after inhalation of increasing doses of methacholine. After a certain fall in FEV_1 (for example 15 or 20 %) or when the maximum cumulative dose is reached, the test is stopped. A subject is defined as being hyperresponsive if a certain cumulative dose of methacholine leads to a certain fall in FEV_1 (Pronk et al., 2007, Sterk et al., 1993). Besides BHR alone a narrower definition of asthma proposed for epidemiology is the concurrent presence of BHR and wheezing (Toelle et al., 1992). Specific inhalation challenge tests (with the diisocyanate suspected as the cause of sensitisation) are regarded as the reference standard against which other tests for the diagnosis of asthma are validated. The specific challenge test is time consuming, expensive, and needs special facility and expertise (Toelle et al., 1992). These are not performed in larger groups required in epidemiological studies but are rather used in clinical practice and for worker compensation purposes.

Exposure assessment

A further problem in selecting studies for dose-response assessment is related to exposure assessment. To assign a quantitative exposure value to a specific effect requires reliable quantitative measurements. However, measurement of airborne isocyanates is still a challenge today (Section 6.1.). In addition, the methods for measurement/analysis of inhalation exposure have changed over time and therefore different methods were used in the epidemiological studies (sometimes within the same study) and results may not be comparable. For example, in the older studies the Marcali method (Marcali, 1957) was used for analysis, which is reported to significantly underestimate exposure (Ott et al., 2003a). Also the site of measurement is of importance, as discrepancies between simultaneously measured area and personal exposure levels are reported (Butcher et al., 1977).

There are also questions concerning the dosimetry and temporal exposure patterns relevant for the effect (see animal experiments). An important issue is the fact that peak exposures are thought to be relevant in inducing sensitisation (see above). The risk of sensitisation may therefore be better reflected by an index that quantifies the occurrence of short intense peaks of exposure than by average or cumulative exposure measures ((Checkoway et al., 2004)p. 310). However for elicitation of clinically manifest respiratory sensitisation, Pronk et al. (2009) found in their study in Dutch spray painters an association between the cumulative exposure and hyperresponsiveness and Collins et al. (2017)

reported an association both between cumulative and peak exposure and the incidence of TDI-induced asthma. The inherent problem is that these two exposure metrics are highly correlated. For another risk industry and risk factor of OA, bakeries and wheat flour and α-amylase, there is indication that tasks with peak exposures are actually an important determinant in the overall exposure (Meijster et al., 2007).

Setting aside the role of peak exposures it remains also unclear whether cumulative exposure, (average) exposure intensity, or some combination that also accounts for time ordering of intermittent exposure, is the most relevant exposure metric and if a specific time-window after start of exposure, or the entire working life should be considered setting exposure limits based on scientific studies relying on elicitation of respiratory sensitisation. For example, in the case-control study of Meredith et al. (2000) there was little evidence of a dose-response by any exposure metrics among OA cases that occurred later than 1 year after start of employment in the exposure job. For another occupational sensitizer, platinum salts, it has been reported in a prospective study that among newly hired workers, the risk of sensitisation (as measured by skin prick tests) was somewhat more strongly determined by recent exposure than average or cumulative exposure during the follow-up (Heederik et al., 2016). During the average follow-up of 3.9 years the risk of becoming sensitized peaked between 500 to 600 days since start of employment.

Routes of exposure

Dermal exposure as an important route of entry may contribute to induction of respiratory sensitisation which precedes elicitation (North et al., 2016). This was shown in animal models and is thought to be relevant for humans as well (Bello et al., 2007) and with further animal evidence recently published by Pollaris et al 2019. Dermal exposure is difficult to measure and to quantify and is often not reported and never quantified in epidemiological studies. For another occupational sensitizer, beryllium salts, it was recently reported that metrics of peak inhalation exposure, indices of skin exposure, and using material containing beryllium salts were all significantly associated with beryllium sensitisation (Virji et al., 2019). However it was not possible to tease apart the independent effects of skin exposure from inhalation exposure, as these exposures occurred simultaneously and were highly correlated.

Last but not least, the quality of exposure assessment in epidemiological studies also depends on the level at which exposure is described. In some studies, exposure levels are given on factory or area level only. For example, longitudinal studies on TDI asthma often report mean exposure levels for a group of workers and the respective incidence of disease (Appendix 3). Some studies investigate exposure groups using ranks (low/medium/high) without assigned quantitative exposure levels. Despite of the apparently high number of human studies available, only few studies provide quantitative exposure estimates on an individual worker level. These also differ regarding their quality, because they may be based on personal sampling of the individual worker or may be task-based.

A further uncertainty in exposure assessment relates to the use of personal protective equipment. Many studies do not report on it. Other studies try to account for the use. For example, in a retrospective study, the sampling record was not considered if it indicated that respiratory protection was used. Respiratory protection was taken into account by subtracting 50 % of calculated exposure values for exposed jobs in a longitudinal study (Clark et al., 2003). Another longitudinal study considered exposure only when not wearing respiratory protection (Hathaway et al., 1999). All these approaches to account or not for RPE introduce error in the exposure assessment, may bias the results, and make it harder to compare results from different studies. In addition, the use of personal protective equipment may be associated with the exposure level, as is indicated by the report of Gui et al. (2014). Here, self-reported glove use differed significantly between the exposure risk groups (25 % of the workers in the low, 32 % in the medium, 100 % in high exposure risk group).

Co-exposure

Co-exposures to other isocyanates or to other substances, such as irritants, are likely to be present at several of the workplaces studied, and they may influence the observed effect of the studied diisocyanate. Some reports do not even mention potential co-exposures, others report co-exposures, but do not quantify them (for example (Cassidy et al., 2010, Omae, 1984)).

Study design

Limitations due to the study design for example include the lack of an (unexposed) control group, a small number of cases (Collins et al., 2017) and selection bias. The latter includes different issues. Susceptible individuals will not be hired based on entry examinations. Self-selection of workers is likely, as individuals with allergy or respiratory problems will not apply for work at a chemical plant (Hathaway et al., 2014). The studied workers therefore mostly are selective populations that are "healthier" in terms of respiratory diseases. The selective loss of exposed symptomatic individuals is especially important in cross-sectional studies on diisocyanate related health effects. These studies are likely to underestimate the risk for workers, because workers with symptoms may already have left their job and are not available for the study. Cross-sectional occupational studies therefore are prone to both "healthy worker hire bias" and "healthy worker survivor bias" (Le Moual et al., 2008). The potential for this kind of bias may be reduced in prospective longitudinal studies, but they also miss workers with health problems who have left before the start of the study as well as those who are lost to follow-up. The most meaningful estimate of the incidence of health effects could be achieved by an inception cohort study (which includes newly hired workers) with further investigations also of those workers who left their job.

The inception cohort study of polyurethane foam production workers in Eastern Europe illustrates the healthy worker survivor effect. It describes a loss to follow-up of 25 % (12 out of 49 exposed workers) after the first year of employment. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up.

Likewise, a study of health effects of HDI in painters and auto body refinish workers found significant differences between the workers who left the auto body shops and those who stayed. This 1-year follow-up subsequent to a cross-sectional study investigated whether or not a healthy worker effect may exist in the auto body industry (Redlich et al., 2002). Fourty-eight workers from seven shops were contacted (Redlich, 2010), 13 of these (27 %) had left their original shop and three (6 %) were lost to follow-up. Those who left were less experienced in the industry and more likely to have a history of asthma and bronchial hyperresponsiveness. The authors conclude: *"The differences in workers who stayed at their shop compared to those who left, combined with the low asthma prevalence and high job turnover rate, all suggest that a healthy worker effect may exist in the auto body industry, and may in part account for the low prevalence of asthma noted in SPRAY and other cross-sectional studies of diisocyanate workers."*

Other (modifying) risk factors

From epidemiological studies reviewed (Mapp et al. (1988), Redlich and Karol (2002), Vandenplas et al. (1993) Wisnewski et al. (2013b)) it is generally concluded that exposure is the major risk factor for developing occupational diisocyanate asthma. Atopy is not considered a risk factor for diisocyanate sensitization and asthma, as, in contrast, it is known to be for high molecular weight sensitizing agents. Smoking also does not modify the risk for developing diisocyanate sensitization and asthma.

In conclusion:

1. The immunological pathways central to diisocyanate asthma are not fully understood (see Ch 7.9). There is no single reliable marker of induction of respiratory sensitisation to diisocyanates that could be used to identify either a

threshold or a dose response relationship for induction of sensitisation from the human data reviewed.

2. The epidemiological studies reviewed do not suggest a definite threshold for elicitation of respiratory sensitisation and the studies also have limitations for assessing dose response relationships if using strict criteria. However, two studies (Collins et al., 2017, Pronk et al., 2009) and one meta-regression analysis of eight studies (Daniels, 2018) come close to meeting such strict criteria. As explained, each of them has one or more methodological limitations linked to: distinguishing the role of peak exposures and cumulative exposure; the effect of respiratory protection in the estimation of exposure; healthy worker effect; effect of dermal exposure; combining exposures of several (di)isocyanates with possibly different sensitisation potential; and using outcomes other than (occupational) asthma caused by diisocyanates. However, each study detected an exposure-response relationship.

This conclusion is in line with the recent conclusion of ECHA's Committee for Risk Assessment (ECHA, 2018b). More precisely:

- *Regarding human data, there are a large number of studies available. However, none of them is considered adequate for deriving a reliable exposure-response relationship curve due to a number of limitations in those studies. The limitations include lack of reliable information on exposure (including difficulties in assessing dermal exposure and peak inhalatory exposures), lack of sensitive predictive markers for diisocyanate sensitisation, low statistical power (e.g. due to small sample size or low disease incidence), inadequate correction for the presence of confounding factors (e.g. for concomitant exposure to other respiratory sensitisers and irritants or for previous exposure to sensitising agents), lack of an unexposed control group or the "healthy worker effect".*
- *In addition, respiratory sensitisation to diisocyanates can be induced both via the dermal and the inhalation route, and thus both exposure routes have to be considered. An important role of dermal route in respiratory sensitisation to diisocyanates has been shown in animal studies (e.g. Pauluhn, 2013; North et al. 2016), and is considered to be relevant for humans as well (Bello et al., 2007). However, as for either route a threshold is unknown, and neither the quantitative nor mechanistic interaction between the inhalation and dermal route is sufficiently understood, it is not possible for RAC to set any DNEL that will be meaningful for the risk characterisation.*

It is noted that the studies of Collins et al. (2017) and Daniels (2018) were not yet available at the time of the above RAC conclusion. Furthermore, Section 8.1 describes national or international approaches taken to overcome the above uncertainties and to provide science-based values either to identify a threshold or a dose-response to inform on setting an occupational limit value.

7.5.1.2 Skin sensitisation

As explained above diisocyanates are potent respiratory sensitisers and they also test positive in animal tests of skin sensitisation. In case reports they have also been reported to cause allergic contact dermatitis in humans, but such cases seem to be less frequent than cases of occupational asthma (Bello et al., 2007, Ebino et al., 2001, Engfeldt et al., 2013, Goossens et al., 2002, Nguyen and Lee, 2012).

7.5.2 Animal data

Respiratory sensitisation

Several studies investigating the effects of different diisocyanates in *in vivo* asthma models have been published. A dose-response relationship has been observed for TDI-induced bronchial hyperreactivity in guinea pigs and rabbits (ATSDR, 2018, Montelius, 2001).

It is noteworthy that unlike for many other hazard endpoints, there are no internationally accepted *in vivo* test guidelines for respiratory sensitisation (ECHA (2017), North et al. (2016)). Different published protocols exist for assessing respiratory sensitisation and some of them have been used for diisocyanates, but no systematic undertaking has validated any of the methods for a broad range of materials. Historically, the guinea pig has traditionally been the species of choice for research on respiratory sensitisation due to physiological similarities of respiratory reactions compared to humans. Time and cost considerations, as well as a lack of suitable immunochemical or molecular probes for mechanistic evaluations, have led many to look for other animal, and non-animal alternative, test systems. Experimental models using rats and mice have been successful in inducing chemical respiratory sensitisation, but the parameters providing best predictive performance remain unknown.

Inhalation tests

In the study by Marek et al. (1999), challenge tests showed increased bronchial responses to acetylcholine or methacholine in guinea pigs previously exposed to 0.01 or 0.02 ppm TDI, MDI or HDI, five times one hour (NOAEC 0.005 ppm). Airway hyperresponsiveness was also seen shortly after a shorter (1 h) exposure to 3 ppm (21 mg/m^3) TDI (corresponding to 10 mg/m^3 NCO). The effect persisted for 48 h (Gagnaire et al., 1996).

Exposure of guinea pigs to 0.2 ppm (1.4 mg/m^3) TDI (corresponding to 0.68 mg/m^3 NCO), 3 h/d, 5 days, followed by challenge at 0.02 ppm (0.14 mg/m^3, corresponding to 0.068 mg/m^3 NCO) resulted in increased respiratory rates. Such effects were not detected if the original exposure concentration was 0.02 ppm. (Aoyama et al., 1994).

Airway irritation/hypersensitivity symptoms, including exertional breathing, was observed upon challenge in rats exposed to 1.14 ppm (8.1 mg/m^3) 2,4-TDI (corresponding to 3.9 mg/m^3 NCO) for 4 days (4 h/d), or 0.41 ppm (2.9 mg/m^3, corresponding to 1.4 mg/m^3 NCO) 4 or 5 days. The symptoms were more severe in the high-dose group. Inflammatory events, involving a prominent eosinophil infiltration in the central and peripheral airways, were observed in lung histopathological analyses (Kouadio et al., 2014).

(Karol, 1983) exposed guinea pigs via inhalation to 0.12-10 ppm TDI for 3 h/day during 5 days. Evaluation of TDI-specific antibodies, skin sensitivity and pulmonary sensitivity (assessed by bronchial provocation challenge with TDI-protein antigen) started on day 22. Pulmonary sensitisation was observed in the groups exposed to ≥0.36 ppm TDI, but not at 0.12 ppm.

Subchronic TDI-exposure of mice (0.02 ppm (0.14 mg/m^3, corresponding to 0.068 mg/m^3 NCO), 4h/day, 5 days/week, 6 weeks) followed by challenge with 0.02 ppm TDI (1 h) 14 days later demonstrated a variety of responses. The findings included airway inflammation, eosinophilia, goblet cell metaplasia, airway hyperresponsiveness, a mixed Th1/Th2 cytokine expression in the lungs, and increased levels of serum IgE and TDI-specific IgG antibodies. Similar findings were also detected in animals with an original acute exposure (0.5 ppm, 2 h) instead of the repeated exposure, followed by 0.02 ppm TDI challenge after 14 days. However, no effects on serum IgE, cytokine expression or lung eosinophila were observed (Matheson et al., 2005).

Pauluhn and Poole (2011) presented a dose-dependent increase in respiratory rate and bronchioalveolar lavage parameters in rats exposed to MDI (sensitisation 5 days, 1000, 5000, 10 000 mg/m^3 *x* minutes (336, 1680, 3380 mg NCO/m^3 *x* minutes), duration 10 or 360 minutes; challenge four times 30 minutes, 40 mg/m^3 *x* minutes (13.44 mg NCO/m^3 *x* minutes). When analysing the results, the authors identified an elicitation threshold of 5

mg/m^3. The potential to cause sensitisation was slightly higher for high-dose, short-term exposure than equal cumulative exposure during a longer exposure period.

Inhalation exposure of guinea pigs with 0.069 mg/m^3 (0.01 ppm) monomeric HDI (corresponding to 0.034 mg/m^3 NCO) during eight weeks (6 h/day, 5 days/week) did not cause any alterations in basal respiratory mechanical or cardiovascular parameters. Also, a 60-minutes challenge to the same concentration of HDI did not induce any marked effects in functional parameters. An increase in airway constriction was observed immediately after exposure in one studied animal when assessing the nonspecific airway responsiveness with 1% or 2% acetylcholine, but not with lower concentrations. After an eight-week latency period, no such effects were seen. (Marek et al., 1997)

Combined dermal and inhalation exposure studies

Diisocyanates have also been shown to cause respiratory hypersensitivity upon dermal exposure (Selgrade et al., 2006, Karol et al., 1981, Rattray et al., 1994, Pauluhn, 2005, Pauluhn, 2008). In the study by Pollaris et al. (2019), repeated intranasal exposure (5 days/week during 5 weeks) of mice to 0.1% TDI resulted in immunological alterations indicative of sensitisation (mixed Th1/Th2 cell response), but no airway hyperreactivity. However, when the mice first received two dermal applications (0.5% TDI), followed by repeated intranasal exposure by the same protocol as for the other group, airway hyperreactivity was observed (Pollaris et al., 2019).

Pauluhn et al. (Pauluhn, 2015, Pauluhn, 2014, Pauluhn and Poole, 2011, Pauluhn, 2008, Pauluhn, 2005) have, specifically for diisocyanates, developed a respiratory sensitisation testing protocol with Brown-Norway rats, aiming at evaluation of the acute ethiopathology rather than chronic airway inflammation. Basically, initial systemic sensitisation is achieved by dermal application of the chemical, followed by recurrent inhalation priming, aiming at inducing and amplifying the allergic characteristics of airway inflammation. Hereby, the aim is to avoid tolerance of the lungs towards the allergen during the initial sensitisation phase. Pauluhn et al. (Pauluhn, 2005, Pauluhn, 2008, Pauluhn, 2015, Pauluhn and Poole, 2011)) evaluated concentration *x* time (C *x* t)-response relationships for elicitation-based endpoints and identified the importance of minimising respiratory irritant effects on breathing patterns when optimising the inhalation doses in respiratory sensitisation studies. Allergic pulmonary inflammation was identified by measuring neutrophilic granulocytes in bronchoalveolar lavage fluid. The Brown-Norway model has been evaluated as appropriate for the identification of NOAEC/LOAEC values for the elicitation-response of diisocyanates (North et al., 2016).

In the rat asthma model with MDI, sensitisation by two topical applications (40 µl MDI, days 1 and 7) followed by inhalation challenges (four times 38 mg/m^3 (3.7 ppm; corresponding to 12 mg/m^3 NCO) or three times 37 mg/m^3 (3.6 ppm) and a fourth challenge at 8, 18 or 30 mg/m^3 (0.78, 1.8, 2.9 ppm; corresponding to 2.7, 6.0, 10 mg/m^3 NCO); duration 30 minutes) induced an increased influx of neutrophils and delayed-onset respiratory responses. The results showed a correlation between the elicitation dose and respiratory response. The authors concluded that the asthma-like responses seemed to be more dependent on the inhalation challenge dose than the dose used for dermal induction. (Pauluhn, 2005, Pauluhn, 2008). Also with TDI and HDI, respiratory sensitisation occurred in Brown-Norway rats after epicutaneous sensitisation (days 0 and 7) and four inhalation challenge doses starting two weeks after the last topical application (110 mg/m^3, followed by three doses of 72-120 mg/m^3 for HDI, and four doses of approximately 85 mg/m^3 for TDI) (Pauluhn, 2014, Pauluhn, 2015).

In a guinea pig study comparing the effects of HDI monomers with HDI biuret and HDI isocyanurate, a sensitising effect was observed upon sensitisation with the HDI monomer (intradermal injections 3x0.3%, or one injection and inhalation 27 mg/m^3 (3.9 ppm; corresponding to 13 mg/m^3 NCO), 3 h/day for five days) and challenge with an HDI-conjugate. The findings were increased respiratory rate and recruitment of eosinophilic

granulocytes. The highest responses were seen when induction was by intradermal injection. In contrast, no signs of respiratory sensitisation were seen in the guinea pigs exposed to HDI biuret or HDI isocyanurate. (Pauluhn et al., 2002)

The study by Rattray et al. (1994) indicated a more clear induction of bronchial hyperreactivity in guinea pigs by a single intradermal or epidermal application of MDI (doses 0.0003-0.3% and 10-100% MDI, respectively) followed by inhalation challenge 21 days later at concentrations of 25.9-36.5 mg/m^3 (2.5-3.6 ppm; corresponding to 8.7-12 mg/m^3 NCO) than by exposure to MDI by inhalation only [19.4-23.7 mg/m^3 (1.9-2.3 ppm; corresponding to 6.5-8.0 mg/m^3 NCO) 3 h/day for 5 consecutive days, and challenge 21 days after the first exposure at 34.6-44.1 mg/m^3 (3.4-4.3 ppm; corresponding to 12-15 mg/m^3 NCO)].

Other considerations

The review by Schupp and Collins (2012) suggested that respiratory irritation and sensitisation caused by diisocyanates may be interdependent events with thresholds. The NOAECs and LOAECs for irritation and sensitisation appeared to be in the same order of magnitude. When reviewing TDI data on different species of test animals, the LOAECs for respiratory sensitisation where normally 0.02-0.4 ppm (0.14-2.8 mg/m^3, corresponding to 0.068-0.19 mg/m^3 NCO); NOAECs 0.005-0.03 ppm (0.036-0.21 mg/m^3, corresponding to 0.017-0.10 mg/m^3 NCO). The lowest LOAEC was obtained when an induction protocol with six weeks of inhalation exposure was used. (Schupp and Collins, 2012, Matheson et al., 2005).

In a few studies, varying levels of cross-reactivity (0-13%) has been presented between rat and guinea pig antibodies of various diisocyanates with antigens related to other diisocyanates (summarised in ECHA, 2018a).

No statistically significant cross-reactivity was observed in relation to airway hyperreactivity when mice were sensitised with MDI and challenged with TDI, or the other way around, although positive cross-reactivity reactions were seen in some of the animals. In addition, there was only a nonsignificant increase in lung inflammation in bronchioalveolar lavage fluid in the cross-exposed groups. A significant asthma-like response, including airway hyperreactivity, occurred only if sensitisation and challenge were performed with the same substance (MDI or TDI). The potency of the responses obtained with MDI were similar to those of TDI. (Pollaris et al., 2016).

Skin sensitisation

The skin sensitisation potential of several diisocyanates has been know already long ago (Thorne et al., 1987, Tanaka, 1980, Tominaga et al., 1985, Koschier et al., 1983, Rattray et al., 1994, Gad et al., 1986, Hilton et al., 1996, Zissu et al., 1998).

Studies on delayed hypersensitivity showed sensitisation in 18/20 guinea pigs treated with TDI (grade V allergen on the Magnusson-Kligman scale (Magnusson and Kligman, 1969), induction concentration 5%, test concentration 1%) and in 14/20 animals treated with HDI (grade IV allergen; induction concentration 1%, test concentration 0.1% (Zissu et al., 1998).

Thorne et al. (1987) studied the sensitising potential of HDI, TDI and MDI in mice using the mouse ear-swelling test. The results of this study showed significant potency differences with HDI being the most potent one, followed by MDI and TDI. The doses that caused sensitisation in 50% of the animals were 0.088 mg/kg bw, 0.73 mg/kg bw and 5.3 mg/kg bw for HDI, MDI and TDI, respectively. Cross-reactions between each of the tested diisocyanates were also demonstrated when sensitisation and challenge were induced using different diisocyanates. The responses were however greater when the sensitisation and challenge treatments were done with the same diisocyanate, than with one diisocyanate for sensitisation and another for challenge. TDI, which was the weakest sensitiser, was also less potent to cause cross-reactions than MDI or HDI.

Treatment with a 5% solution of TDI (2,4-TDI:2,6-TDI 4:1) resulted in ear swelling of previously unexposed mice in a skin sensitisation test. No effects were seen with an 1% test solution. After sensitisation, positive reactions could also be observed upon exposure at the lower test concentration (1%) (Tanaka, 1980).

The study by Stadler and Karol (1984) showed contact hypersensitivity in guinea pigs upon topical application four days after exposure to HMDI by inhalation (3 mg/m3, 2 h/day, 3 days).

7.5.3 In vitro data

No relevant data available.

7.5.4 Summary

The respiratory sensitisation potential of diisocyanates is well established based on both human and animal evidence. The most important clinical manifestation of this respiratory sensitisation is occupational asthma. Unlike in the case of high molecular weight OA causing substances, in the case of diisocyanates, the diisocyanate-specific IgE have been detected only in a small fraction of symptomatic subjects. Other immunological mechanisms may be involved (see Ch 7.9). Consequently there is no reliable overall marker for induction of respiratory sensitisation to diisocyanates that could be used to identify either a threshold or a dose-response relationship for induction of sensitisation from the human data reviewed. However, a number of observations have been made as regards factors influencing the risk of elicitation of respiratory sensitisation (i.e. occurrence of asthma).

The studies exploring the factors influencing the risk of diisocyanate induced asthma have indicated that average, cumulative and peak exposure all may influence the risk. None of the studies has been able to take into account in the same model the relative contributions of these mutually interlinked exposure metrics. Collins et al. (2017) observed an increased risk of cases consistent with TDI asthma both for cumulative exposure (OR = 2.08, 95% CI 1.07-4.05, per unit increase in log ppb-years) and for peak TDI exposures (OR = 1.18, 95% CI 1.06-1.32, per unit increase in ppb). When using cumulative exposure as an exposure metric, the probability of being an asthma case increased with 153% from 5 to 20 ppb-years, and when using estimated peak exposure the probability increased with 962% from 5 to 20 ppb. In a cross-sectional study, Pronk et al (2009) reported that the interquartile increase in cumulative exposure (about 9000-fold increase) was associated with a prevalence ratio of 2.0 (95% CI 1.1 – 3.8) of bronchial hyperresponsiveness (BHR) and a prevalence ratio of 2.7 (95% CI 1.0 – 6.8) when outcome was defined as BHR combined with asthma-like symptoms. The exposure was mainly for HDI. An association between a single short-term exposure to 20 ppb of TDI with minimal but detectable changes in airway calibre and in epithelial barrier permeability has also been observed in a human volunteer study (Vandenplass et al., 1999)

There is evidence that the risk of diisocyanate induced occupational asthma is higher during the first one or two years after the start of exposure than several years later, while there is no study that would have followed workers over a period close to a full 40 year working career. Meredith et al (2000) reported in a case-control design that the OR for each 0.1 ppb increase in current exposure (expressed as 8-h TWA) was higher for cases with symptoms occurring within a year from start of employment (1.5, 95% CI 0.82 – 2.7, p = 0.18) than among those with a later onset of symptoms (1.04, 95% CI 0.95 – 1.13, p = 0.41). Although this analysis was based on relatively small numbers of cases and referents in each of the time windows, the authors concluded that there seemed to be no association between current exposure to isocyanates and the development of asthma more than 1 year from employment. The exposure was mainly to TDI. Similar observations were made by Collins et al (2017) in a longitudinal study which reported that of the seven cases with findings consistent with TDI-induced asthma, four had less than 1 year of job tenure (range

1 to 7 months), one had worked for 2 years when beginning participation, and the other two had worked at the job for 7 and 8 years.

Asthma is a disease characterised by symptoms and airflow limitation that vary over time and by intensity. Respiratory sensitisation may manifest itself by symptoms that occur well before a clinical diagnosis of asthma can be made. There is evidence that the longer the symptomatic exposure before removal from exposure (to TDI), the more persistent the features of occupational asthma at follow-up (Pisati et al., 2007).

Human workplace equivalent concentrations (HEC) corresponding to the elicitation results of rat studies were calculated by Pauluhn (2015, 2014). The HEC 8-hour values for TDI and HDI were estimated as 0.003 ppm (0.02 mg/m3) and 0.03 ppm (0.2 mg/m3), respectively.

Human and animal data indicate that a chemical may induce respiratory disease after sensitisation via dermal exposure even when the air levels are too low to cause sensitisation via the respiratory tract (Tsui et al., 2020). There is evidence that also dermal exposure to diisocyanates is a risk factor for the induction phase of respiratory sensitisation (North et al., 2016). This was shown in animal models and is thought to be relevant for humans as well (Bello et al., 2007) and with further animal evidence recently published by Pollaris et al 2019. Dermal exposure is difficult to measure and to quantify and is often not reported and never quantified in epidemiological studies.

Diisocyanates also test positive in standard animal skin sensitisation assays and cases of human allergic contact dermatitis have been reported. However, the human evidence does not indicate skin sensitisation being subject to a similar occupational epidemics as respiratory sensitisation.

It is considered that it is appropriate to derive a dose-response based on the concentration of the NCO group and to apply that to all diisocyanates (see Section 7.9).

The recent conclusion of ECHA's Committee for Risk Assessment (ECHA, 2018b) was that none of human studies available was considered adequate for deriving a reliable exposure-response relationship curve due to a number of limitations in those studies (see concluding remarks of Section 7.4.1 for details). It is noted that the studies of Collins et al. (2017) and Daniels (2018) have provided quantitative estimates of exposure response relationship and were not yet available at the time of the above RAC conclusion. Furthermore, Section 8.1 describes national or international approaches taken to overcome the above uncertainties and to provide science-based values either to identify a threshold or a dose-response to inform on setting an occupational limit value.

7.6 Genotoxicity

7.6.1 Human data

The alkaline Comet assay was used to analyse DNA strand breaks in lymphocytes of workers having respiratory symptoms and with a history of exposure to diisocyanates (Marczynski et al., 2005). In a controlled atmosphere chamber, five workers (TDI-exposure history 2.5-12.5 years) were exposed during four times, 30 minutes to increasing concentrations of TDI (0.036-0.22 mg/m^3 (0.005-0.03 ppm; corresponding to 0.017-0.10 mg/m^3 NCO); 80:20 mixture of the 2,4- and 2,6-isomers). Whole-blood samples were taken before the start of the experiment and 30 min and 19 h after the end of exposure. Analysis of Olive tail moments (product of the Comet tail length and the fraction of total DNA in the tail) revealed no statistical differences before and after exposure or between subjects exposed to TDI or to one of the other diisocyanates tested (MDI, HDI). The authors reported a small susceptible group of the workers (about 10%) with elevated Olive tail moments (increase ≥1.0) showing much higher frequencies of DNA strand breaks in lymphocytes after exposure (no further details were provided).

7.6.2 Animal data

Negative results, indicating no concern for genotoxicity, were obtained in a number of *in vivo* studies using TDI.

Positive results were obtained when assessing the potential of TDI to induce chromosomal aberrations or sister chromatid exchange (ATSDR, 2018, Ji et al., 2008). An inhalation study with TDI and MDI produced an increase in haemoglobin adducts, which might indicate a genotoxic potential, but no effects were seen in micronucleus tests (Lindberg et al., 2011).

Positive results were obtained with MDI in the rat micronucleus test of Zhong and Siegel (2000), whereas another study (Pauluhn et al., 2001) was negative.

HDI did not induce mutagenicity in a mouse micronucleus test (Wagner et al., 2000).

In vivo studies are summarised in Table 29.

Table 29: *In vivo* genotoxicity studies

Species (test system)	Investigation	Route of administration	Result	Reference
2,4-TDI:2,6-TDI (80:20)				
Mouse and rat	Micronuclei (bone marrow)	Inhalation	Negative	(Loeser, 1983)
Mouse	Micronuclei (bone marrow and peripheral blood)	Inhalation	Negative	(Lindberg et al., 2011)
Mouse	Chromosomal aberration, sister chromatid exchange (bone marrow)	Inhalation	Positive	(Ji et al., 2008)
4,4'-MDI				
Mouse	Micronuclei (bone marrow and peripheral blood)	Inhalation	Negative	(Lindberg et al., 2011)
Rat	Micronuclei (bone marrow)	Inhalation	Positive	(Zhong and Siegel, 2000)
Rat	Micronuclei (bone marrow)	Inhalation	Negative	(Pauluhn et al., 2001)

Species (test system)	Investigation	Route of administration	Result	Reference
Rat	DNA adduct formation (epidermis and liver)	Dermal	Negative	(Vock and Lutz, 1997)
Rat	DNA adduct formation (epidermis)	Dermal	Negative	(Vock et al., 1995)

7.6.3 In vitro data

Inconclusive/equivocal results were seen in Ames tests with TDI and MDI. All studies showed negative results in the absence of metabolic activation, whereas some were positive when metabolic activation was induced. Chromosomal aberration studies and sister chromatid exchange tests with TDI and MDI have shown equivocal results. HDI, on the other hand, was tested negative for mutagenicity in bacteria (Ames test) and mammalian cells, as well as in the CHO/HPRT mutation assay. NDI was negative in the Ames test, but induced chromosomal aberrations and was tested positive in the hypoxanthine-guanine phosphoribosyl transferase forward mutation assay (V79 cells). IPDI did not cause positive results in the Ames test or in the CHO/HPRT forward mutation assay (ATSDR, 2018, DECOS, 2018, IARC, 1999, OECD, 2001)

7.6.4 Summary

Based on the available data, some studies indicate that diisocyanates may cause genotoxicity. The study results are however inconclusive/equivocal.

7.7 Carcinogenicity

7.7.1 Human data

Epidemiological data on cancer consist of studies on TDI. IARC (1999) reviewed three cohort studies in Sweden, UK and USA. Based on these three studies, IARC concluded that there is inadequate evidence for the carcinogenicity of TDI in humans. After the IARC review, updates have been published for all three cohorts. It is concluded that the results of these updates are in line with the initial IARC conclusion (see below).

In the Swedish cohort of 4175 workers, non-significant increases in rectal cancer and non-Hodgkin's lymphoma (NHL) were observed in the first analysis (Hagmar et al., 1993). In an update with 11 more years of follow up, fewer total cancer cases than expected were observed, although the lung cancer incidence was increased in women (Mikoczy et al., 2004). Women with "apparent exposure" to TDI or MDI did not, however, have a higher lung cancer incidence than those with "no or low exposure".

In the UK cohort of 8288 workers, slight increases in pancreatic cancer (standardised mortality ratio (SMR) 2.71, 95% CI 1.00-5.95) and lung cancer (SMR 1.76, 95% CI 1.00-2.85) were found that were not statistically significant (Sorahan and Pope, 1993). In an update, with 10 years of additional follow up, no significantly increased risk was observed in workers exposed to isocyanate and no trends were found between risks of lung cancer or risks of non-malignant diseases of the respiratory system and durations of "lower" or "higher" exposures to diisocyanates (Sorahan and Nichols, 2002). For pancreatic cancer, SMRs were increased for males and females, but without statistical significance.

In the US cohort, involving 4,611 men and women employed in four polyurethane foam manufacturing plants for at least 3 months between the late 1950s and 1987, mortality from non-Hodgkin's lymphoma was increased, but not to statistically significant levels (SMR 1.54, 95% CI 0.42-3.95). The study was considered inconclusive because of the low number of deceased persons in the short follow-up time (Schnorr et al., 1996). This cohort

was updated with an extended follow-up of 18 years (Pinkerton et al., 2016). Mortality from all causes (SMR 1.16; 95% CI 1.10-1.23) and all cancers (SMR 1.27; 95% CI 1.14-1.42) was significantly elevated. Among cancer causes of death, mortality from larynx (SMR 4.00; 95% CI 1.99-7.16), lung (SMR 1.59; 95% CI 1.32-1.89), and other and unspecified cancer (SMR 1.51; 95% CI 1.00-2.18) was significantly increased. No exposure-response was, however, observed for these cancers. The risk estimates were not adjusted for the effect of smoking. Mortality from breast, intestine, and brain cancers and non-Hodgkin lymphoma were slightly increased, although not significantly, and was somewhat associated with either exposure duration or cumulative TDI exposure.

Before the latest updates of the three cohort studies, Bolognesi et al. (2001)reviewed the data on carcinogenicity of TDI and MDI and concluded that the few epidemiological studies available have been based on young cohorts and short follow-up and are not conclusive.

Prueitt et al. (2013) reviewed the human, animal and mode of action data on carcinogenicity of TDI concluding that a causal association between TDI exposure and carcinogenic effects is not plausible in humans. Prueitt et al. (2017) reviewed the data on TDI and respiratory cancer, with focus on dermal exposure. They reported that overall, several of the epidemiology studies reported associations between respiratory cancers and female polyurethane foam manufacturing workers, but there were no positive exposure-response relationships in any of these cohorts, and the evidence indicates that the increased respiratory cancer risks in female workers were likely unrelated to exposure to diisocyanates. It was considered more likely that the observed associations were related to one or more confounders, such as smoking, but specific information on smoking was not available for any of the cohorts. The epidemiology studies reviewed did not indicate that occupational exposure to TDI *via* inhalation in the polyurethane foam manufacturing industry, with some degree of dermal exposure to TDI, is associated with an increased risk of developing respiratory cancer.

7.7.2 Animal data

Whole-body inhalation exposure of 60 male and 60 female rats with MDI (6 h/day, 5 days/week, 2 years; nominal concentrations 0.2, 1.0, 6.0 mg/m^3 (0.020, 0.098, 0.59 ppm), corresponding to 0.067, 0.34, 2.9 mg/m^3 NCO) resulted in six cases of lung adenoma and one lung adenocarcinoma in male rats of the high-dose (6.0 mg/m^3) group. Among females, lung adenomas were found in 2/59 animals exposed to the highest dose. No other tumour findings were reported. (Reuzel et al., 1994). The development of local irritation and cytotoxicity and subsequent hyperplasia is suggested as the mechanism for tumour formation.

One bronchio-alveolar lavage adenoma was observed among 80 female rats exposed to MDI (2.05 mg/m^3 (0.20 ppm), corresponding to 0.69 mg/m^3 NCO) 18 h/d, 5 days/week, 2 years). No other findings indicating a carcinogenic potential were reported (Feron et al., 2001).

Inhalation exposure of male and female rats to TDI (0.05 and 0.15 ppm (0.36 and 1.1 mg/m^3, corresponding to 0.17 and 0.53 mg/m^3 NCO), 6 h/day, 5 days/week, two years) did not provide any evidence of carcinogenicity (IARC, 1999, Loeser, 1983).

No indications of a carcinogenic potential were observed when rats were exposed to monomeric HDI at concentrations up to 1.13 mg/m^3 (0.16 ppm; corresponding to 0.56 mg/m^3 NCO) for two years (Shiotsuka et al., 2010).

In contrast to the negative findings observed upon inhalation exposure, increased frequencies of several types of tumours (*rat*: subcutaneous fibromas and sarcomas in males and females, pancreatic acinar cell adenomas in males, pancreatic islet cell adenomas, neoplastic nodules of the liver and fibroadenomas in females; *mice*: mammary gland hemangiomas, hemangiosarcomas, hepatocellular adenomas in females) were observed when male/female rats and mice were exposed to TDI in corn oil (0, 60, 120

mg/kg bw/day female rats; 0, 30, 60 mg/kg bw/day male rats; 0, 120, 240 mg/kg bw/day male mice; 5 days/week, 105 weeks (mice) or 106 weeks (rats), oral gavage) (Dieter et al., 1990, NTP, 1986). It has been discussed that these findings are likely to have been results of exposure to toluene diamines, formed from TDI in the acidic gastric environment, an event which is not considered relevant for worker exposure (Dieter et al., 1990, Sielken et al., 2012).

7.7.3 Summary

In an assessment of the carcinogenic potential of TDI, IARC (1999) concluded that there is inadequate evidence for the carcinogenicity of TDI in humans and sufficient evidence for the carcinogenicity of TDI in experimental animals. The overall conclusion was that TDI is possibly carcinogenic to humans (Group 2B).

Regarding monomeric and polymeric MDI, IARC (1999) concluded that there is inadequate evidence for carcinogenicity in humans, and there is limited evidence in experimental animals for carcinogenicity of a mixture containing monomeric and polymeric MDI. Overall, IARC evaluated that MDI (industrial preparation) is not classifiable as to its carcinogenicity to humans (Group 3).

Taking into consideration the update-publications related to the old cohorts, and the animal data published after the IARC review, it is concluded that there is no new information indicating a carcinogenicity potential of diisocyanates and the current data is still in line with the harmonised CLP-classification of several diisocyanates (Carc 2; Suspected of causing cancer).

7.8 Reproductive toxicity

7.8.1 Human data

No epidemiological studies were identified concerning reproductive toxicity and exposure to diisocyanates.

7.8.2 Animal data

Diisocyanates have not been reported to cause effects on reproduction or development in animal studies.

No effects on parameters related to reproductive toxicity were observed in a 2-generation inhalation study with TDI in rats (0.3 ppm (2.1 mg/m^3), corresponding to 1.0 mg/m^3 NCO; 6 h/day, 5 days/week) (Tyl et al., 1999). In a 2-year study with rats and mice no histological alterations in gonads were observed (Loeser, 1983).

HDI did not cause any effects on reproduction, gestation or early neonatal development in rats exposed by inhalation at doses up to 0.3 ppm (2.1 mg/m^3), corresponding to 1.0 mg/m^3 NCO, in a combined reproductive/ developmental/ neurotoxicity screening test (Astroff et al., 2000).

Exposure of pregnant rats to 0.5 ppm (3.6 mg/m^3) TDI (80% 2,4-TDI:20% 2,6-TDI), corresponding to 1.7 mg/m^3 NCO, during gestation days 6-15 showed a higher incidence of litters with poorly ossified cervical centrum no. 5 as compared to controls. However, the maternal body weight was significantly decreased, and dams showed respiratory symptoms and the litter findings were therefore considered as secondary to maternal toxicity. (Tyl et al., 1999)

In the developmental toxicity study of Buschmann (1996), no significant treatment related effects were observed when rats were exposed to 9 mg/m^3 (0.88 ppm) monomeric MDI, (corresponding to 3.0 mg/m^3 NCO) on gestation days 6-15. The increase in asymmetric sternebrae observed in exposed litters was within normal variations.

Exposure to polymeric MDI aerosols during gestation days 6-15 at concentrations of 12 mg/m^3 resulted in developmental toxicity effects (reduced placental and foetal body weights, increased incidence of skeletal variations and retardations) in rat offspring. At this dose level there was however severe maternal toxicity effects. No indications of maternal or developmental toxicity were observed at the lower dose levels of 1 and 4 mg/m^3. (Gamer et al., 2000)

No developmental toxicity effects were seen in a pre-natal developmental toxicity test performed in rats with inhalation exposure to HDI up to 0.3 ppm (2.1 mg/m^3, corresponding to mg/m^3 NCO) (Astroff et al., 2000).

7.8.3 Summary

There are no indications of reproductive or developmental toxicity effects of diisocyanates.

7.9 Mode of Action consideration

Based on the activity of the NCO-group, a common mechanism of action can be assumed for all diisocyanates. The NCO group is responsible for binding to proteins, which is considered to be the "molecular initiating event" of sensitisation induced by low molecular weight substances. This assumption is partly supported by data indicating immunological cross-reactivity between diisocyanates in humans, but it is noted that lack of cross-reactivity has also been reported in human and mouse studies (Aul et al., 1999, Baur, 1983, Grammer et al., 1990, Lushniak et al., 1998, Malo et al., 1983, Mapp et al., 1985, Pollaris et al., 2016, Redlich, 2010, Wass and Belin, 1989).

Additionally, it is important to notice that for most of the cases of respiratory sensitisation the specific (di)isocyanate (or oligomer) which caused the effect is not known. Workers may often be exposed to more than one diisocyanate at the workplace when mixtures of isocyanates are being used, or as a result of the reactivity of diisocyanates.

Respiratory sensitisation

Studies generally report very similar diisocyanate-induced hazardous effects in humans and test animals, namely irritation and sensitisation. Upon exposure, the NCO-group of the diisocyanate molecule is expected to form biomolecular conjugates when reacting quickly with the NH_2–group of proteins, like albumin. Glutathione is likely to play an important role in the formation of the diisocyanate-albumin conjugates, and glutathione S-transferase polymorphisms may have an influence on the outcome. The conjugated proteins are captured by immature dendritic airway cells, which, after maturation, migrate to lymph nodes and present the diisocyanate conjugates to naïve T-cells. Available data indicates a mixed Th1/Th2 cell response, involving both type I and type IV (identified by CD^{8+}-T-cells and secretion of IFNγ and delayed reactions and lack of atopy as a recognized risk factor for diisocyanate-induced asthma) hypersensitivity. Also alternative mechanisms, like oxidative stress, have been suggested to be involved in triggering the development of asthma (DECOS, 2018, Cartier et al., 1989, Sastre et al., 1990, Wisnewski et al., 2013a, Wisnewski et al., 2015, Shin et al., 2013, Liu and Wisnewski, 2003)

Diisocyanate-induced asthma has been reported following exposure to several different diisocyanates. There is evidence that even a single low level exposure to TDI may result in minimal but detectable changes in airway calibre and in epithelial barrier permeability compatible with those observed in asthmatics. Once a person becomes sensitised, asthmatic responses may be triggered upon exposure to very low concentrations of diisocyanates. At higher doses, the asthmatic reactions may also be linked to local irritation and non-specific bronchial hyperresponsiveness. It is not clear whether mechanisms involving IgE are occurring simultaneously with cellular (delayed-type) responses, but obviously the development of diisocyanate-induced occupational asthma is due to complex mechanisms, differing from those related to conventional respiratory sensitisation. Bronchial challenge tests with subjects having TDI-induced asthma were not able to detect

specific IgE and atypical/delayed responses have been reported in subjects with TDI-induced asthma (Son et al., 1998, DECOS, 2018).

An enhanced production of MCP-1 (monocyte chemoattractant protein-1), suggesting an activation of macrophages, has been detected in peripheral blood mononuclear cells of persons with diisocyanate-induced occupational asthma (Bernstein et al., 2002, Lummus et al., 1998).

Dermal exposure seems to have an impact on respiratory sensitisation, but the mechanisms are unclear. Human and animal data indicate that a chemical may induce respiratory disease after sensitisation via dermal exposure even when the air levels are too low to cause sensitisation via the respiratory tract (Tsui et al., 2020).

There are marked variations in response between animal species, as well as in protocols and allergens used, and there are only few studies that assessed these discrepancies in order to determine the best model (Aun et al., 2017). Another limitation is that, compared to humans, relatively high diisocyanate monomer doses are applied in animal experiments (e.g. 7.8-39.1 MDI/m^3, 85 mg TDI/m^3, and around 72 mg HDI/m^3 in elicitation dose-response studies; Pauluhn, 2008, 2014, 2015). Inhalation exposure studies are technically challenging for diisocyanates (Pauluhn, 2014) because low concentrations of diisocyanates (especially TDI and HDI) may be scrubbed in the nasal passages, especially in obligate nasal breathers such as rats, mice or Guinea pigs, and adequate penetration of the compounds in the lower respiratory tract occurs only at higher concentrations (Arts et al., 2006, Pauluhn, 2014). On the other hand, respiratory tract irritation is a dose-limiting factor in pulmonary toxicity studies of diisocyanates in rodents. Following inhalation of an irritant, there could be a marked, dose-dependent decrease in respiration rate and minute volume (and consequently a reduction of inhaled dose), resulting from nociceptive reflexes in rodents, but not in humans (Alarie, 1966). Differences between species have been reported for this effect as well (Chang et al., 1981).

Irritation

Diisocyanates can cause skin, eye and respiratory irritation, including histological changes. The physico-chemical properties of different diisocyanates determine their deposition and thereby the main area of the respiratory tract where the local effects occur. Repeated inhalation exposure can result in local inflammatory effects. At high exposure concentrations, non-specific bronchial hyperresponsiveness may occur as a result of direct tissue injury and epithelial cell inflammation (Shin et al., 2013).

Animal studies providing a dose-response relationship on diisocyanate-induced irritative respiratory response in non-sensitised animals are rather limited. Diisocyanate-induced sensory irritation of the upper respiratory tract in animal models (i.e. rodents), quantified as a reflex reduction in the respiratory rate, is not considered relevant for irritation threshold derivation in humans. Cytotoxic and tissue damaging effects are not well predicted by this endpoint (Bruning et al., 2014), and other limitations are described in ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7a and 8). Additionally, experimental human data showed that subclinical increase in airway permeability following short-term exposure to TDI (0.036 mg/m^3 for 6 h, followed by 0.145 mg TDI/m^3 for 20 minutes), occurred below the threshold for upper respiratory tract irritation in healthy humans (0.35 – 0.92 mg TDI/m^3) (Henschler et al., 1962, IPCS, 1987).

Regarding other effects of respiratory irritation (i.e. "tissue irritation" endpoints; reviewed in DFG 2013), due to differences in toxicokinetics of inhaled diisocyanates between humans and animals, different exposure patterns (e.g. repeated-dose studies in animals vs. single inhalation challenge studies in humans), as well as limitations in experimental methodology or reporting, it is hard to put animal data into human perspective. In addition, only few animal studies assessed early effects of isocyanate-induced respiratory irritation such as increased protein concentration in BAL (e.g. Pauluhn, 2000a, 2000b, Ma-Hock et al., 2007),

although this biomarker is considered to be among the most sensitive indicators of injury of the bronchoalveolar region by pulmonary irritants (Pauluhn, 2004). It reflects increased airway permeability, which is a sensitive indicator of pulmonary epithelial injury and/or compromised function of pulmonary epithelium (OEHHA, 2016)(OEHHA MDI, 2016), and it is considered that it can increase the risk for respiratory sensitisation in humans (Georas and Rezaee, 2014). In Pauluhn (2000a) study in rats, at LOAEL of 0.7 mg/m^3 BAL protein level increased by approximately 50% following 6-hour exposure to MDI/polymeric MDI mix aerosol (approximately 54% monomeric MDI, 34% 3-oligomeric MDI and 9% 4-oligomeric MDI). NOAEL was not found in this study. In Ma-Hock et al. (2007) study in rats, 6-hour exposure to HDI-based polyisocyanate mixture at the level of 2.7 mg/m^3 (mainly as aerosol) statistically significantly increased BAL protein concentration (by approximately 2.5 times). NOAEL was 0.5 mg/m^3. When relevant assessment factors are applied, DNEL of 0.046 mg NCO/m^3 in case of MDI/polymeric MDI mixture, and of 0.054 mg NCO/m^3 in case of HDI–based polyisocyanate mixture could be derived for short-term (15 minutes) exposure. These values are, however, based on mixtures of monomeric diisocyanates, polyisocyanates and polymeric isocyanates, so it is difficult to differentiate separate contribution of these constituents.

Potency

The general understanding is that all diisocyanates can cause respiratory sensitisation and irritation. It is however not clear whether some diisocyanates are likely to be more potent, i.e. causing effects at lower doses than others. The rest of the molecule may influence the electrophilic strength of the NCO group and it may be speculated that there can be differences in the reactivity of aromatic diisocyanates compared with aliphatic diisocyanates, for example.

The human studies do not allow evaluation of differences in potency between different diisocyanates. Studies on the same diisocyanate do shown considerable differences in risk estimates which may be explained by differences in exposure but also study methodology, choice of health endpoints evaluated and exposure assessment strategy.

Regarding animal data, there are very few studies involving exposure to several different diisocyanates. Furthermore, there are not many comparable study reports using same/comparable study protocols. In addition, for the most critical endpoint (respiratory sensitisation) there are no internationally validated standard test protocols, which may be a reason why the available, published studies are focusing on a wide variety of endpoints. All these aspects make it difficult to directly compare the potencies of diisocyanates. Consequently, there are still no assays that would allow for the characterisation of the relative potency of chemical respiratory allergens (Basketter and Kimber, 2011).

When comparing the acute toxicity LD50-values of HDI, TDI and MDI, it can be seen that HDI is the most toxic one (LD50 746-959 mg/kg), whereas the LD50-values of TDI and MDI are similar (>2000 mg/kg).

The study by Thorne el al. (1987) compared the potential of diisocyanates to induce skin sensitisation, and the results indicated that HDI was clearly the most potent one, followed by MDI, and TDI, causing sensitisation only at significantly higher doses. Similar results were obtained (Ohtake et al., 2018) in a mouse LLNA test, showing one order of magnitude higher potency of HDI compared to MDI and TDI. However, it should be noted that although most (if not all) low molecular weight (LMW) respiratory allergens are also positive in the skin sensitisation assays (e.g. LLNA), a relationship between skin and respiratory sensitisation potency is not clear, either from mechanistic or quantitative aspect. Differences in sensitisation potency for LMW following dermal and inhalation route have

been noted when comparing dermal and respiratory LLNA[15] (Arts et al. 2008). Also, Pauluhn (2014) showed that bronchoalveolar lavage indices of respiratory sensitisation after MDI inhalation did not depend on topical sensitisation dose, but were positively related to the sequence and dose of MDI inhalation challenges.

With respect to respiratory irritation, TDI and HDI seem to be equally irritant (RD_{50}-value 0.60-0.68 mg/m^3 as NCO at 3 h exposure) (Sangha and Alarie, 1979, Sangha et al. 1981, Weyel and Schaffer, 1985). MDI on the other hand is less irritating (RD_{50} 11 mg/m^3 as NCO, 4 h). The skin irritation profiles are in line with these findings; TDI and HDI are corrosive, whereas MDI causes skin irritation but not corrosion (ECHA, 2019).

Using the Brown-Norway rat model with dermal induction and inhalation challenge, Pauluhn (Pauluhn 2014, Pauluhn 2015) identified very similar elicitation points-of-departure of 900 mg HDI/m^3 *x* min and 1000 mg TDI/m^3 *x* min for vapours of TDI and HDI. With respect to MDI-aerosol, the identified elicitation point-of-departure was markedly lower; 90 mg MDI/m^3 *x* min. Nevertheless, even these experiments, which were performed to the highest standards, by the same author(s) and on the same species and strain (Brown Norway rats, BN/Crl BR strain), do methodologically differ. In case of MDI, aerosolised polymeric 4,4'-MDI with around 44% of monomeric MDI was used, while for TDI and HDI monomeric forms were applied as vapours. The elicitation dose-response curve was derived in a different way for MDI versus TDI and HDI, due to technical reasons: for MDI, exposure time was constant and the concentration varied (including non-irritative dose), while for TDI and HDI, due to their prominent irritant properties, one (mildly irritant) dose level was applied, with varying exposure time.[16] Also, as pointed out by Pauluhn (2014), "seemingly less potent diisocyanates may be affected by volatility which also influences the potential of inhalation and dermal exposure intensities"

In conclusion, when looking at the available data on several different health hazard endpoints, including respiratory sensitisation, it is not possible to observe any clear trend in toxicity potential of the most widely studied diisocyanates. As none of those is not clearly more potent than another, the argument to give common limit values instead of substance specific values, is supported.

7.10 Lack of specific scientific information

The mechanisms of diisocyanate sensitisation are not fully understood. Unlike in high molecular weight substances that cause occupational asthma, specific IgE antibodies are not frequently detected and therefore mechanisms other than IgE mediated may play a role. Consequently there is no reliable marker of induction of respiratory sensitisation to diisocyanates that could be used to identify either a threshold or a dose-response relationship for induction of sensitisation.

[15] Nevertheless, respiratory LLNA model has not been extensively validated, and very limited number of respiratory sensitisers has been tested till now (ter Burg et al. 2014).

[16] Pauluhn (2014): "While MDI can technically be aerosolized to be deposited within the lower airways, the dosimetry of TDI-vapor is profoundly more complex. Reactive TDI-vapor is retained concentration-dependently throughout the entire respiratory tract and too low concentrations may be scrubbed to an appreciable extent within the upper airways of obligate nasal breathing rats. Additionally, any predominating upper respiratory tract irritation prompts a reflex-induced, concentration-dependent depression of ventilation which may further affect the inhaled dose and depth of vapour-penetration into the lung. For MDI-aerosol a variable concentration (Cvar) × constant exposure duration (t const) protocol was used for challenge due to negligible upper respiratory tract irritation (Pauluhn, 2000)."

8. Occupational asthma risk assessment and exposure limit values

8.1 Published approaches for occupational asthma risk assessment and OELs for diisocyanates

Relevant publications presenting approaches for occupational asthma risk assessment or other bases for OELs for diisocyanates are summarised below.

8.1.1 ACGIH 2016

The American Conference of Governmental Industrial Hygienists (ACGIH, 2016) reviewed the human and animal data to estimate an exposure level below which induction of TDI-induced sensitisation is unlikely. Comparison was made between annual incidence of TDI-induced OA in various populations (Adams 1975, Ott et al. 2000) and (average) exposure levels associated with those incidences as well as animal experimental data. ACGIH established an 8-hour TWA of 1 ppb expected to result in further reduction of TDI-induced OA. ACGIH acknowledged, however, that when applying the 8-hour TWA of 1 ppb:

- not all new cases of TDI-induced OA may be eliminated; and
- workers who have already been sensitised to TDI may not be protected.

The report acknowledged that health effects associated with time-weighted average concentrations may be influenced by the occurrence of single or multiple peak exposures. With reference to the review of Ott et al. 2003 it was stated that among employees exposed up to 5 ppb, more recent longitudinal studies with ongoing medical surveillance have produced no consistent evidence of accelerated FEV_1 loss. Therefore, ACGIH recommended also a STEL of 5 ppb, which is intended to minimise the number and magnitude of peak exposures.

The 8-hour TWA of 1 ppb (7 µg/m^3) and STEL of 5 ppb (35 µg/m^3) of TDI correspond to 3.4 and 17 µg NCO/m^3, respectively.

It is noted that in the absence of a reliable marker for induction of respiratory sensitisation, it is difficult to quantitatively assess a possible threshold or dose-response for induction of sensitisation to TDI. Consequently, it is difficult to assess the uncertainties related to the approach applied by ACGIH to derive a limit under which no induction of OA would occur. However, as explained in Section 7.5.1., accelerated FEV_1 loss is not considered a sensitive predictive marker of asthma, as asthma is characterised by variable airflow limitation, and lung function may not be decreased permanently.

ACGIH general position framework of setting Threshold limit values and Biological exposure indices (TLVs/BEIs) is acknowledged. More specifically: "ACGIH® formulates a conclusion on the level of exposure that the typical worker can experience without adverse health effects. The TLVs® and BEIs® represent conditions under which ACGIH® believes that nearly all workers may be repeatedly exposed without adverse health effects. They are not fine lines between safe and dangerous exposures, nor are they a relative index of toxicology" [17]. Since ACGIH TLVs and BEIs are based solely on health factors, there is no consideration given to economic or technical feasibility.

8.1.2 DECOS 2018

[17] https://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations/tlv-bei-position-statement
https://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations/tlv-bei-policy-statement

The Dutch Expert Committee on Occupational Safety (DECOS) prepared an advisory report for the Dutch Health Council recommending a health-based occupational exposure limit for di- and triisocyanates (DECOS, 2018). For the purpose of setting an exposure limit of sensitisers The Dutch Ministry of Social Affairs and Employment has set a risk level of 1% extra risk of sensitisation due to occupational exposure. This refers to an extra risk of 1% unit, for example from a general population prevalence of 2 per 100 to a prevalence of 3 per 100 among those occupationally exposed. Consequently the DECOS risk assessment was focused on the dose-response in the range of 1-5% of extra risk.

DECOS used the data from studies of Pronk (Pronk et al., 2009, Pronk et al., 2007) and Collins et al. (2017). DECOS performed risk calculations from the published data of Collins et al. (2017) or performed further in-house analyses from the original data made available to them concerning the studies of Pronk et al. (2007 and 2009). Pronk et al., performed a logisitic regression analysis to associate exposure to bronchial hyperresponsiveness (BHR20) and BHR20 in combination with wheeze. Regression coefficients for these associations were given. The respective regression coefficients from the logistic regression models for log NCO exposure were 0.0775 for BHR20 and 0.0467 for asthma (BHR20 and wheeze). These slopes lead exposure levels at which the extra risk is 1% of respectively 0.10 and 0.20 µg/m^3.

As regards the data of Pronk et al. (2009) and Pronk et al. (2007), both individual level and group level data were used for an exposure-response analysis. Based on individual level data and using bronchial hyperresponsiveness (BHR_{20}) as outcome lead to an exposure level of 0.10 µg NCO/m^3 corresponding to an extra risk of 1% (of BHR_{20}). Slightly higher exposure levels were calculated when the outcome was defined as BHR_{20} + wheeze (See Table 30). However, the model based on BHR_{20} was statistically more significant. Based on group level data analysis similar results were achieved.

Table 30: Extra risk of bronchial hyperresponsiveness (BHR_{20}) and BHR_{20} + wheeze by exposure to NCO calculated by DECOS from the original data of Pronk et al. (2009).

Outcome	Prevalence in the reference category	p	Exposure µg NCO/m3 corresponding to the extra risk level (% unit) of outcome			
			1%	2%	3%	5%
BHR20	4/48 (6.3%)	0.039	0.10	0.19	0.37	1.39
BHR20 + wheeze	2/48 (4.2%)	0.098	0.13	0.36	0.97	7.09

It is noted that the extra risk of 1% refers to an increase of 1 percentage unit. I.e. from a background risk of 6.3% of BHR_{20} in the reference category to a risk of 7.3% of BHR_{20} among those with an exposure level of 0.10 µg NCO/m^3 or an increase from 4.2% to 5.2% at 0.13 µg NCO/m^3 when BHR_{20} + wheeze was used as health outcome.

As regards Collins et al. (2017), DECOS used the published exposure-response relationship for a risk calculation for cases with (symptoms of) TDI-induced occupational asthma by cumulative exposure to TDI. DECOS established a linear relationship between log transformed cumulative exposure and log transformed odds ratio of TDI-induced occupational asthma and used it to calculate cumulative exposure levels that corresponded to extra risks of 1%, 2%, 3% and 5% (referring to increases of percentage units). More specifically Collins et al. (2017) presented probabilities of disease for different exposure scenarios. The probability of disease was used by DECOS to calculate the disease odds (=probablity of disease/probability of no-disease=p/(1-p). The log(odds) is linearly associated with the log(cumulative exposure). Based on the Collins data, this linear relation was reconstructed and subsequently used to calculate the exposures for any assumed risk level. The cumulative exposures to TDI were converted to 8 hour TWAs and then converted

to an exposure metric of concentration of NCO groups (µg/m^3). An exposure level of 0.14 µg NCO/m^3 for 8 hours was associated with an extra risk of TDI-induced asthma of 1% (Table 31).

Table 31: Extra risk of TDI-induced asthma by exposure to NCO calculated by DECOS from the data of Collins et al. (2017).

Outcome	Exposure µg NCO/m3 corresponding to the extra risk level (% unit) of outcome			
	1%	2%	3%	5%
TDI-induced asthma	0.14	0.38	0.65	1.34

It is noted that in these calculations the cumulative exposures (ppm-years) reported in the original paper of Collins et al. (2017) were converted to a TWA value assuming an exposure duration of 11.8 years. The 11.8 years is the reported mean duration of job tenure at the time of enrolment to the study. However, according to Collins et al. (2017) the cumulative exposures reported in the study were calculated using the self-reported date of first TDI exposure for those about 25% participants who reported that date. For the rest, the exposure was assumed to commence at the start of the study when the hire-date preceded the start of the study, or was assumed to begin at their hire date when this occurred after the start of the study. The study was conducted during a 5-year period from June 2007 to June 2012, so the cumulative exposures used and reported by Collins et al. (2017) were accumulated over a clearly shorter period than the average 11.8 years' employment time at the start of the study. Meaning that the average exposure level resulting to the calculated cumulative exposure during those years was higher than when using the 11.8 years assumption. The above convention of calculating the cumulative exposure also fails to capture altogether the cumulative (or peak) exposure that preceded the start of the study for that majority of the study participants that did not self-report the start date of their exposure.

As explained in Section 7.5.1 Collins et al. (2017) observed an increased risk of cases consistent with TDI asthma both for cumulative exposure (OR = 2.08, 95% CI 1.07-4.05, per unit increase in log ppb-years) and for peak TDI exposures (OR = 1.18, 95% CI 1.06-1.32, per unit increase in parts per billion). So both cumulative exposure and peak exposure predicted an increased risk. When comparing probability of being an asthma case by exposure it was reported that by cumulative exposure the probability increased by 153% from 5 to 20 ppb-years while by estimated peak exposure it increased 962% from 5 to 20 ppb. These comparisons are based on statistical models based only on seven cases, and on estimated rather than measured peak exposures. However, they indicate that also peak exposures may play a role while the study did not try discerning the effect of cumulative and peak exposure.

The risk-based OEL recommended by DECOS (2018) is 0.1 µg NCO/m^3 which is based on the Dutch Ministry of Social Affairs and Employment reference risk level of 1% extra risk of sensitisation due to occupational exposure.

8.1.3 Daniels 2018

Daniels (2018) calculated BMD_{01} and $BMDL_{01}$ values and used a low dose extrapolation to calculate a risk-based OEL for TDI corresponding to a working lifetime (45 years) extra risk of 1/1000 using first several models and finally both a linear no threshold (LNT) and a quadratic rate function. The quadratic model had the best fit and resulted in an OEL of 0.3 ppb of TDI corresponding to 1/1000 extra risk. It is noted that the 0.3 ppb of TDI would correspond to a NCO concentration of 1 µg NCO/m^3. It is to be noted that with LNT rate function the exposure concentration corresponding to a 1/1000 excess was lower (0.018

ppb of TDI). An extra risk of 1/100 corresponded to an exposure of 1 ppb (quadratic rate function) or 0.2 ppb (linear rate function), i.e. 3.4 and 0.7 µg NCO/m^3, respectively.

Table 32: Extra risk of TDI-induced OA from continuous TDI exposure over a 45-year working lifetime by exposure expressed as µg NCO/m^3 (from Daniels (2018)).

Average TDI exposure as µg NCO/m^3	Extra risk (cases per 1000 persons)	
17	238	245
3.4	10	55
1.0	1	-
0.34	<1	6
0.069	-	1
0.034	<1	<1

The role of peak exposures was not assessed. Moreover, Daniels (2018) acknowledged that *"Data on the appropriate exposure index for dose-response modeling are uncertain. It remains unclear whether TDI-induced asthma is a consequence of low cumulative exposure, exposure intensity, or some combination that also accounts for time ordering of intermittent exposure."* And "*For this study, it is assumed that the risk of TDI sensitization is related to average exposure, which may also be a correlate of peak exposures."* The case definition varied between the studies and was based either on work-related symptoms compatible with OA, a diagnosis by a physician or review of medical files. The extra risk per average exposure was calculated per 1000 workers who are continuously exposed to that average level of TDI over a 45-year working lifetime. This seems a conservative assumption given the case-control study of Meredith et al 2000 were exposure intensity did not correlate with risk of asthma occurring several years after onset of employment in the risk job.

However, for reason further elaborated in Chapter 7.5.1 It is considered that the Daniels study should not be used for a quantitative risk assessment and that instead of condensing the exposure-response experience from each study into a single data point, a meta-regression analysis should preferably use exposure response relations from individual studies, adjusted for confounding variables, which are combined into one meta-exposure response relation. It was therefore evaluated whether the studies included in the review by Daniels (2018) could supply individual exposure-response which could be of use in an alternative exposure-response analysis. For reasons further elaborated in Chapter 7.5.1. It is considered that no individual studies were included in the Daniels study that would allow a robust evaluation of an (internal) quantitative exposure-response relation to be used in further analyses.

8.1.4 DFG

The German MAK commission (DFG, 2019) has used different approaches when proposing substance specific limit values (MAK values) for some diisocyanates.

The values for MDI (see Table 6) are derived based weight of evidence of data indicating slight breathing difficulties in workers at MDI concentrations of 0.1 mg/m^3. No effects had been reported at 0.05 mg/m^3 (5 ppb, corresponding to 17 µg/m^3 NCO) which is set as the 8-hour MAK-value. The value applies also for polymeric MDI, as the reactive NCO groups are attached to MDI and polymeric MDI to the same extent. In long-term inhalation studies in rats, the NOAEC for MDI, as well as for polymeric MDI was identified as 0.2 mg/m^3 (local lung effects; UBA 1995 reviewed in DFG, 2008), indicating no need to adjust the MAK value. (DFG, 2008)

For HDI, the MAK value (see Table 8), is set on the basis of the occurrence of metaplasia and/or hyperplasia with hyaline degeneration of the respiratory epithelium and the mucus-

secreting glands in a two-year inhalation study with rats (Mobay 1989, reviewed in DFG, 2013). The NOAEC was considered to be 5 ppb (35 µg/m^3, corresponding to 17 µg/m^3 NCO), which was selected as MAK value. (DFG, 2013)

No MAK value has been established for TDI (DFG, 2015).

8.1.5 ANSES (2019)

In its draft recommendation for occupational limits for TDI[18] (currently ongoing consultation), ANSES considered that the available epidemiological studies reporting data on respiratory effects suffer from several limitations for the establishment of dose-response relationships. ANSES concluded that the available animal studies indicate that the induction of respiratory sensitisation (as well as respiratory irritation) is a threshold phenomenon and the effect levels of respiratory irritation and induction of respiratory sensitisation are similar and therefore an OEL based on irritation adequately protects against both irritation and sensitisation. Consequently respiratory irritation was selected as the critical end point for the OEL, while it was considered that protection against irritation will avoid sensitisation, but not allergic reactions in "sensitised" individuals. To determine the point of departure to establish a STEL for respiratory irritation, ANSES retained the study of Vandenplass et al. (1999) as the key study. A LOAEC of 20 ppb was identified from this human experimental study of in which healthy volunteers were exposed to TDI (see Section 7.5.1.1). When applying an assessment factor of 3 for the conversion from LOAEC to NOAEC and an intra-species assessment factor of 5, they ended up with a 15-minute STEL value of 1.3 ppb (9.5 µg /m^3, corresponding to 4.5 µg /m^3 NCO).

As there was no reliable data from which an 8-hour OEL could be derived, a pragmatic 8-hour value was calculated by dividing the 15-minute STEL with a factor of 32 (32 times 15-minutes during an 8-hour work shift; aiming at minimising the risk of exceeding the STEL), resulting in a value of 0.04 ppb (0.28 µg /m^3, corresponding to 0.14 µg /m^3 NCO).

8.2 Exposure limit values

8.2.1 Occupational Exposure Limits (OELs)

It is considered that the most appropriate way to prevent asthma caused by diisocyanates would be to prevent respiratory sensitisation altogether, i.e. to prevent its induction. However, in the absence of a reliable marker for induction of respiratory sensitisation due to diisocyanates, it is not possible to identify a threshold or to derive a dose-response for the **induction** of respiratory sensitisation.

The next best approach is to derive an exposure limit to prevent elicitation of respiratory sensitisation, i.e. the occurrence of clinically manifest asthma. However, it is considered that the data available do not allow identification of a threshold average exposure concentration below which no cases of asthma would occur among those workers where the induction of respiratory sensitisation to diisocyanates has already taken place. It is noted furthermore that while Article 3 of Directive 98/24/EC sets the procedures to be followed and factors to be considered when establishing indicative or binding occupational exposure limit values at Community level, it does not define a level of residual excess risk to be considered in case a safe threshold cannot be identified.

It is considered that the available data obtained from animal studies cannot as such be used to derive OELs.

[18] Document for public consultation:
https://www.anses.fr/fr/system/files/REC_NEC_VLEP_TDI_pourconsult_paraphV3.pdf

Therefore, an OEL was not proposed but proposes to further develop the approach to derive an exposure response from the human data and then establish an OEL and a STEL, according to the principles of Directive 98/24/EC.

8.2.1.1 Dose-response (Exposure-response)

It is considered that it is appropriate to derive an exposure-response based on the concentration of the NCO group and to apply that to all diisocyanates. Also the recent recommendation for occupational exposure limits for diisocyanates by DECOS (2018) followed the group approach (NCO group). In the restriction Background Document (ECHA, 2018a) all diisocyanates were grouped together as "*the functional (di)isocyanate group is the important chemical group of these substances*". As presented in Table 5, several countries have already set their current OEL values for the group, based on the NCO concentrations.

It is noted that the exposure intensity resulting in a 1/100 extra risk differs between DECOS (0.10 µg NCO/m^3 based on Pronk data and 0.14 NCO/m^3 based on Collins data). As the model by DECOS is not a linear one and is only presented for extra risks of 1, 2, 3, and 5 %, it is difficult to compare the dose-responses further. However the (best fitted) quadratic rate function model of Daniels estimates an extra risk of 1/1000 per 1 µg NCO/m^3, while a 10 times lower exposure (0.1 µg NCO/m^3) was associated with a 10 times higher extra risk (1/100) with the DECOS model regardless if BHR_{20} or BHR_{20} + asthma symptoms was used as outcome measure. There are methodological differences and differences in exposure (HDI or TDI) between the two methods. The model of Daniels calculated the extra risk for a continuous exposure during a 45 year working lifetime, while it is not clear how the duration of exposure was taken into account in the in-house calculations of DECOS.

Overall, it is noted that none of the dose-responses addressed the effect of peak exposures or included dermal exposure. It is noted that data from other causative agents of OA indicate that peak and cumulative exposure are highly correlated and so are dermal and inhalation exposure (see section 7.5.3.1) indicating that it would be difficult to discern their individual effects. It is also noted that the calculation spreading the cumulative exposure over a period of 45 years seems relatively conservative given the risk calculations by onset of employment by Meredith et al. (2000), the similar descriptive data of Collins et al. (2017) that indicate that 1-2 years after the onset of exposure the risk is clearly levelling off, and similar observations for OA causative agents other than diisocyanates. Some further uncertainties are also described in Sections 8.1.2 and 8.1.3 for each of the three exposure-response approaches. Finally It is noted that the exposure-response by Collins et al (2017) is based on TDI exposure which accounts for 60% of current diisocyanate use in Europe while the dose-response from Pronk et al (2007, 2009) is predominantly based on HDI exposure which accounts for 4% of current use in Europe.

It was not considered possible to conclude that either of the two exposure-responses is clearly more reliable than the other. Therefore it was recommended to RAC to consider both exposure-response relationships in a weight of evidence approach to establish an overall exposure-response taking into account the uncertainties described above.

8.2.1.2 Effect levels in animal studies

Not many animal studies have involved inhalation exposure at several concentrations, based on which a correlation between doses and irritation/sensitisation responses could be identified. The interpretation of animal study results is also complicated by the fact that there are no internationally accepted *in vivo* test guidelines for respiratory sensitisation.

Respiratory irritation is traditionally followed by looking at RD_{50} values obtained by the Alarie method. RD_{50} values (4 h) of 0.199 ppm (1.4 mg/m^3, corresponding to 0.68 mg/m^3 NCO), 32 mg/m^3 (3.1 ppm, corresponding to 11 mg/m^3 NCO) and 1.2 mg/m^3,

corresponding to 0.60 mg/m^3 NCO; 3 h exposure) were reported for TDI, MDI, and HDI, respectively (Sangha and Alarie, 1979, Sangha et al., 1981, Weyel and Schaffer, 1985).

Non-specific airway responses, indicative of irritation or hypersensitivity, have been reported upon repeated exposure to diisocyanates at doses of 0.01-3 ppm (Marek et al., 1999, Gagnaire et al., 1996, Aoyama et al., 1994, Kouadio et al., 2014). In the study by Shiotsuka et al. (2006) three-week exposure of rats with HDI resulted in chronic inflammation at 0.12 and 1.03 mg/m^3 (0.017 and 0.15 ppm; corresponding to 0.06 and 0.51 mg/m^3 NCO) and degeneration of the olfactory epithelium (at 1.03 mg/m^3). Both types of effects persisted two weeks after exposure.

Subchronic exposure of mice with 0.02 ppm TDI followed by a challenge dose of 0.02 ppm (1 h) resulted in airway inflammation, eosinophilia, goblet cell metaplasia and airway hyperresponsiveness. Such effects were also seen upon acute exposure (0.5 ppm, 2 h) followed by 0.02 ppm challenge (Matheson et al., 2005). No firm conclusions on dose-responses or thresholds, or on potency differences between diisocyanates, can be drawn from these studies. Also, as the methods are not well-established, there is a lot of uncertainty on how the results could be used in relation to human exposure, considering interspecies differences.

Pauluhn and Poole (2011) presented a dose-dependent increase in respiratory rate and bronchioalveolar lavage parameters in rats exposed to MDI.

Pauluhn (2015, 2014) estimated 8-hour human workplace equivalent concentrations (HEC) corresponding to the elicitation results of rat studies performed with vapours of TDI, or HDI or polymeric MDI-aerosol using a protocol with dermal sensitisation and inhalation challenge. The points-of-departure for elicitation in rats were considered to be 1000 mg TDI/m^3 *x* min, 900 mg HDI/m^3 *x* min and 90 mg MDI/ m^3 *x* min. Based on this, the 8 h HEC values for TDI and HDI were estimated as 0.03 ppm (0.21 mg/ m^3, corresponding to 0.11 mg/m^3 NCO) and the MDI HEC value as 0.063 mg/m^3 (0.006 ppm; corresponding to 0.02 mg/ m^3 NCO) when applying adjustment factors for inhalation dosimetry (considering the specific conditions of the tests) but no adjustment factors for intraspecies susceptibility differences (Pauluhn 2015). For the calculation of an 8 h occupational exposure limit, Pauluhn (2015) recommended the use of an additional factor of 5 for intraspecies differences. When following that, the resulting limit values would be 0.006 ppm (0.04 mg/m^3, corresponding to 0.021 mg/m^3 NCO) for TDI and HDI, and 0.001 ppm for MDI (0.0126 mg/m^3 corresponding to 0.004 mg/m^3 NCO). It is noted that these values are in the same order of magnitude as OELs derived by e.g. ACGIH and DFG.

8.2.2 Short Term Exposure Limits (STELs)

The risk of asthma from diisocyanates is influenced by both cumulative and peak exposures. For the same reasons as above, it is not possible to identify a threshold or exposure-response for induction of respiratory sensitisation by peak exposures. Likewise it is not possible to identify a threshold peak exposure below which no cases of asthma would occur among those workers where the induction of respiratory sensitisation to diisocyanates has already taken place. Furthermore, there are no data available to derive an exposure-response describing the extra risk of asthma by peak exposure level.

Nevertheless, it is considered that setting a 15 minute STEL would further enhance prevention of diisocyanate induced asthma. It is noted that ACGIH (2016) has proposed for TDI a STEL value (0.005 ppm, 0.035 mg/m^3 of TDI) that is 5 times higher than their recommended value for an 8-hour TWA (0.001 ppm, 0.007 mg/m^3) for TDI. DFG (2008) recommended for MDI and polymeric MDI a 'momentary value' (0.1 mg/m^3) which is two times higher than the 8-hour MAK value (0.05 mg/m^3), as it was considered that exposure to concentrations above 0.2 mg/m^3 may be relevant for the induction of specific hyper-reactivity in the airways. AGS (2006) has for TDI set a peak (ceiling) value which is four times higher than the 8-hour limit value [0.02 ppm (0.14 mg/m^3) vs 0.005 ppm (0.035 mg/m^3)]. The AGS 15-minute short-term limit value is identical with their 8 h limit value

(0.005 ppm). ANSES (2019) recently proposed a 15 minute value of 0.0013 ppm (0.0091 mg/m^3) for TDI.

It is noted that the above relations between 15 minute and 8 hour limit values are based on generic national conventions rather than substance-specific considerations. Furthermore, no OEL value was propsoed, but recommends to establish a dose-response (exposure-response) and to use that to decide an appropriate OEL (8-hour TWA). Consequently, it is considered that the ratio between the 15 minute and 8 hour limits may be influenced by the level of the finally agreed 8 hour limit value.

It is considered that when using the exposure-responses described in Section 8.2.1 to establish an OEL (8-hour TWA), a 15 min STEL of not more than 5 times higher than that OEL value should be established**.**

As explained above, the epidemiological studies do not allow identifying a threshold or exposure-response of induction or elicitation of respiratory sensitisation by peak exposures. However, It is noted firstly the study of 17 human volunteers of Vandenplas et al. (1999) regarding inflammatory and air calibre changes triggered by a short-term (20 minute) exposure of 20 ppb of TDI (see Chapter 7.5.1) and secondly the animal data that indicate that the induction of respiratory sensitisation and respiratory irritation are threshold phenomena and the effect levels of respiratory irritation and induction of respiratory sensitisation are similar. Considering a LOAEC of 20 ppb from the study of Vandenplas et al. (1999) and applying assessment factors of 3 for LOAEC/NOAEC extrapolation and 5 for intraspecies variation among workers, as done by ANSES for TDI, would result in a short-term limit value equalling 0.00458 mg /m^3 NCO (see Chapter 8.1.5).

It is noted firstly that the proportion of study subject with non-specific bronchial hyperresponsiveness at baseline (12/17) was quite high indicating a relatively high sensitivity of the studied population towards respiratory airway effects. Consequently, an intraspecies assessment factor lower than the default 5 could also be considered. However, given the small size of the population (only 17 subjects) and in view of potential intraspecies differencies through mechanisms unrelated to bronchial hyperresponsiveness, it seems justifiable to apply also the default factor.

It is noted secondly that none of the subjects experienced significant respiratory symptoms in response to the exposures and the inflammatory and air calibre effects observed were minimal and might be reversible, while there was no follow-up for their persistency. An indication of reversibility was seen in the study by Pauluhn et al. (2000a). 6-hour exposure of rats to MDI aerosol resulted in a statistically significant increase in several markers indicative of injury of the bronchoalveolar region measured in BAL-fluid directly after exposure or one day later. In samples collected one week after exposure, the levels were similar as in unexposed animals.

Therefore, the adversity of those effects is not fully established and one might argue the 20 ppb to represent a NOAEC instead of LOAEC. However, it is also noted that the effects were observed after a single exposure while no effects of repeated short term exposures at this level were tested. Neither were tested effects of single exposures at any other levels of exposure than 20 ppb. It is noted also the longitudinal inception cohort study of Gui et al. (2014) among 49 TDI exposed newly hired workers in a newly built European polyurethane factory (see Chapter 7.5.1.1 subsection longitudinal studies). Although no OA cases could be confirmed due to lack of more definitive medical examinations, over the first year of employment 7 workers (14 %) had findings that could indicate TDI-related health effects (new asthma symptoms, TDI-specific Immunoglobin G, new airflow obstruction or decline in $FEV_1 \geq 15$ %). Exposure to TDI measured by continuous fixed-point air sampling was below the LOD (0.1 ppb) in 90 % of the samples. The maximum recorded was 10.0 ppb (72 µg TDI/m^3, 34 µg NCO/m^3). No air sampling period exceeded an 8-h TWA of 5 ppb and peak exposures recorded were below 20 ppb. These observational

data under modern real working life situations support considering the 20 ppb 20 minute exposure in the Vandenplas study a LOAEC and not a NOAEC.

It is noted finally that the exposure period in the Vandenplas study was 20 minutes. When deriving a 15 minute STEL value, the 0.00458 mg/m^3 NCO above should be multiplied by 20/15 (= 0.0061 mg /m^3).

In view of this volunteer study with a limited number of participants It is considered that the 15 minute STEL established after having agreed on the 8 hour limit value, should not be higher than 0.006 mg /m^3 NCO.

Also animal studies indicate the relevance of peak exposures. Pauluhn and Poole (2011) showed that a more vigorous response was seen when rats were exposed to a high concentration during 10 minutes, than when the same dose was administered during 6 hours.

Using a single animal study as the starting point for the derivation of a STEL is not considered relevant.

A ceiling value is not proposed as the available direct-monitoring devices are only for monomers of specific diisocyanates and not for monitoring air levels of several diisocyanates at a time.

8.2.3 Biological Limit Value (BLV)

It is difficult to find a correlation between air monitoring data for total NCO group and biomarkers. Most correlations between air and urine concentrations (diisocyanates vs related diamine) found in literature are for the specific diisocyanates compounds and not to the concentrations of diisocyanates as a group. Also for specific diisocyanates the data is fairly limited and it is difficult to compare correlations. Another limitation is related to variations in excretion kinetics of different diisocyanates. Thus, no biological limit value is proposed.

8.2.4 Biological Guidance Value (BGV)

The background levels of the general population are in most cases non detectable. It is proposed to establish a BGV at the level of the analytical limit of quantification for relevant diisocyanates metabolites (diamines) in urine.

8.3 Notations

As diisocyanates cause skin and respiratory sensitisation, and as a result, the notations 'skin sensitisation' and 'respiratory sensitisation' are proposed.

According to ECHA Guidance (Appendix to Chapter R.8, 2019), chemical agents identified as skin and/or respiratory sensitizers are assigned a "skin sensitisation" and/or "respiratory sensitisation" notation. Since all diisocyanates considered in this document are classified according to the criteria of the CLP Regulation (EC No 1272/2008) either as skin sensitisers, respiratory sensitisers or both (Annex 1, section 2), it is considered that both notations, namely "skin sensitisation" and "respiratory sensitisation" are warranted

An additional aspect is the contribution of dermal exposure in the induction of respiratory sensitisation. Such an immunological pathway from skin to the respiratory tract can be considered to indicate a systemic effect following dermal exposure. It is noted that the 'skin' notation, has been used when there was a possible significant uptake through the skin, typically where it could be assumed that dermal exposure may contribute to about

10 % or more of the body burden by inhalation exposure at the OEL[19]. It is noted that in the case of diisocyanates, the contribution of dermal route is actually not related to systemic uptake of diisocyanates as such via dermal exposure, but rather to systemic immunological effects following dermal contact. Thus the effects via dermal contact might already be covered by the 'skin sensitisation' notation instead 'skin' notation. However, the above-mentioned guidance also states that "the assessment whether a skin notation is required considers various types of information and is not necessarily quantitative" and that these considerations include also "health effects observed in workers following skin exposure". Therefore, it is considered that, in order to ensure prevention of systemic immunological effects from dermal contact of diisocyanates, also a 'skin' notation' is warranted. It is also noted that, in addition to notations for dermal and respiratory sensitisation, DFG has assigned a skin notation for MDI (DFG 2008) and ACGIH for TDI (ACGIH 2016).

8.4 Other considerations

Recommendations concerning establishment of an OEL and a STEL to limit exposure via inhalation are detailed above, as well as notations, acknowledging that a residual excess risk for bronchial asthma or occupational asthma may still exist. Therefore two further aspects are highlighted that are particularly relevant for prevention of asthma due to diisocyanates (see Chapter 7.5 for further details):

1. There is compelling evidence of the contribution of dermal exposure in the induction of respiratory sensitisation,
2. Asthma is a disease characterised by symptoms and airflow limitation that vary over time and by intensity. Respiratory sensitisation may manifest itself by symptoms that occur well before a clinical diagnosis of asthma can be made. There is evidence that the longer the symptomatic exposure before removal from exposure (to TDI), the more persistent the features of occupational asthma at follow-up.

It is noted firstly that the restriction proposal concerning diisocyanates aims at ensuring that adequate training of workers takes place in order to prevent exposure, not only via inhalation (including peaks) but also via the dermal route and thus to prevent diisocyanate induced health effects (ECHA 2017).

It is noted secondly that Articles 6.3 and 10 of the Chemicals Agents Directive (Council Directive 98/24/EC) stipulate the need for Member States to introduce arrangements for carrying out appropriate health surveillance if it is appropriate to the nature of the risk. These arrangements, including the requirements specified for health and exposure records and their availability, shall be introduced in accordance with national laws and/or practice. Article 10 further specifies that *health surveillance, the results of which shall be taken into account in applying preventive measures in the specific workplace, shall be appropriate where:*

- *the exposure of the worker to a hazardous chemical agent is such that an identifiable disease or adverse health effect may be related to the exposure, and*
- *there is a likelihood that the disease or effect may occur under the particular conditions of the worker's work, and*

[19] Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace. ECHA 2019. https://echa.europa.eu/documents/10162/23036412/ircsa_r8_appendix_oels_en.pdf/f1d45aca-193b-a7f5-55ce-032b3a13f9d8

- *the technique of investigation is of low risk to workers.*

Furthermore, there shall be valid techniques for detecting indications of the disease or effect.

It is noted that under the EU OSH legislation, substance-specific health/medical surveillance modalities are introduced e.g. for lead and its compounds (Annex II of Directive 96/24/EC) and asbestos (Annex I of Directive 2009/148/EC), some more generic modalities are also defined for health surveillance of carcinogens and mutagens (Annex II of Directive 2004/37/EC) and in the non-chemical domain e.g. for noise (Article 10 of Directive 2003/10/EC). It is considered that in the case of diisocyanates such specific health surveillance would seem appropriate. Taking into account the provisions of Article 10 of Directive 98/24/EC and the characteristics of diisocyanate asthma summarised in the above bullet 2, It is considered that this health surveillance, carried out in accordance with the principles and practices of occupational medicine, should aim to identify early signs and symptoms of respiratory sensitisation with a personal interview, enhance to report such symptoms and include any further examinations considered necessary by the doctor and/or authority responsible for health surveillance. In view of indications that diisocyanate-induced asthma can occur already within a year of start of exposure, yearly health surveillance would seem justified. It is noted that Appendix 8 of the Background document of the diisocyanate restriction proposal proposed that "Workers are offered to undergo a medical consultation at the start of job and offered after that yearly."

9. Groups at Extra Risk

Workers who have been sensitised to (di)isocyanates are at increased risk to develop respiratory symptoms, also at very low exposure concentrations. This is, however, already covered by the derived exposure-responses which are based on elicitation of asthma in already (di)isocyanate sensitised persons.

Workers with pre-existing asthma or other respiratory problems may have an increased risk to develop respiratory symptoms caused by diisocyanate-induced irritation.

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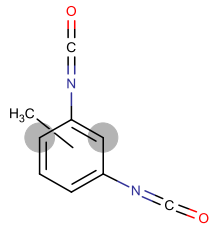
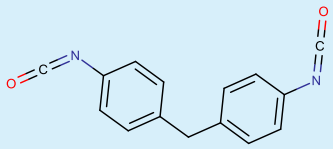
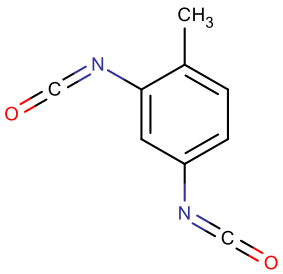
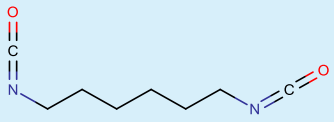
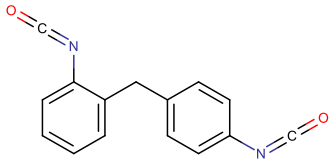
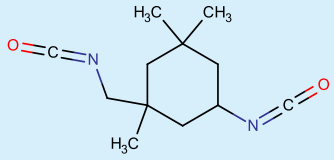
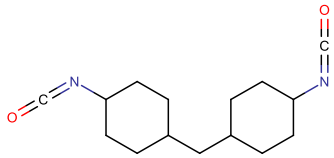
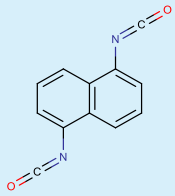
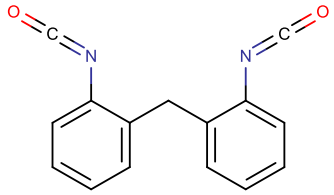
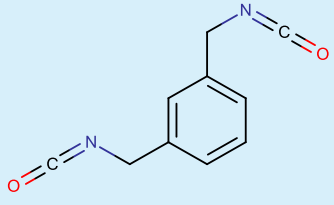
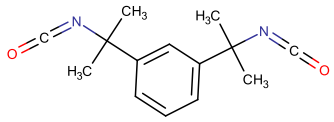
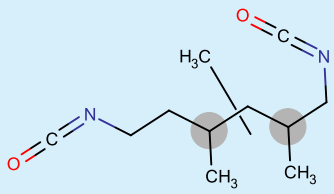
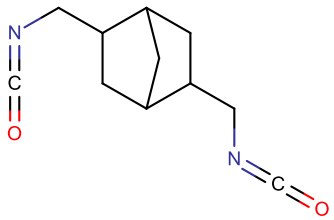
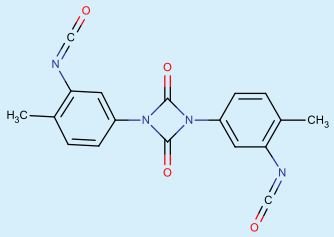
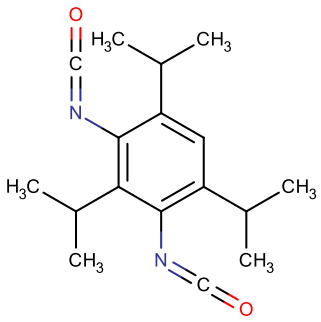
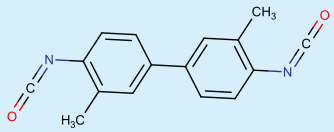
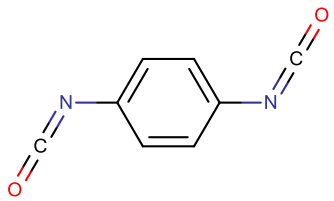
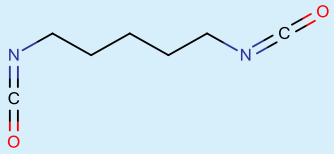
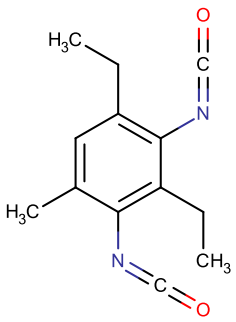
Appendix 1. Tabulated summaries for substance identification and physico-chemical properties of diisocyanates

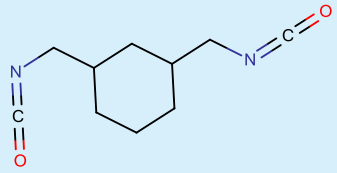
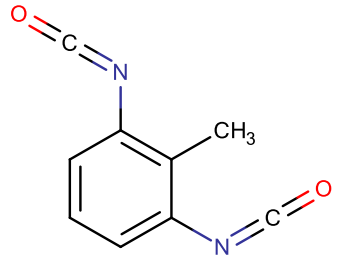
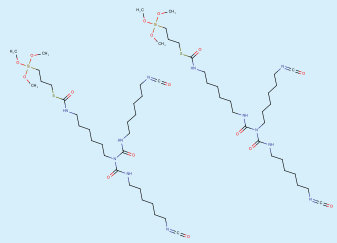
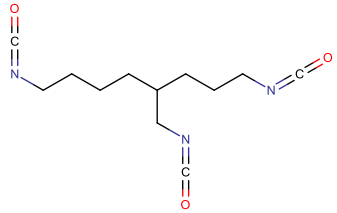
Table 33: Substance identification

Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	247-722-4	26471-62-5	m-tolylidene diisocyanate	TDI	174.159
	202-966-0	101-68-8	4,4'-methylenediphenyl diisocyanate	4,4'-MDI	250.257
	209-544-5	584-84-9	4-methyl-m-phenylene diisocyanate	2,4-TDI	174.159
	212-485-8	822-06-0	Hexamethylene diisocyanate	HDI	168.196
	227-534-9	5873-54-1	o-(p-isocyanatobenzyl)phenyl isocyanate	2,4'-MDI	250.257

Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	223-861-6	4098-71-9	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	IPDI	222.288
	225-863-2	5124-30-1	4,4'-methylenedicyclohexyl diisocyanate	hydrogenated 4,4'-MDI (H12-MDI)	262.353
	221-641-4	3173-72-6	1,5-naphthylene diisocyanate	1,5-NDI	210.192
	219-799-4	2536-05-2	2,2'-methylenediphenyl diisocyanate	2,2'-MDI	250.257
	222-852-4	3634-83-1	1,3-bis(isocyanatomethyl)benzene	m-XDI	188.186

Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	220-474-4	2778-42-9	1,3-bis(1-isocyanato-1-methylethyl)benzene	m-TMXDI	244.294
	915-277-1	32052-51-0	2,2,4(or 2,4,4)-Trimethylhexane-1,6-diisocyanate	TMDI	210.277
	411-280-2	74091-64-8	2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane	NBDI	206.245
	247-953-0	26747-90-0	2,4-dioxo-1,3-diazetidine-1,3-bis(methyl-m-phenylene) diisocyanate	2,4-TDI dimer	348.318

Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	218-485-4	2162-73-4	2,4,6-triisopropyl-m-phenylene diisocyanate		286.375
	202-112-7	91-97-4	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	TODI	264.284
	203-207-6	104-49-4	p-phenylene diisocyanate	PPDI	160.132
	807-040-5	4538-42-5	1,5-Diisocyanatopentane		154.169
	813-050-0	2162-70-1	1,3-diethyl-2,4-diisocyanato-5-methylbenzene		230.267

Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	609-567-4	38661-72-2	1,3-bis(isocyanatomethyl)cyclohexane	hydrogenated 1,3-XDI	194.234
	202-039-0	91-08-7	2-methyl-m-phenylene diisocyanate	2,6-TDI	174.159
	402-290-8	85702-90-5	A mixture of: S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate; S-(3-(trimethoxysilyl)propyl 17-isocyanato-9-(isocyanatohexyl-aminocarbonyl)-10-oxo-2,9,11-triazaheptadecanethioate		674.938
	429-140-4	79371-37-2	1,8-diisocyanato-4-isocyanatomethyloctane		251.286

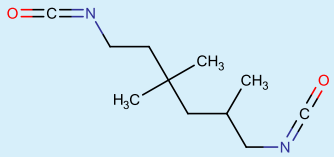
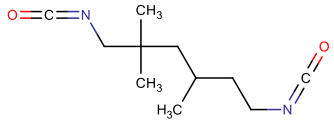
Structure	EC / list Number	CAS	Name	Abbrev.	Mol. weight [g/mol]
	239-714-4	15646-96-5	2,4,4-trimethylhexa-1,6-diyl diisocyanate		210.277
	241-001-8	16938-22-0	2,2,4-trimethylhexa-1,6-diyl diisocyanate		210.277

Table 34: phys.-chem. properties

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³
TDI	247-722-4	m-tolylidene diisocyanate	21 °C	251 °C	0.015 hPa (20 °C)[r]	7.12
4,4'-MDI	202-966-0	4,4'-methylenediphenyl diisocyanate	38 °C	314 °C	$1.2 \cdot 10^{-3}$ Pa (25 °C)	10.23
2,4-TDI	209-544-5	4-methyl-m-phenylene diisocyanate	21 °C	251 °C	2.8 Pa (25 °C)	7.12
HDI	212-485-8	Hexamethylene diisocyanate	-67 °C	255 °C	2.2 Pa (25 °C)	6.88
2,4'-MDI	227-534-9	o-(p-isocyanatobenzyl)phenyl isocyanate	34-38 °C[r]	decomp 241 °C[r]	$9.7 \cdot 10^{-4}$ Pa (25 °C)	10.23
IPDI	223-861-6	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	-60 °C	158-159 °C (15 Torr)	0.3 Pa (25 °C)	9.09

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³
hydrogenated 4,4'-MDI (H12-MDI)	225-863-2	4,4'-methylenedicyclohexyl diisocyanate	no crystalisation	167-168 °C (1.5 Torr)	$2.3 \cdot 10^{-3}$ Pa (25 °C)	10.73
1,5-NDI	221-641-4	1,5-naphthylene diisocyanate	130-132 °C	220-221 °C (40 Torr)	0.06 Pa (25 °C)	8.59
2,2'-MDI	219-799-4	2,2'-methylenediphenyl diisocyanate	43 °C[r]	270 °C[r]	$7.8 \cdot 10^{-4}$ Pa (25 °C)	10.23
m-XDI	222-852-4	1,3-bis(isocyanatomethyl)benzene	-7 °C[r]	126 °C (1 Torr)	0.2 Pa (25 °C)	7.69
m-TMXDI	220-474-4	1,3-bis(1-isocyanato-1-methylethyl)benzene	4 °C[r]	249 °C[r] 106 °C	0.08 Pa (25 °C)	9.99
TMDI	915-277-1	2,2,4(or 2,4,4)-Trimethylhexane-1,6-diisocyanate	-80 °C[r]	291 °C[r]	0.005 hPa (25 °C)[r]	8.60
NBDI	411-280-2	2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane	-74 °C[r]	decomp 208-220 °C[r]		8.43
2,4-TDI dimer	247-953-0	2,4-dioxo-1,3-diazetidine-1,3-bis(methyl-m-phenylene) diisocyanate	156 °C[r]	decomp 160-310 °C[r]		14.24
	218-485-4	2,4,6-triisopropyl-m-phenylene diisocyanate	115 °C	305-306 °C[r]	$1.7 \cdot 10^{-3}$ Pa (25 °C)	11.71
TODI	202-112-7	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	72 °C[r] 69.5-70.5 °C	decomp 371-373 °C[r]	$5.3 \cdot 10^{-4}$ Pa (25 °C)	10.81

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³
PPDI	203-207-6	p-phenylene diisocyanate	93-94 °C (sublm)	124-125 °C (10 Torr)	6.4 Pa (25 °C)	6.55
	807-040-5	1,5-Diisocyanatopentane		116 °C (11 Torr)	8.8 Pa (25 °C)	6.30
	813-050-0	1,3-diethyl-2,4-diisocyanato-5-methylbenzene	18 °C[r]	272-289 °C[r]	0.01 Pa (25 °C)	9.41
hydrogenated 1,3-XDI	609-567-4	1,3-bis(isocyanatomethyl)cyclohexane	0 °C[r]	255 °C[r]	0.2 Pa (25 °C)	7.94
2,6-TDI	202-039-0	2-methyl-m-phenylene diisocyanate	18.3 °C	129 °C (18 Torr)	3.2 Pa (25 °C)	7.12
	402-290-8	A mixture of: S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate; S-(3-(trimethoxysilyl)propyl 17-isocyanato-9-(isocyanatohexyl-aminocarbonyl)-10-oxo-2,9,11-triazaheptadecanethioate		>140 °C[r]		27.60
	429-140-4	1,8-diisocyanato-4-isocyanatomethyloctane	< -50 °C[r]	129-132 °C (0.1 Torr)	$1.9 \cdot 10^{-3}$ Pa (25 °C)	10.27
	239-714-4	2,4,4-trimethylhexa-1,6-diyl diisocyanate			0.4 Pa (25 °C)	8.60

ABBR	RML_EC	RML_NAME	Melting Point	Boiling Point	Vapor Pressure	1 ppm in mg/m³
	241-001-8	2,2,4-trimethylhexa-1,6-diyl diisocyanate			0.4 Pa (25 °C)	8.60

Values retrieved from SciFinder (https://scifinder.cas.org) August 2019 and completed with data submitted in registrations (marked with [r]).

For the calculation of the corresponding concentration [mass/volume air] from concentration in ppm, the conversion factor is calculated as:

$$1\ ppm\ in\ \frac{mg}{m3} = \frac{1}{10^6}\left[molar\ weight\ in\ \frac{g}{mol}\right] \cdot 1000 \cdot \frac{[pressure\ = 101300\ Pa]}{[temperature\ = 298\ K] \cdot \left[gas\ constant = 8.314\ \frac{\mathrm{m^3 \cdot Pa}}{\mathrm{K \cdot mol}}\right]}$$

For the calculation of the corresponding NCO concentration [isocyanate mass/volume air] from diisocyanate concentrations in mg/m³, the following formula is used:

$$conc_{NCO}\left[\frac{mg}{m^3}\right] = conc_{diisocyanate}\left[\frac{mg}{m^3}\right] \cdot \frac{(number\ of\ NCO\ groups)(molecular\ weight\ of\ isocyanate = 42)\left[\frac{g}{mol}\right]}{(total\ diisocyanate\ molecular\ weight)\left[\frac{g}{mol}\right]}$$

Appendix 2. REACH REGISTRATIONS

Table 35: REACH registrations

Abbrev.	EC Number	NAME	Intermediate registration t/a (count of registrations)	full registration t/a (count of registrations)
TDI	247-722-4	m-tolylidene diisocyanate		>100 000 (32 reg)
4,4'-MDI	202-966-0	4,4'-methylenediphenyl diisocyanate		>100 000 (55 reg)
2,4-TDI	209-544-5	4-methyl-m-phenylene diisocyanate	(<5 reg)	>100 000 (9 reg)
HDI	212-485-8	hexamethylene diisocyanate		10 000-100 000 (19 reg)
2,4'-MDI	227-534-9	o-(p-isocyanatobenzyl)phenyl isocyanate		10 000-100 000 (5 reg)
IPDI	223-861-6	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate		10 000-100 000 (20 reg)
hydrogenated 4,4'-MDI	225-863-2	4,4'-methylenedicyclohexyl diisocyanate		10 000-100 000 (20 reg)
1,5-NDI	221-641-4	1,5-naphthylene diisocyanate		1000-10 000 (<5 reg)
2,2'-MDI	219-799-4	2,2'-methylenediphenyl diisocyanate		1000-10 000 (<5 reg)
m-XDI	222-852-4	1,3-bis(isocyanatomethyl)benzene		1000-10 000 (<5 reg)
m-TMXDI	220-474-4	1,3-bis(1-isocyanato-1-methylethyl)benzene		1000-10 000 (<5 reg)
TMDI	915-277-1	Reaction mass of 2,2,4-trimethylhexa-1,6-diyl diisocyanate and 2,4,4-trimethylhexa-1,6-diyl diisocyanate		10-1000 (<5 reg)
NBDI	411-280-2	2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane		10-1000 (<5 reg)
2,4-TDI dimer	247-953-0	2,4-dioxo-1,3-diazetidine-1,3-bis(methyl-m-phenylene) diisocyanate		10-1000 (<5 reg)
	218-485-4	2,4,6-triisopropyl-m-phenylene diisocyanate		10-1000 (<5 reg)
TODI	202-112-7	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate		10-1000 (<5 reg)

Abbrev.	EC Number	NAME	Intermediate registration	full registration
PPDI	203-207-6	p-phenylene diisocyanate		10-1000 (<5 reg)
	807-040-5	1,5-Diisocyanatopentane		10-1000 (<5 reg)
	813-050-0	1,3-diethyl-2,4-diisocyanato-5-methylbenzene		<10 (<5 reg)
hydrogenated 1,3-XDI	609-567-4	1,3-bis(isocyanatomethyl)cyclohexane		<10 (<5 reg)
2,6-TDI	202-039-0	2-methyl-m-phenylene diisocyanate		<10 (<5 reg)
	402-290-8	A mixture of: S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate; S-(3-(trimethoxysilyl)propyl 17-isocyanato-9-(isocyanatohexyl-aminocarbonyl)-10-oxo-2,9,11-triazaheptadecanethioate		<10 (<5 reg)
	429-140-4	1,8-diisocyanato-4-isocyanatomethyloctane		

Appendix 3. Overview of available epidemiological data on respiratory sensitisation/asthma

This Appendix is based on the work reported by ECHA (ECHA, 2018a). However, some details from the original studies have been added that are relevant for dose-response considerations, like quantification and timing of exposure, consideration of peak, cumulative or average inhalation exposure as well as dermal exposure. Also some studies published only more recently have been added.

Abbreviations

FEF_{25-75}: Forced expiratory flow between 25 and 75 % of FVC

FEV_1: Forced expiratory volume in one second

FEV_1 %: FEV_1/FVC x 100

FVC: Forced vital capacity

HDI: Hexamethylene diisocyanate

IPD: Isophorone diamine

IPDI: Isophorone diisocyanate

JEM: Job exposure matrix

LOD: Limit of detection

MDI: Methylenediphenyl diisocyanate

MMF: Maximum mid-expiratory flow

n. s.: not significant

OA: Occupational asthma

OR: Odds Ratio

PEFR: Peak expiratory flow rate

PR: Prevalence ratio

PU: Polyurethane

RR: Relative Risk

TDA: Toluene diamine

TDI: Toluene diisocyanate

TWA: Time-weighted average

Epidemiological data on the exposure-response relationship of diisocyanates and respiratory disease

Table 36: Reviews

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(DFG, 1997, DFG, 2008)	Derivation of a "MAK-value" → adoption as national OEL	MDI		The OEL of 5 ppb for MDI and "polymeric MDI" was derived from occupational epidemiological studies with workers in plastic foam production, insulation foam production and MDI production. Available studies have a lot of limitations concerning exposure measurement, existing coexposures, disregard of both allergic aspects and preexposure to higher concentrations, lack of more objective outcome measurements (spirometry vs. whole body plethysmography). No significant changes in lung spirometry found when exposure was generally below 20 ppb. Whereas at this concentration there were sometimes respiratory symptoms (however not clearly attributable to isocyanates), such symptoms were not significantly more frequent at concentrations less than or equal to 10 ppb. At even lower concentrations of 0.05 mg/m^3 or less, the workers, sometimes exposed for many years, were without symptoms and had better lung function than the control groups. Respiratory sensitisation: Long-term exposure to MDI concentration of 0.05 mg/m^3 or less is thought to neither cause bronchial hypersensitivity and its associated symptoms nor the formation of specific antibodies. For the induction of specific	

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				airway hypersensitivity (with or without immunological parameters) an exposure to MDI concentrations above 0.2 mg/m^3 or intensive skin contact is of great importance. To protect from increased peak exposure, 8-h TWA and short-term exposure limit value for 15 minutes have been put on the same level (0.05 mg/m^3). Ceiling exposure limit has been set to 0.1 mg/m^3.	
	Derivation of a "MAK-value" → adoption as national OEL	TDI		The OEL of 5 ppb (0.035 mg/m^3) for TDI is based on gradual deterioration in lung function. This effect was evaluated in several occupational epidemiological studies with workers from polyurethane foam factories in Japan, North America and Europe. From these data it was deduced *"that with observance of an 8-hour-average value at the workplace of 0.005 ml/m^3 and limitation of exposure peaks to 0.02 ml/m^3 no significant deterioration in lung function is to be expected."* Concerning respiratory sensitisation it was concluded from three epidemiological studies, that under a TDI concentration below 0.01 to 0.02 ml/m^3, *"generally no new cases of TDI asthma are observed ".*	
	Incidence of OA due to TDI was estimated from nine longitudinal studies, based on 2751 workers.	TDI Longitudinal studies: Manufacture/ research and development/	Sparse and mostly qualitative information	**TDI asthma:** Reviewed studies are heterogeneous (population, case definition/validity of diagnosis of TDI asthma, industry, exposure), of limited validity and difficult to interpret.	Incidence data are not interpreted with regard to the exposure level. Reviewed studies overlap with other reviews (Ott, 2002b, Ott et al., 2003a).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Prevalence of OA due to TDI was estimated from ten cross-sectional studies, based on 788 workers. The 38-year period from 1954 to 1992 was covered.	flexible foam production Cross-sectional studies: Manufacture/foam production/ sewing laminated nylon/ laquer varnishing/ foam coating of steel/ adhesive tape production/varnish application/paint application		Annual incidence of TDI asthma shows downward trend over the past half century and was reported to be around 5 % in earlier times and between 0 and 0.7 % since 1980. The downward trend is attributed to the downward trend of TDI exposure. The prevalence of TDI asthma has been reported to be > 10 % before 1985 and between 0 and 10 % in the more recent years at workplaces with mean TDI exposures < 15 ppb.	
(Ott 2002)	Review of studies on OA, lung function decrement and TDI exposure, with a focus on assessing exposure-response relationships TDI-induced asthma: Nine cross-sectional studies, eight longitudinal studies Lung function: Three cross-sectional studies, eleven longitudinal studies	TDI Manufacture and TDI-using industries (PU foam production and others)	Earlier years (1950s and 1960s): 60 ppb as mean area concentration or major portion of samples > 20 ppb, multiple spills reported Decline in exposure over the years More recent years (1980s and 1990s): < 5 ppb TWA, short-term concentrations > 20 ppb	**TDI asthma:** Case definitions varied widely across studies. Prevalence across nine cross-sectional studies in TDI using industry ranged from 0 to 41 %. Annual incidence rates were 5-6 % in earlier times both in TDI manufacture and in TDI using industries. Rates declined to < 1 % with reduction of TDI concentrations to < 5 ppb (8h personal samples) (see Table C-2 below). Studies with more extensive exposure measurements indicate that majority of asthma cases may arise from TDI short-term concentrations > 20 ppb. Decline in **lung function** (FEV_1):	Reviewed studies overlap with other reviews (Diller, 2002, Ott et al., 2003a) .

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Decrements in FEV_1 were seen in earlier studies and in follow-up studies of workers who continued to work after their diagnosis of OA. No consistent evidence of accelerated loss in FEV_1 was found in more recent studies with exposure up to 5 ppb (8h TWA) and even with short-term TDI concentrations > 20 ppb.	
(Ott et al., 2003a)	Review of clinical/epidemiological literature on respiratory health effects of TDI and assessment of exposure-response-relationships in humans TDI-induced asthma: Nine cross-sectional studies, eight longitudinal studies Lung function: Three cross-sectional studies, eleven longitudinal studies	TDI Manufacture and TDI-using industries (PU foam production and others)	Different methods: Marcali method used in 1950s to 1970s Test-paper method developed 1968 and used in epidemiological studies published since 1980, equally sensitive to 2,4- and 2,6-isomers, not affected by presence of toluene diamine HPLC analytical methods since mid-1970s, lower LOD, separate determination of 2,4- and 2,6-isomers OSHA method 42 Manufacturing:	Hazards from single exposures are described, but will not be reported here. Hazards from repeated and long-term exposures: **Asthma**: Annual induction rates: About 5 % in earlier years (1950s-1970s) Between 0.7 to 1.1 % in four newer studies (1970s to 1990s). Here TWA concentrations mostly < 5 ppb, but short-term TDI concentrations > 20 ppb and occasionally > 80 ppb. Findings indicate a downward trend in incidence rate over time concurrent with lower TDI exposures. OA cases might be attributable to overexposure incidents (> 20 ppb). **Hypersensitivity pneumonitis**: Incidence due to TDI exposure seems to be very low.	Reviewed studies overlap with other reviews (Diller, 2002, Ott, 2002b). Marcali method (Marcali, 1957) may have underestimated exposure to 2,6-TDI by as much as 47 %, positive interference if aromatic amines are present

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			Early years: Concentrations up to 60 ppb, frequently > 20 ppb, peak concen-trations up to 200 ppb during leaks, spills. After 1980: TWA < 5 ppb, short-term exposure > 20 ppb (less frequently). Foam production: Early years: similar to manufacturing. Since 1980: < 5 ppb (TWA), short-term exposure > 40 ppb, (less frequently)	**Lung function** decrement: Mostly no evidence for accelerated decline from the larger, more recent longitudinal studies (8h TWA mostly ≤ 5 ppb). However, decline in lung function in workers with symptoms or TDI-asthma and continued exposure.	
(BelgianCA, 2005)	Human health assessment sections "respiratory sensitisation" and "repeated dose toxicity" cover eleven and nine studies in humans, respectively	MDI		*"MDI is a potential respiratory sensitiser in animals and humans...At the present time it is not possible to define reliable exposure-response relationships with regard to the risk of sensitisation for MDI."* *"In humans, some, but not all, epidemiological studies have found long-term decreases in ventilatory function and respiratory symptoms, in workers exposed to MDI even below current occupational standards."* "… chronic exposure to even low levels (but mostly undetermined or below 0.05 mg/m³) of MDI involves a respiratory risk, "	Last literature search 2003

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Dodge and Silva, 2016a)	Methylene Diphenyl Diisocyanate (Monomer and Polymeric Forms) Reference Exposure Levels Technical Support Document for the Derivation of Noncancer Reference Exposure Levels	MDI (monomer and polymeric forms)		REL derived from animal data Acute REL = 12 µg/m^3 (1.2 ppb) 8-h REL = 0.16 µg/m^3 (0.015 ppb) Chronic REL = 0.08 µg/m^3 (0.008 ppb)	Covers relevant published literature for MDI through spring 2015
(Dodge and Silva, 2016b)	Toluene Diisocyanate Reference Exposure Levels Technical Support Document for the Derivation of Noncancer Reference Exposure Levels	TDI (mixed isomers)		Acute REL (infrequent 1-h exposures) = 2 µg/m^3 (0.3 ppb) LOAEL = 71 µg/m^3 (10 ppb) (≥ 100 % increase in Raw in asthmatics;) LOAEL uncertainty factor = 10 (for severe effect) Intraspecies toxicodynamic uncertainty factor = $\sqrt{\mathbf{10}}$ (asthmatic children) *"reasonably protective against sensitisation under a scenario of infrequent exposures"* 8-h REL (repeated daily 8h-exposures up to 7 days/week) = 0.015 µg/m^3 (0.002 ppb) LOAEL = 13.5 µg/m^3 (1.9 ppb) (accelerated decline in FEV_1; NOAEL = 0.9 ppb (6.4 µg/m^3)	*"The RELs are intended to reasonably protect the general population from these health effects resulting from exposure to both 2,4- and 2,6-TDI, but may not protect all individuals previously sensitized to TDI."* Covers relevant published literature for TDI through spring 2015

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				time adjustment = 5/7 subchronic uncertainty factor = $\sqrt{10}$ intraspecies toxicokinetic uncertainty factor = 10 intraspecies toxicodynamic uncertainty factor = 10 Chronic REL (continuous exposure over a lifetime) = 0.008 µg/m^3 (0.001 ppb) LOAEL and NOAEL see 8h REL time adjustment = 10/20 * 5/7 subchronic uncertainty factor = $\sqrt{10}$ intraspecies toxicokinetic uncertainty factor = 10 intraspecies toxicodynamic uncertainty factor = 10	
(Daniels, 2018)	Review of data suitable for dose-response modelling of TDI-related OA and estimation of $BMDL_{01}$ value and an OEL linked to a 1/1000 lifetime extra risk	TDI		Studies judged suitable for dose-response analyses were those reporting data sufficient to estimate three key variables for dose-response modeling: i) the number of potential OA incidence cases; ii) the average TDI airborne exposure level over the observation period; and iii) the number of person-years at risk. Data sources were limited to study populations exposed to average TDI concentrations below 20 ppb. Data on eight TDI-exposed populations were suitable for analysis. There were 118 OA cases in a population contributing 13	The role of peak exposures was not assessed. Moreover the author acknowledged that "Data on the appropriate exposure index for dose-response modeling are uncertain. It remains unclear whether TDI-induced asthma is a consequence of low cumulative exposure, exposure intensity, or

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				590 person-years. The $BMDL_{01}$-based OEL was 0.4 ppb. The OEL based on low-dose extrapolation to working lifetime extra risk of 1/1000 was 0.3 ppb.	some combination that also accounts for time ordering of intermittent exposure." And "For this study, it is assumed that the risk of TDI sensitization is related to average exposure, which may also be a correlate of peak exposures." The extra risk was calculated per 1000 workers who are continuously exposed to TDI over a 45-year working lifetime.
(DECOS, 2018)	Review of data and proposal of limit value corresponding to an extra risk of 1 % unit increase in asthma prevalence	Di- and triisocyanates		In-house statistical analyses of original data of Pronk et al. (2009). Based on estimated 1% unit increase in prevalence of BHR_{20}, a limit value of 0.10 µg/m^3 as NCO was proposed	For the purpose of setting an exposure limit of sensitisers The Dutch Ministry of Social Affairs and Employment has set a risk level of 1% extra risk of sensitisation due to occupational exposure. This refers to an extra risk of 1% unit, e.g. from a general population prevalence of 2 per 100 to a prevalence of 3 per 100 among those occupationally exposed. Consequently the DECOS risk assessment

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
					was focused on the dose-response in the range of 1-5% of extra risk.

Table 37: Data taken from Ott (2002)

Study	Time period	Annual incidence of TDI-induced occupational asthma [%]	TDI concentration [ppb]	Exposure sampling
TDI production units				
(Adams, 1975)	1961 - 1970	5.6	1962 - 1964: 58 % - 72 % of samples > 20 1965 - 1966: 4 % - 21 % of samples > 20 1967 - 1970: 1 % - 2 % of samples > 20	Area samples
(Porter et al., 1975)	1956 - 1959	1.6	1956 - 1957: 60 (mean area conc.)	Area samples
	1960 - 1969	0.8	1960 - 1969: steady decline in area conc.	
	1970 - 1974	0.3	1974: < 4 (mean area conc.)	
(Weill H, 1981)	1973 - 1978	1.0	1.6 - 6.8 (TWA; range by job) (STC > 20 5 % - 11 % of time in moderate to high exposure jobs)	Area samples 1973-75 Personal samples 1975-78
(Ott et al., 2000)	1967 - 1979	1.8	3.4 - 10.1 (TWA; range by job)	Area samples 1967-75 Personal samples 1976-96
	1980 - 1996	0.7	0.3 - 2.7 (TWA; range by job) (STC > 20 0.5 - 0.9 times/shift in moderate to high-exposure jobs)	
PU foam production facilities				
(Woodbury, 1956)	1954 - 1955	5	Multiple TDI spill episodes described in 18-month period	No sampling data
(Williamson, 1964)	1962 - 1963	> 2.7	Samples mostly < 20 (up to 200 detected during spills)	Area samples
(Bugler et al., 1991)	1981 - 1986	0.8	0.9 - 2.6 (TWA; range by job) 22 % of 8-hr samples with short-term conc. > 20 and 10 % > 40	Personal samples
(Jones et al., 1992)	1982 - 1986	0.7	1.4 - 4.5 (TWA; range by job) (STC > 20 3 % time in production and 0.1 % of time in finishing jobs)	Personal samples

STC: short-term concentration (9-12 minutes)

TWA: time-weighted average

Table 38: Longitudinal studies with quantitative exposure-response estimates

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Collins et al., 2017)	Prospective cohort study (5 years) 3 US plants 197 workers followed from June 2007 to June 2012. Mean job tenure at enrollment 11.8 years. New asthma cases were identified from the medical monitoring program by application of standardised annual medical assessment, including spirometry and questionnaires on symptoms and exposure. Workers could also report symptoms consistent with asthma at any time. If symptoms or spirometry indicated possible asthma, further medical	Manufacture TDI	TDI air concentrations and questionnaires were used to estimate exposure for different exposure groups. Air samples representing shift length duration TWA exposures and exposures during the defined short-term high potential exposure tasks were collected. Cumulative TWA exposure estimates for individuals were developed based on the log means for the TWA exposure clusters and the length of exposure. The range for the estimated cumulative TWA exposure was 0.04 to 21.6 ppb-years unadjusted for respirator use. Peak exposure values were not directly used but were assigned a value corresponding to the highest 95th percentile TWA of all the plant specific TWAs that applied to that worker's task history.	Seven cases were identified as consistent with TDI-induced asthma (0.009 per person-years). Two more cases were considered consistent with asthma but indeterminate regarding work-relatedness (total asthma incidence rate of 0.012 per person-years). Increased risk of cases consistent with TDI asthma was observed for cumulative exposure (OR = 2.08, CI 1.07-4.05, per unit increase in log ppb-years) and peak TDI exposures (OR = 1.18, 95% CI 1.06-1.32, per unit increase in parts per billion). When comparing probability of being an asthma case by exposure it was reported that by cumulative exposure the probability increased by 153% from 5 to 20 ppb-years while by estimated peak exposure it increased 962% from 5 to 20 ppm.	Indication that also peak exposures may play a role while the study did not try discerning the effect of cumulative and peak exposure. The cumulative exposure captured the exposure prior to 2007 only for those 25% of workers who specifically reported the start date of exposure. For the rest exposure was estimated only as from start of study or start of hire which ever occurred latest. I.e. exposure during the average 11.8 years job tenure prior to start of the study was mostly not taken into account. Healthy worker effect possible

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	evaluation was performed.		Overall the arithmetic mean for all TWA exposures was 0.65 ppb, and the TWA exposures ranged from an estimated 0.01 ppb to a measured 92 ppb. The maximum peak exposures observed in the 3 plants were 19, 200 and 1726 ppb. In 60% of measurements the value was below LOQ (about 0.1 ppb).		

Table 39: Longitudinal studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Adams, 1975)	Prospective cohort study (9 years) 2 plants 565 have been employed for some period between 1961 to 1972 A) Comparison of respiratory symptoms in TDI plant workers (n = 76) with control	TDI Manufacture	Area samples taken at points in the plant where free TDI might be expected (ca. 250 measurements a week; Marcali method, (Marcali, 1957)) Samples > 20 ppb: 1962-64: 58 – 72 % 1965-66: 4 – 21 % 1967-70: 1 - 2 %	A) **Respiratory symptoms** (questionnaire): No significant difference in symptoms between men working in TDI plant and controls with the exception of higher frequency of wheezing in controls. B) **Lung function**: Duration of exposure had no effect on FEV_1 or FVC in the regression analysis. C) **Respiratory symptoms** (questionnaire): Prevalence of symptoms in TDI-sensitised men significantly higher than in controls → persistence of symptoms	Reviewed in Ott (2002b) Method of analysis did not calculate individual decline in lung function Regression analysis included duration of exposure, but no exposure level Area measurements Lung function measurements in the afternoon

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	workers (n = 76) in another plant B) Lung function in healthy workers (n = 180) C) Long-term effects in men who were removed due to symptoms and had no exposure to TDI since two to 11 years (n = 46) compared to age-matched control group (n = 46) D) Lung function in men who were removed due to symptoms and had no exposure to TDI since two to 11 years (n = 61)			D) **Lung function**: FEV_1 and FVC smaller than predicted by equation obtained from a control group: FEV_1 -267 mL, FVC -269 mL	Only healthy workers included Smoking not included in regression analysis
(Wegman et al., 1977)	Follow-up of 1972: n = 112 1974: n = 63 (available for re-survey) n = 57 with personal exposure levels	TDI PU cushion manufacture	118 area samples + 14 personal samples taken during study period to characterise 20 work stations Marcali method (Marcali, 1957) Each individual was classed according to his or her usual work station	**Lung function** (because of acute effect seen on Monday: Monday morning following three-day weekend): Dose-response relationship for two-year change in FEV_1 (-12 mL/-85 mL/ -205 mL from low to high exposure groups). Only those in lowest exposure group showed normal declines in FEV_1.	High attrition rate Followed up: Possible confounding variables explored: age, months employed, smoking habits, variables related to lung size. Authors report that none of those was able to explain the differences.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			Three exposure groups (ppm): ≤ 0.0015 (n = 20) 0.0020 – 0.0030 (n = 17) ≥ 0.0035 (n = 20)	Those in highest group had three- to fourfold higher FEV_1 declines than expected (103 mL/year). Significant association between acute and chronic decrement in FEV_1. **Respiratory symptoms** (questionnaire): Prevalence of cough and phlegm increased with increase in exposure. Wheezing and dyspnea not associated with exposure.	
(Butcher et al., 1977)	Prospective cohort, 2.5 years Visits: April 1973 (before TDI production), November 1973 (after production had started), every 6 months thereafter Initially n = 166 Study in TDI-sensitive persons (specific and unspecific challenge)	TDI Manufacture	Area sampling (1973): frequent excursions of 8h-TWA value of 5 ppb; many above 20 ppb Personal monitoring (1975) Frequent and large discrepancies between simultaneously measured area and personal exposure levels Four groups: 1) Mainly in TDI area: n = 77 2) Intermittently in TDI area: n = 36 3) Comparison group: n = 53 4) (added later) workers transferred from control group to exposure group after production had begun	**Lung function** changes (n = 102): Mean values of FVC and FEV_1 increased in all groups. Other lung function parameters decreased slightly (n. s. different from zero or predicted). Paradoxical differences for lung volumes and diffusion capacity (greater declines in the groups with higher exposure). No exposure-related excess decline in lung function determined. **Respiratory symptoms** (questionnaire administered by interviewers): No significant increase in prevalence of bronchitis, atopic disorders, upper respiratory symptoms from April 1973 to October 1975. Significant proportion of exposed workers (26 of 89) reported onset of	Attrition rate = 7.2 % Two workers had left the study by October 1975 after developing reactivity to TDI. No quantitative exposure estimation for the four exposure categories Smoking not considered in analysis of change in lung function

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				lower respiratory symptoms after beginning work in TDI areas (due to symptom development in non-smokers). **Inhalation challenge** with TDI: 9 out of 13 workers had an adverse bronchial response (immediate type, late type or dual type). Some reacted at 5 ppb, some to a higher concentration only.	
(Pham et al., 1987)	5 years follow up 1976: n = 318 workers (104 women) 1981: n = 156 (45 women) Two factories producing PU foam Follow up of Pham et al. 1978	Mainly MDI Production of PU foam	Isocyanate concentration: 1976: < 20 ppb 1981: ≤ 5 ppb 1976: Group I (n = 83): unexposed Group II (n = 117): indirectly exposed Group III (n = 118) directly exposed 1981: Only results for men reported for the longitudinal analysis. Group A (n =45): unexposed at both studies Group B (n = 24): undirectly exposed at both studies Group C (n = 30): directly exposed at both studies Group D (n = 15): exposed in 1976, but removed in 1981	**Lung function** (flow volume curve, single breath CO diffusion test (D_{LCO})): Ventilatory function and lung transfer factors significantly impaired in male exposed workers compared to group I. Only in the subgroup of workers exposed for more than 5 years. Decline of ventilatory function variables not significantly different between the groups. Significant larger loss of D_{LCO} in subjects with persisting exposure (group C) compared to reference group. Results returned to normal for the subjects no longer exposed (group D). **Respiratory symptoms** (questionnaire): Increased prevalence of asthma in group II men and group III women and of chronic bronchitis in both sexes.	High loss to follow up (half of the initial cohort still active after 5 years) Rare information on exposure In females, the proportion of smokers was the same in groups I – II. In males, there were slightly (n.s.) more smokers in groups II and III. Coexposure to other isocyanates? ("mainly MDI")

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Number of workers with asthma or chronic bronchitis increased over the five years, but this was not limited to the exposed group.	
(Wegman et al., 1982)	Four-year follow up (Wegman et al. 1974 and 1977) 1972: n = 111 1974: n = 63 1976: n = 48 (all those who were still at work in 1976) → n = 37 with exposure history and acceptable spirograms On all three occasions workers were examined before work and as many as possible six to ten hours later.	TDI Automobile seat cushion manufacture	Environmental sampling at selected work sites on the same day as lung function was measured. Additional sampling during the first two years of the study. Personal sampling in production area, area samples in warehouse and nonproduction sites. Marcali method Occupational histories taken from personnel records Cumulative exposure of each worker calculated and from this the usual exposure level. Three exposure groups: Low (< 0.0020 ppm) Medium (0.002 – 0.0034 ppm) High (> 0.0033 ppm)	**Lung function**: Acute change in FEV_1 (during work shift) observed at the beginning of the study was weakly associated with long-term change in FEV_1. Chronic change in FEV_1 (over four years): Mean exposure to TDI was the best predictor of four-year change in FEV_1 in a stepwise regression model. Change in FEV_1 increased with exposure and was significantly different between the exposure groups. Decline in FEV_1 in high exposure group (60 mL/year) was higher than annual decline observed in other studies of normal populations (32-47 mL). **Respiratory symptoms** (questionnaire; upper respiratory symptoms: sneezing, sinus trouble or postnasal drip, hay fever; lower respiratory symptoms: coughing, wheezing, shortness of breath): Prevalence of respiratory symptoms was unrelated to exposure category.	Uncertainties in exposure assessment High attrition rate Lung function decline evaluated from 3 occasions only

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Musk et al., 1982)	5 years follow-up n = 259 from three sites were examined in 1971; one of the sites closed in 1972 and there was high worker turnover; 107 subjects were available for re-examination in 1976	TDI and MDI for the manufacture of PU automobile components	2573 environmental samples were collected by plant personnel in the breathing zone of subjects pouring urethane plastic (exposure in areas with the highest exposures was measured) During lung function survey further measurements were made by plant personnel and study personnel at selected sites with highest TDI and MDI concentrations Marcali method (Marcali, 1957) All environmental measurements made over the 5 years together with the occupational history of the subjects determined the exposure category (No exposure/TDI/MDI/TDI and MDI). 90 % of all measurements of TDI taken over the four years prior to the follow-up study were < 5 ppb (plant 1) and < 4 ppb (plant 2) Geometric mean TDI concentration: 1.5 ppb	**Lung function** (spirometry (FEV_1, FVC); change over 5 years/change over the course of a day/change between before and after two weeks of vacation): Mean annual decrement in FEV_1 of 0.02 L was interpreted as being only age-related No significant acute change in FEV_1 over the course of a day before or after vacation reported After two weeks of vacation FEV_1 was increased in those who had taken the vacation (n = 49, n. s.) and was decreased in those who had worked (n = 31, n.s.). Exposure category did not affect daily change in FEV_1/pre- to post-vacation change in FEV_1/five-year change in FEV_1. **Respiratory symptoms** (questionnaire): No association between exposure to isocyanates and bronchitis or dyspnea found No acute exposure-related symptoms reported by subjects	Uncertainties in exposure assessment and spirometry Smoking, age, height, sex were considered in the regression analysis of FEV_1. Healthy worker survivor effect (Although it is reported that subjects who left had similar lung functions to the remaining subjects, it seems possible that workers left due to earlier symptoms of sensitisation).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			(plant 1) and 1 ppb (plant 2) MDI levels tended to be lower than TDI levels		
(Diem et al., 1982)	5 years prospective (9 surveys) First survey in 1973 (5 months before start of production) Initially: n = 168 After 5 surveys: n = 274 (males) Median follow-up time for n = 223 men who met inclusion criteria of spirometric data 4.1 years (1 – 5.5)	TDI manufacture	2093 personal samples from 143 workers representing all job categories 8h-TWA from 0.1 ppb - 25 ppb, geometric mean 2.00 ppb Average exposure: Three TWA exposure job categories: Geometric mean in ppb (time per shift < 20 ppb): Low: 0.02 (1.3 min) Medium: 2.0 (8.6 min) High: 4.5 (28.2 min) Cumulative exposure calculated from number of months spent in each of the three TWA exposure categories and their respective geometric means. Workers were divided into two groups using a division point of 68.2 ppb-months (= 1.1 ppb x 62 months). Low exposure group n = 149,	**Lung function** (spirometry, annual change): Decrease in FEV, %FEV and FEF_{25-75} was significantly larger in the high cumulative exposure category than in the low category (adjusted for pack-years of smoking). No association of the other lung function annual changes with exposure. A more detailed analysis of FEV_1 and FEF_{25-75} in six categories of cumulative TDI exposure and smoking showed a significant effect of TDI exposure in never smokers only and a significant effect of smoking in the low exposure group only. → effects not additive Effects similar for six categories of TDI peak exposure and smoking with the exception that a significant exposure effect was found in current smokers also. → higher TDI exposure seems to mask smoking effect → peak exposure analysis suggests additive effect (lacking in cumulative exposure analysis) **Respiratory symptoms** (questionnaire): No significant	No unexposed group "The present data do not identify a specific exposure below which no effect upon FEV_1 annual decline will occur. However, they do suggest that the NIOSH-recommended standard of a 5 ppb 8-h time-weighted average and a 20 ppb 10-min short-term exposure limit is reasonable." Low cumulative exposure group was older and initially had higher prevalence of respiratory symptoms than high exposure group → possible underestimation of excess decline in lung function due to TDI 75 % of the low exposure group had follow-up time > 2.5 years and 99 % of the higher exposure group

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			high n = 74. Working time spent > 5 ppb: 2 % in low exposure group, 15 % in high exposure group. Peak exposure categories: division point 0.19 months > 20 ppb	correlation in increase in prevalence from initial to final interview and exposure to TDI.	Atopy, race and smoking were considered Age and FEV_1 level were considered in the more detailed analysis of FEV_1 and FEF_{25-75}
(Omae, 1984)	2-year follow up Four TDI-producing plants, two research laboratories 1980: n = 106 male exposed workers n = 39 male controls (office workers) 1982 (one plant had closed): n = 64 workers (follow-up rate 60 %) n = 21 controls (follow-up rate 62 %)	TDI Manufacture ; research laboratory	Mean duration of TDI exposure: 9.0 years (subjects in 1980) 11.2 years (subjects in 1982) Personal paper tape monitor (gives continuous profile; n = 161 samples in 1980, 106 in 1982) Means of individual TWA: 0.7 ppb (1980) 1ppb (1982) Short-term exposure ≥ 20 ppb in 9.3 % (1980) and 1.9 % (1982) of collected samples	**Lung function** (Maximum expiratory flow volume curve, respiratory impedance): n = 8 workers with asthmatic reactions, shortly after having begun work with TDI. Percentage of predicted values significantly less than 100 % in some of the expiratory flow parameters. No significant differences in lung function between the exposed workers and the referents. Change in lung function over the day (1980; n = 68 TDI workers + n = 31 controls): No meaningful daily changes in lung function in either group. Change in lung function over two years: When adjusted for aging, no remarkable intra-individual two-year decreases in lung function parameters in both groups and no significant difference between the groups.	High loss to follow-up Co-exposures: TDI plant workers: occasionally various irritants such as phosgene, chlorine, nitric acid, sulfuric acid; Research laboratory workers: irritative amines, organic tin compounds , MDI, HDI during experimental mold foaming Effects of age, physical factors and smoking on lung function considered in analysis Survival worker effect considered to be small by the authors Hyperreactive persons to TDI may have already

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				No difference in the two-year decrement between the workers with asthmatic reactions and the other TDI workers. **Symptoms** (interviewed by the use of a questionnaire): No significant differences in prevalence of respiratory symptoms between exposed workers and referents. Significantly higher prevalence of throat and eye irritation in exposed workers than in referents. May be due to peak exposures to TDI or other irritants (phosgene).	been transferred out of TDI sections
(Musk et al., 1985)	Re-analysis of the data of (Musk et al., 1982)				The spirometries performed 1971 in the study by were criticised ("inadequate", "lack of reproducibility", "leak in the spirometer"). concluded that the original conclusions are valid.
(Gee and Morgan, 1985)	10-year follow up (includes significant proportion of subjects included in Musk et al. 1982) Examinations in 1971 and in 1981 n = 68 exposed n = 12 controls	TDI and MDI Manufacture of fittings, seat covers, other fixtures used in the interior of cars	Routine area and some individual sampling had been carried out monthly or more frequently Mean annual concentrations between 1973 and 1980 for TDI: 1- 5 ppb Mean annual concentrations between 1975 and 1981 for MDI: 1- 5 ppb	**Lung function** (compared to predicted values): Three subjects had impaired lung function (two exposed, one control). Lung function of subjects studied previously had mean FVC and mean FEV_1 > 100 % of the predicted values. Control group of one plant had a significantly lower percentage of the predicted FVC and FEV1 than the exposed group. No	Mean annual exposure values on factory level only Uncertainties in spirometry data (no reproducibility, leak in spirometer possible in 1971; learning effect from pre- to post-shift measurements)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 65 subjects with pre- and post-shift measurement n = 42 studied in 1971 and 1981			other significant difference between any of the groups. Lung function (change over shift): Change not higher than 10 % in any subject. No comparison between controls and exposed. Mean shift change in FEV_1 was -57 mL in exposed and +69 in controls in one plant and -23 and -80 in the other plant, respectively.	Results on annual decline in lung function seen as "not realistic" (small increase in FVC, small decrease in $FEV_{1)}$.
(Omae et al., 1992)	4-year follow up (cross-sectional results see) Cross-sectional: 1981 Follow-up visits: 1983 and 1985 Japan: n = 57 PU foam workers (follow-up rate 66 %; n = 2 excluded) n = 24 reference workers (follow-up rate 61 %; n = 3 excluded)	TDI PU foam manufacture	Personal paper-tape monitors (n = 59 samples in 1981, 48 in 1983 and 52 in 1985) n = 28 group L (low exposure with little variation), 17.4 years in the PU foam factories (mean), TWA (mean, max) 0.1 ppb, 1 ppb; Peak exposure level < 1 ppb n = 29 group H (exposed workers), 16.5 years in the PU foam factories (mean), TWA (mean, max) 5.7 ppb, 30 ppb; Peak exposure level 3-80 ppb Two subgroups of group H:	**Lung function** (Flow-volume indices in 1981; Average annual loss of the indices during 1981-1985 (forced expiratory flow-volume test at follow-ups; slope of the regression equation for every subject)): No "noteworthy" differences in pulmonary function indices and average annual losses between groups H, L, reference. Group H1: Significantly larger average annual lung function losses (% MMF, $\%FEV_1$ %, $\%MEF_{25}$) than expected. Significantly larger average annual losses in some obstructive pulmonary function indices than in group L or reference group.	No individual exposure estimates No significant differences between group H1 and H2 (as suggested in the abstract) Workers in slab-type factories intermittently exposed to relatively high levels of TDI and concurrent other chemical gases/aerosol → group H divided into two subgroups Smoking rate significantly lower in group H than in group L and reference group

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			n = 15 group H1 (high short-term exposures), 13.8 years in the PU foam factories (mean), TWA (mean, max) 8.2 ppb, 30 ppb; Peak exposure level 30-80 ppb n = 14 group H2, 19.4 years in the PU foam factories (mean), TWA (mean, max) 1.7 ppb, 4 ppb; Peak exposure level 3-14 ppb		Comparison of average annual losses of smokers and non-smokers in the 4 groups showed similar trends. Higher losses in smokers than non-smokers. Based on a comparison between lung function of followed-up and lost workers, survival-worker effect was evaluated to be small.
(Tornling et al., 1990)	Six years follow-up (initial study:) 1978: 46 male car painters and 142 male controls (car platers and mechnics) randomly chosen from 14 garages in Stockholm Reinvestigation in 1984: Participation rate 78 % for car painters and 81 % for controls n = 36 car painters	HDI monomer and HDI biuret trimer Car painting	Individual exposure assessments by industrial hygienist (interview about working routines, respirator use, hygienic standards). Exposure measurements at seven representative shops 98 samples inside and outside the respirator Individual exposure was calculated from workplace data, proportion of work tasks, use of respirators. 18 peak exposure measurements (sampling time < 3 min) Calculated TWA exposure:	Decline in **lung function** over six years (1978: Monday morning values were used; 1984: Workers were examined during the first three hours of a working day): Smoking and ex-smoking car painters had significantly larger lung function decrease compared with respective controls. Nonsmoking car painters displayed no faster deterioration in lung function than corresponding controls. Decrease in FVC correlated significantly with number of HDI-BT exposure peaks, but not with mean exposure. **IgG and IgE**, specific IgE in car painters:	Participation rate at follow-up 78 % among car painters and 81 % among controls. Selection bias (drop outs may have quit job because of respiratory symptoms, one asthma case known) Smoking not quantified

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 115 controls		HDI: 0.0015 mg/m^3 HDI-BT: 0.09 mg/m^3, frequently peak exposures > 0.2 mg/m^3 Calculated yearly number of peak exposure situations up to 6000 for each car painter No close correlation between exposure peaks and mean exposure	No significant differences in Ig levels between car painters and controls. No specific IgE found. **Symptoms**: Car painters reported significantly higher frequency of wheezing than the controls. Differences for other symptoms n.s.	
(Dahlqvist et al., 1995)	Reanalysis of data from (Tornling et al., 1990) and (Alexandesson et al., 1987) Evaluation if lung function decrease within the week is a marker of vulnerability of further decrement in lung function Six-year follow up, two study occasions Original group of workers were randomly chosen from 14 garages in Stockholm, 28 car painters participated	HDI Monomer and biuret trimer Car painters working with polyurethane paints	Individual exposure assessments by industrial hygienist (interview about working routines, respirator use, hygienic standards). 81 exposure measurements for three tasks in 25 spray painting chambers. Peak exposure measurements were performed (sampling time < 3 min) TWA between 1978 and 1984 for the workers studied: HDI: 0.0014 mg/m^3 HDI-BT: 0.09 mg/m^3	**Lung function** (1978: spirometry on Monday before work after two days of no exposure and on Friday; 1984: spirometry during the first three hours of a working day) Changes in FEV_1 and FVC within the week were dichotomised. Ten workers had a decrease in FVC within the week. Ten workers had a decrease in FEV_1 within the week. Car painters in the initial study who showed a decrease of FVC within the week in 1978 had a significantly greater decline in FVC from 1978 to 1984 than car painters who did not (adjusted for smoking).	Uncertainties in exposure assessment Current smokers had on average a higher yearly number of peak exposures to HDI-BT than did ever smokers. May indicate less use of protective equipment by smokers. Smoking not quantified

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	in all three spirometric examinatins, only those 20 were chosen who had been working during the entire six years period n = 20			Significant correlation between changes within the week and six years decline in FVC. Decline in FVC was not significantly correlated with the mean exposure to HDI or HDI-BT estimated during the entire follow up. Six year decline in FVC was correlated to the yearly number of peak exposures to HDI-BT. **Respiratory symptoms** reported (for example three of 10 workers with change in FVC within the week in 1984 have cough, dyspnoea and/or wheeze).	
(Jones et al., 1992)	Cross-sectional, follow up Two plants n = 394 at the start of the study, through the fourth examination n = 435 had ever worked in one of the plants	TDI Production of flexible PU foam products	258 workers wore monitors on 507 shifts resulting in 4845 12-min samples: 9 % > 5ppb 1 % > 20 ppb TDI concentrations were assigned to groups of jobs. Information on the number of months spent in each exposure grouping was taken from personal records. Mean by plant and job area ranged from 1.17 to 4.47 ppb. Exposure measures:	**Lung function** (spirometry, standing position, nose clips): Significant adverse effect of cumulative TDI exposure on initial level of FVC and FEV_1 in current smokers. TDI exposure had no significant effect on lung function decline. **Respiratory symptoms** (questionnaire administered by trained interviewers): Chronic bronchitis more prevalent among those with higher cumulative exposure (controlled for smoking, age, sex).	Co-exposure to different amines and other substances in foam production healthy worker (predicted values) differential misclassification of exposure (large number of samples < LOD)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			cumulative exposure from hire to first study examination cumulative exposure from hire to the end of study cumulative exposure during the study period length of time exposed to concentrations > 5 and 20 ppb	**Metacholine challenge** (n = 303): Metacholine responsiveness in 22 % of tested workers. Skin prick test with common inhalant allergens Total IgE, RAST	
(Akbar-Khanzadeh and Rivas, 1996)	1) Cross-sectional (daily, weekly changes) 2) Longitudinal (2.5-year follow up) 1) n = 16 urethane mold operators n = 19 controls (final assembly department, office area) 2) Oct 1989 – March 1992: n = 65 exposed to diisocyanates and solvents n = 40 exposed to solvents	HDI monomer and polyisocyanate, combined with organic solvents (MDI) Encapsulated automobile glass plant	1) HDI monomer, HDI polyisocyanate, volatile organic compounds Personal and area samples HDI: 92 % < LOD (set to 50 % of LOD); mean concentration (personal, area): 1.55 ppb (n = 6), 0.65 ppb (n = 3) HDI polyisocyanate: 75 % < LOD; mean concentration (personal, area): 0.09 mg/m^3 (n = 6), 0.02 mg/m^3 (n = 3) 2) Mean concentration:	1) **Lung function** (spirometry on Monday and Friday before and after shift): No significant differences between exposed and control group No significant reduction in lung function during workshift or during week in the exposed group compared to the control group. Some findings in subgroups by sex. **Respiratory symptoms** (questionnaire): Some symptoms more prevalent in control group (n. s. or not tested?). 2) **Lung function** (spirometry before the shift):	No individual exposure estimates Very small number of air samples Control group appropriate? 1) HDI in control area 0.67 ppb Co-exposure Smoking was significantly more prevalent in the exposed group 2) Co-exposure

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 68 controls (office, assembly, hardware department)		HDI 1 ppb (n = 8 samples) HDI polyisocyanate 0.29 mg/m^3 (n = 5 samples) MDI 0.45 ppb (n = 7 samples)	Significant decrease in lung function parameters in isocyanate/solvent-exposed group. Significant differences in lung function change (FEV_1 and FVC) among groups **Respiratory symptoms** (questionnaire): Proportion of subjects who developed respiratory symptoms in the isocyanate-exposed group was not significantly greater than that of the non-exposed group.	Controls had no occupational exposure "between the two tests"
(Clark et al., 1998)	5 years longitudinal UK n = 780 workers in 12 factories (n = 623 original + 157 naïve workers)	TDI Manufacture of PU foam	Personal monitoring (2294 measurements) for 100 job categories. Cumulative exposure between first and last lung function measurement was calculated for each subject based on job histories. 8-h TWA exposure limit of 5.8 ppb (46 ppbh for an 8h working day) was exceeded on 107 (4.7 %) occasions. Five of the 780 subjects (0.6 %) had a mean daily exposure exceeding the limit value. Peak exposure limit value of 20 ppb was exceeded in 500 (19 %) samples.	Longitudinal decline in **lung function** (spirometry; three or more measurements): No significant effect of TDI on annual lung function change. For the naïve population, regression analysis showed a significant effect of mean daily exposure on annual changes of FEV_1 and FVC. Due to irritant effect? **Respiratory symptoms** (questionnaire): Increase in respiratory symptoms in exposed group and handling group, significant for wheezing. 24 cases of respiratory sensitisation were identified during the study.	Followed up by Clark et al. 2003 High attrition rate (47 %) Leavers reported excess breathlessness and wheeze compared to non-leavers of the total population. Linear regression considered sex, group, age, age^2, smoking, mean daily exposure, peak exposure, pre-study exposure.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			8.8 % of the peak measurements > 40 ppb Exposed group (n = 521): manufacture of PU foam or handling freshly manufactured products; mean daily exposure 9.6 ppbh (1.2 ppb 8-h TWA) Handling group (n =123): handling cold PU products Low-exposure group (n =136): shopfloor and office workers		
(Hathaway et al., 1999)	Follow up (9 years) Production began in 1988, follow up through 1997 n = 43 "potential cases" and n = 42 "potential controls" of another unit at the same plant n = 32 matched pairs (by smoking, sex, age and by race and height if multiple possibilities were available)	HDI Production of HDI biuret and trimer from monomer	Average number of years of potential exposure: 8.4 Area and personal sampling (different methods and equipment over time) Exposure when not wearing respiratory protection was considered 1992-1995 (personal monitoring): average (range): TWA during work not requiring respiratory protection in the unit (1 – 4 hours/day): 0.5 ppb (0.0 – 2.0 ppb); calculated as 8h-TWA: 0.13 ppb	**Lung function** (as part of annual evaluation of workers): Average number of available tests for calculating slope: 7.8 (exposed) and 8.2 (controls). No significant difference in annual change of lung function (slopes) between exposed and control group. By smoking status, the results show more variation. Results seen as being within the range of lung function declines reported in other studies.	Exposure not measured on individual level Smoking not quantified Height and race only partially controlled Co-exposure in control group reported (depending on work area): cerium and neodymium oxides, nitric acid, ammonia, kerosene, tributyl phosphate Qualitative information on potential drop outs: low turnover rate, few transfers between the units, subject attrition not been a problem

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			Highest daily peak exposure: 2.9 ppb (1.0 – 10.0) Exposure before 1992 believed to be somewhat higher (no quantification)		
(Petsonk et al., 2000)	Health surveys prior to the use of diisocyanates and every six months thereafter over two years n = 276 workers were employed over the 2-year period; n = 144 had baseline and follow-up data as well as data on occupational history	MDI oligomer and prepolymer for coating wood products	Two exposure indices were assigned to individuals and to work areas, each with three categories. 1) individual: reported involvement with diisocyanates or diisocyante-containing products 2) work area: level of potential exposure to liquid MDI resin, based on the percentage of workers reporting exposure	**Asthma-like symptoms** based on a questionnaire: initial asthma-like symptoms (IAS) follow-up asthma-like symptoms (FAS) new-onset asthma-like symptoms (NAS) Prevalence of NAS was 27 % in workers of the highest exposure potential to liquid MDI and 0 % in the lowest exposure category. Prevalence of NAS and FAS cases increased with categories of potential exposure to liquid MDI. FAS and NAS were significantly more prevalent among workers that reported that they had briefly removed respiratory protection than among workers who reported that they never do this. Prevalence of NAS and FAS were higher in the workers who reported a MDI stain on their skin than in workers that reported they had never observed a stain.	Not suitable for deriving reference values because of missing exposure measurements Current smoking was considered in the logistic model of FAS. Prevalence data of FAS and NAS were stratified by current smoking (n = 32).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Individual reports of work involving exposure to liquid MDI were significantly associated with FAS (logistic regression model).	
(Ott et al., 2000)	Historic cohort study using medical records and exposure records from 1967 to 1997 n = 313 employees ever assigned to the TDI production unit for >= 3 months; n =158 referent employees; 40 records were not found (16 of the study group and 24 of the reference group)	TDI manufacturing	Duration of TDI unit assignments: 5.7 years (average, men) 4.7 years (average, women) 3 months to 30 years (range) 1967 (area sampling): < 10 ppb in most areas and 25 ppb in the residue handling area 1969-1973: < 10 ppb in most areas with 60 to 80 ppb in certain areas 1976-1988 (personal 8 hour samples, paper type method): 5.9 ppb (average) 1989-1997 (personal 8 hour samples, filter method); 2.8 ppb (average) JEM: Industrial hygiene measurements were linked to job-specific work history per person; peak exposure and 8h-TWA concentration were aggregated on a job and time specific basis for three job groups (potentially	**Occupational asthma**: Case identification was based on site physician. One episode of asthma-like symptoms was not enough to be an OA case. 19 asthma cases presumed to be due to TDI, 9 skin allergies, 1 case of asthma and skin disease Yearly incidence: 19 cases in 1779 work-years = 1.1 %; before 1980: 1.8 %; since 1980: 0.7 % Cumulative incidence for people assigned to TDI unit at least 20 ys: 11.5 % (95 % CI 5.3-17.7 %) 7 of 19 cases had reported previous incidents of exposure to TDI (2 related to rashes that had developed while handling TDI or waste products containing TDI) **Respiratory symptoms**: Since 1980 a standardised questionnaire was used that contained four questions with dichotomous answers (concerning wheezing/cough/chest discomfort/shortness of breath).	Long follow-up time Exposure concentration linked to the asthma incidence not clear. The review of Ott et al. 2003 reports for this study an exposure of 0.3 – 2.7 ppb (TWA; range by job) since 1980, assigning this to a yearly incidence of 0.7 %. Peak exposure and dermal exposure make it difficult to evaluate the 8h-TWA. Smoking, non-occupational asthma and allergy were assessed. Exposure to phosgene

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			low/moderate/high TDI exposure); cumulative dose estimates (ppb-months) Average TDI concentration: < 5 ppb for 59 % of the workers Cumulative TDI dose: < 500 ppb-months for 89 % of the workers Frequencies of peak exposure > 20 ppb per shift: 0.5 in moderate exposure jobs, 0.9 in high-exposure jobs	No significant associations with responses in the questionnaires were found for those exposed to TDI versus referents. **Lung function** (spirometry): Neither cross-sectional nor longitudinal analyses of FVC and FEV_1 showed significant dose-response findings relative to exposure to TDI across the total exposed population.	
(Bodner et al., 2001)	Longitudinal, data taken from routine medical surveillance examinations offered every 1 to 2 years Cross-sectional analyses (symptoms before entry and at last examination) Data from 1971-1997, mean follow-up ca. 8 years Dow Chemical, Texas, USA n = 305 TDI exposed workers	TDI Manufacture	Mean observation period of TDI workers 7.8 years (SD 6.2) n = 449 8-h TWA TDI samples in 20 job categories; mean TDI exposure values per category calculated for start-up period (1971-1979) and full production period (1980-1997); individual work histories were matched to the 20 job categories to produce average exposure estimates and cumulative exposure estimates for each work segment for each worker	**Clinical symptoms** (questionnaire): One of the symptoms significantly more prevalent in controls than in exposed subjects at baseline (shortness of breath). Prevalence for all symptoms increased in both groups over time. Prevalence of symptoms not higher in TDI exposed subjects compared to controls at final examination. No effect of TDI on clinical symptoms reported during the study period found in regression models using four cumulative exposure categories or using a continuous cumulative variable or using quartiles of exposure. **Lung function** (spirometry):	Longest follow-up time (together with Ott et al. 2000) for TDI workers until then. Retrospective (change of formats of health surveys) Not enough exposure samples to derive annual TDI concentration estimates for each year for each job category Regression analyses for symptoms were adjusted for observation period and pack-years. Covariates considered for the mixed models for longitudinal

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 581controls (hydrocarbons department)		Mean TDI concentration per individual: 2.3 ppb (SD 1.0), max. 5.2 ppb Average cumulative TDI exposure: 96.9 ppb-months (SD 110.6), max. 639 ppb-months Quartiles of the cumulative TDI estimates: 1-29 ppb-month, 30-70 ppb-month, 71-133 ppb-month, > 133 ppb-month Exposure categories with cut-points at 1 ppb for 1, 5, 10 years, expressed in ppb-month (distribution for all observations): 1-12 (8.3 %), 13-60 (36.6 %), 61-120 (27.1 %), > 120 (27.0 %)	Average annual decline in FEV_1 was 30 mL. No association of TDI and decline in lung function found with mixed regression models using different exposure terms and subgroups.	lung function change were initial FEV_1, initial FVC, age, observation period, height, race, sex, race, entry period, pack-years, asthma, shortness of breath No exposure to MDI (as in some foam-manufacturing operations)
(Clark et al., 2003)	17-year longitudinal 1981-1998 UK Follow-up of Clark et al. 1998 7 of 12 factories remained n = 251 (217 were in the previous study)	TDI Manufacture of PU foam	Personal measurements: n = 1004 valid 1.3 % in excess of 46.4 ppbh (5.8 ppb, 0.02 mg NCO/m^3) Respiratory protection taken into account by subtracting 50 % of calculated exposure values Average daily dose for each exposed job at each factory	Longitudinal decline in **lung function** (same spirometer as in previous study; earliest measurement during 1981-1986 + further measurement in 1997/1998 used): Significantly higher loss in FEV_1 and FVC in handling group vs. low exposure group. Annual decline of FEV_1 and FVC not associated to TDI exposure. **Respiratory symptoms** (questionnaire): Differences in prevalence of respiratory symptoms between initial and final survey (reduction in some, increase in other symptoms).	Study was not designed to identify cases of sensitisation Persons showing evidence of TDI sensitisation would be removed and would no longer be available for study High attrition rate Respiratory illness was the reason for leaving in 2.3 % of cases

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			calculated from the current and previous measurements Mean exposure for the period: Exposed group (n = 175): 8.4 ppbh Handling group (n = 26): 4.8 ppbh Low exposure group (n = 11): 2.3 ppbh		70 subjects out of 251 (28 %) changed groups during the 17-year period Number of present smokers fell from 129 (51 %) to 100 (40 %) between the two studies Only two data points used for lung function decline
(Wang and Petsonk, 2004)	Same cohort as in (Petsonk et al., 2000) (Initial survey before initial use of MDI in the plant, follow-up surveys at 2/8/14 and 20 months after initial use of MDI) n = 132	MDI oligomer and pre-polymer for coating wood products	Any contact with liquid MDI (respiratory or skin) reported: n = 39; no contact reported: n = 93 (Further binary exposure groups for wood dust and smoking)	Five **respiratory symptoms** were assessed by a questionnaire (Attacks of dyspnoea with wheeze/attacks of dyspnoea or cough at rest/Chest tightness/Cough/Phlegm). Symptom incidence was recorded at a follow-up regardless of whether or not it had been reported on a previous or subsequent follow-up. Multiple logistic regression for repeated measurements of symptom onset showed that workers exposed to liquid MDI had about two to four times greater odds of developing these symptoms. Significant for all outcomes except for cough.	Not suitable for deriving reference values because of missing exposure measurements. Logistic regression adjusted for age, smoking, wood dust exposure, tenure
(Dragos et al., 2009)	Prospective inception cohort study, 18 months	HDI monomers and oligomers	Personal breathing zone samples (n = 51) during regular and specific activities	Health assessment included: - Respiratory symptoms (questionnaire) - Lung function (spirometry) - Metacholine challenge - Skin prick tests (only first visit)	Subjects lost to follow-up 21.5 % Short observation period

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 385 apprentice car-painters recruited between 1999 and 2002, complete data for n = 298 First visit upon entry and second visit at the end of the training programme Montreal area, Canada		Area sampling (n = 41) in spray cabins and workplace background Duration for effective exposure to HDI max. 7 months, median 3 months Median (maximum) concentration in µg/m^3, personal samples: Monomer: Spraying 0.001 (0.006) Mixing 0.0003 (0.0003) Brush cleaning < LOD Oligomer: Spraying 0.283 (0.916) Mixing 0.4365 (0.6890) Brush cleaning 0.079 (0.079) Concentrations from area sampling were lower than from personal sampling	- HDI-specific IgE, IgG and IgG4 Aims: - describe changes in specific antibodies to HDI - describe incidence of work-related symptoms - examine association between work-related symptoms and changes in specific antibody levels, and other potential risk factors Increases in specific IgE and IgG levels > 97th and 95th percentile were significantly associated with duration of exposure (9 subjects increased their IgG levels /IgE levels above the cut-off of the 97th percentile). Increases in specific IgG and IgG4 showed a protective effect on the incidence of work-related lower and upper respiratory symptoms, respectively. 13 subjects (4.4 %) developed work-related respiratory symptoms, 19 (6.4 %) developed work-related symptoms of rhinoconjunctivitis. No association between change in IgE levels and incidence of symptoms.	Pre-exposure possible No individual exposure estimates Masks worn when spraying, but not always those recommended and often removed inappropriately for inspecting the work. In regression analysis (dependent variable: IgE or IgG) only duration of exposure was used, but no concentration. At the exposure level in this study and after a few months, a small proportion shows increases in HDI-specific IgG and IgE
(Cassidy et al., 2010)	Matched retrospective cohort study	HDI Two plants manufacturing or	Industrial hygiene personal samples If record indicated that respiratory protection was	**Asthma** (annual medical surveillance history forms; suspect cases were inspected further by a company physician): No new asthma cases were reported.	No quantitative exposure estimations on the individual level

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Expands on Hathaway et al. 1999 (includes an additional plant) Observation period: Plant 1 1988-2007 Plant 2 1987-2006 Southern US n = 57 potentially exposed in plant 1 and 43 in plant 2 (mainly exposed to HDI monomer) controls: plant workers without documented history of exposure to diisocyanates 1:1 matching by age, gender, race, smoking status, date of birth, date of hire	producing monomer and/or polyisocyanates	used, sampling record was not considered Mean (range): Plant 1, 237 samples 0.79 ppb (Non detectable – 31 ppb) Plant 2, 29 samples 0.3 ppb (Non detectable – 2 ppb) Most of the study group reported some instances of dermal exposure	Changes in **lung function** over time (annual spirometry), examined by a random coefficient regression model: Decline in lung function (FEV_1, FVC) over time in the exposed group was significantly greater than in the control group.	Small number of exposure samples to reflect whole study period Smoking was assessed as binary variable. Controls may have been heavier smokers (significant difference in lung function decline between smoking controls and smoking exposed) Potential co-exposures reported: Exposed group: Other aliphatic diisocyanates, HDI polyisocyanates Control group from plant 1: dinitrotoluene, hydrazine, methylene chloride, maleic anhydride, toluene diamine, ethylene oxide Control group from plant 2: cerium, neodymium oxides, nitric acid, ammonia, kerosene, tributyl phosphate (depending on work area)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
					No employee had to be medically removed because of HDI exposure Individuals with asthma were excluded from work with potential exposure (only in plant 1) and there may have been self-deselection.
(Lofstedt et al., 2011)	4-year follow up after improvement in work environment 2001-2005 Sweden Original study see Löfstedt et al. 2009 n = 25 (92 % male) foundry workers n = 55 (85 % male) referents	Isocyanic acid, methyl isocyanate, formaldehyde	Exposure measurements and lung function measurements on the same day Individual exposure measurements Exposure levels were reduced by 50 % at follow-up Geometric mean 2001 and 2005: ICA: 22 and 13 µg/m^3 MIC: 6.0 and 3.1 µg/m^3 Formaldehyde: 66 and 35 µg/m^3 No respiratory protection for workers	**Lung function** (spirometry before and after a day shift): Pre-shift FEV_1 slightly lower in exposed group than in referent group. No significant change in lung function over the shift. **Respiratory and ocular symptoms** (same questionnaire as in 2001): Lower airway symptoms were less frequent in both groups than in 2001, still a high prevalence of nasal and ocular symptoms in both groups.	Loss of almost 40 % of the participants of the original study Higher prevalence of nasal symptoms among workers exposed in 2001 but not exposed in 2005 than workers still exposed in 2005 → Healthy worker effect in the group that was still exposed in 2005 Co-exposures present Unclear if respiratory symptoms are due to irritant or immunological response. Authors think immunological response is unlikely.
(Gui et al., 2014)	Inception cohort study	TDI-based state-of-the-art PU foam	Continuous fixed-point air sampling in foaming hall and cutting areas.	Over the first year of employment, 7 workers (14 %) had findings that could indicate TDI-related health effects	Actual exposure of the individual is not known: TDI air levels may have

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Evaluation of n = 49 newly hired workers pre-employment, after 6 months and after 12 months Grouping of workers in exposure risk groups, based on potential risk of TDI exposure: low n = 8, medium n = 28, high n = 13.	production in Eastern Europe	90 % of the samples < LOD (0.1 ppb). Maximum recorded 10.0 ppb (foaming hall), 5.4 ppb (cutting area) No air sampling period exceeded an 8h-TWA of 5 ppb Peak exposures recorded were below 20 ppb. Personal sampling performed on seven workers. All showed TDI levels < LOD. Dermal exposure occurred (uncured or just cured foam, contaminated surfaces).	(Either new asthma symptoms, TDI-specific IgG, new airflow obstruction or a decline in FEV_1 ≥ 15 %). Twelve workers (25 %) were lost to follow-up. Among these workers, current asthma symptoms were reported (at baseline or 6 months) in a significant higher percentage compared to those who completed the 12-month follow-up. No significant associations were found between the exposure risk group and health outcomes. Self-reported glove use differed significantly between the exposure risk groups (25 % of the workers in the low, 32 % in the medium, 100 % in high exposure risk group). Although this production facility is reported to be state-of-the-art with exposure below the OEL, the study suggests possible TDI-related health-effects.	been higher near the source. Dermal exposure occurred. Glove use differed between exposure risk groups. No unexposed control group No exposure quantification per exposed group Workers with spirometry data at baseline n = 23, with spirometry data at all three time points n = 16. Baseline spirometry conducted at another facility.

Table 40: Case-control studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Tarlo et al., 1997)	Comparison of the level of isocyanate Concentration in 20 "case companies" (with compensated isocyanate asthma claims) with 203 "non-case companies"	TDI, MDI, HDI (or more than one)	Exposure data taken from a database of the Ontario Ministry of Labour (MOL) based on company's regulatory monitoring obligation if a worker is likely to inhale or to come into contact with isocyanates: air samples collected during the same 4-year period during which the OA claims arose. Exposure determined on the basis of the highest level identified. Two categories: Always < 0.005 ppm Ever ≥ 0.005 ppm	56 accepted claims for OA (OA cases with identified isocyanate exposure during the 4-year period from mid-1984 to mid-1988 in the Ontario Workers' Compensation Board) Combined across isocyanate types: Companies with claims in the high exposure category: 10/20 (50 %) Companies without claims in the high exposure category: 50/203 (25 %) OR = 3.1 (95 % CI: 1.1–8.5, p = 0.03). MDI: OR = 1.7 (95 % CI: 0.4–7.6) TDI: OR = 2.7 (95 % CI: 0.7–10.6) Estimated incidence of OA in a 4 year study period: High exposure companies with claims: 2.7 % Low exposure companies with claims: 2.2 % Overall incidence in the total 223 companies surveyed: 0.9 % (56 out of 6308 workers).	Many high exposure companies without claims. Other factors may be important in isocyanate sensitisation, or there may have been quantitative or qualitative differences in exposure that were not assessed. Selection bias possible (some of the air sampling conducted in investigation of submitted claims for OA) Companies with claims had more employees than those without claims (higher probability of at least one employee becoming sensitised in a greater group of employees; larger companies may be more likely to implement a surveillance program).
(Meredith et al., 2000)	Company A: 27 OA cases were matched to 51 referents (sex, work area)	Company A:	Company A:	**Asthma** Data from the two sites were analysed separately. Company A:	Uncertainties in exposure assessment Regression analyses adjusted for smoking and different atopic diseases

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Company B: 7 cases; all non-cases (n = 12) served as controls, because matching was not possible (moving between work areas, few workers)	24 cases attributed to TDI (manufacture of moulded and block flexible PU foam, flame bonding and surface coating of fabrics); 3 cases attributed to MDI (batch moulding of rigid PU components at 200°C) Company B: Cases attributed to MDI from a chemical plant in which MDI and poly-merric MDI mixtures were pro-cessed and poured into drums. Some processes involved heating the mixtures.	Personal exposure measurements by job category (1979-1986) made for a separate study + data collected after 1986 by occupational hygiene consultants were used to estimate 8h-TWA and peak exposure for each subject based on job title and date. Company B: Personal monitoring results from 1988 available (Marcali method to the middle of 1990, HPLC thereafter) For each subject, the proportion of measurements ≥ LOD of the Marcali method (2 ppb) and > 5 ppb were calculated. Measurements < 2 ppb were treated as being 0. 90 % of the 269 TWA samples were < 2 ppb	Conditional logistic regression: 8h-TWA as a binary variable (cut off: median concentration in control group) or continuous variable (0.1 ppb increments) Peak exposures: 1 – 50 ppb In 31 subjects peak exposure > 20 pbb No difference between cases and controls. Mean 8-h TWA: cases: 1.5 ppb; controls: 1.2 ppb OR for exposure > median of the control group: 3.2 (95 % CI 0.96 – 10.6; p = 0.06) Adjusted OR (for 0.1 ppb increase in 8h-TWA): 1.07 (95 % CI 0.99 – 1.16) Adjusted OR higher for smoking (2.4) as well as history of either hay fever, eczema or asthma (3.4), but also n.s. In 11 (41%) of the cases, symptoms began in the first year of employment at the plant. The OR for 0.1 ppb increase in current 8-h TWA was higher for cases with symptoms occurring within a year from start of employment (1.5, 95% CI 0.82 – 2.7, p = 0.18) than among those with a later onset of symptoms (1.04, 95% CI 0.95 – 1.13, p = 0.41) Company B:	Amines are used as catalysts in the manufacture of PU foams and they have been reported to cause respiratory symptoms

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Association between reported chemical accidents and asthma.169/185 TWA samples for controls and 74/84 for cases were < 2ppb. Mean and median exposures were < LOD for cases and controls. Median of the highest concentration recorded for each subject was 3 ppb for both groups. Proportion of measurements ≥ 2 ppb was 0.09 (controls) and 0.18 (cases). Proportion of measurements > 5 ppb was 0.004 (controls) and 0.09 (cases). 3/7 cases and 1/11 controls had at least one 8h-TWA exposure measurement > 5 ppb (OR 7.5; p= 0.09)	

Table 41: Cross-sectional studies with quantitative exposure-response estimates

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Pronk et al., 2007)	n = 581 (n = 241 spray painters n = 50 unexposed office workers n = 290 others) Workplace survey in several companies	HDI monomer and trimers in spray painting (car body repair shops, furniture paint shops, industrial paint shops specialising in ships and harbour	Personal exposure estimates were obtained combining personal task-based inhalation measurements for 23 different isocyanate compounds and time activity information Exposure of n = 241 spray painters, [µg NCO * m-3 * h * mo-1], median (min-max):	Prevalence ratios (PR) and 95 % CI for an interquartile range increase in exposure were calculated based on log-transformed exposure data. **Respiratory symptoms** (grouped into "asthma-like symptoms" and "COPD-like symptoms"), work-related symptoms (questionnaire): Respiratory symptoms were more prevalent in exposed workers than in office workers. Significant positive log-linear exposure-response associations were found for:	For subsample with BHR see Prevalence Ratios were adjusted for age, sex, current smoking and atopy (or some of those) Possible effect modification by atopy was explored

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	between 2003 and 2006	equipment or airplanes)	Total isocyanate 3,682 (4-66464) HDI 27 (0.2-1427) Biuret 269 (0.2-13568) Isocyanurate 2250 (6-87623)	Asthma-like symptoms PR (95 % CI) = 1.2 (1.0-1.5), COPD-like symptoms 1.3 (1.0-1.7), Work-related chest tightness 2.0 (1.0-3.9) and Work-related conjunctivitis 1.5 (1.0-2.1), but not for Work-related rhinitis 1.3 (0.9-1.7) Different HDI-specific (for monomer and oligomers) IgE and IgG antibodies: Prevalence of specific IgE antibodies was low (up to 4.2 % in spray painters). Prevalence of specific IgG was higher (2-50.4 %). One of five specific IgE antibodies and four of five specific IgG antibodies were positively associated with exposure. **Bronchial hyperresponsiveness** (BHR) assessed by methacholine challenge in a subset of 229 workers Individuals with asthma-like symptoms were more likely to have BHR: PR (95 % CI) = 2.2 (1.5-3.2) For COPD-like symptoms, the association with BHR was less strong and n. s.	
(Pronk et al., 2009)	Subset of study by Pronk et al. 2007 n = 229 from 38 companies	HDI monomer and trimers in spray painting	Personal exposure estimates were obtained combining personal task-based inhalation measurements for 23 different isocyanate	Prevalence ratios (PR) and 95 % CI for an interquartile range increase in exposure were calculated based on log-transformed exposure data. **Lung function**:	Associations were adjusted for age, sex, current smoking and atopy Associations for lung function parameters: additionally adjusted for height and race

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	(n = 91 spray painters n = 20 unexposed office workers n = 118 others)		compounds and time activity information Exposure of n = 91 spray painters, [µg NCO/m^3 x h/mo], median (min-max): Total isocyanate 4530 (15.4-66464) HDI 36.2 (1.3-472)	Highly exposed workers had lower FEV1, FEV1/FVC and flow-volume parameters. Percentage of workers who met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD (FEV1/FVC <70 %): office workers 5 other workers 4 spray painters 15 COPD clearly associated with exposure. PR (95 % CI): 2.7 (1.1-6.8) **Bronchial hyperresponsiveness** (BHR) (defined as a provocative cumulative dose of methacholine of ≤ 2.5 mg (~10 µM) required to cause a 20 % fall FEV1): Percentage of workers with hyperresponsiveness (BHR20): office workers 0/ other workers 14.7/ spray painters 20. Hyperresponsiveness was found in 33 subjects and it was clearly associated with exposure expressed as total NCO. PR (95 % CI): 2.0 (1.1-3.8) (adjusted for smoking, age, sex and atopy) BHR combined with asthma-like symptoms was present in 19 subjects and the adjusted PR was 2.7 (1.0-6.8). **Symptoms** (see): Asthma-like symptoms, COPD-like symptoms, work-related chest tightness were more prevalent among workers with higher exposure (n. s.).	Strenghts: Quantitative inhalation exposure assessment based on > 500 measurements and detailed task activity information; Several objective respiratory effect measures investigated in one population Limitations: Use of personal protective equipment, previous exposures and dermal exposure was not taken into account; Not possible to differentiate between cumulative and peak exposure; Complex exposure environment; Healthy worker effect possible

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Workers with asthma-like symptoms had sign. more BHR, sign. lower baseline FEV1, FEV1/FVC and maximal mid-expiratory flow. No sign. association between exposure and exhaled nitric oxide (eNO) IgE and IgE (see): The prevalence of specific IgE antibodies was low (< ~4.4 %). The prevalence of specific IgG was higher (up to 47 % in spray painters). Specific IgG sensitisation was more common in highly exposed workers. Workers with specific IgE/IgG were more often hyperresponsive (overall; statistically significant only for one IgG). *"The current study provides evidence that exposure to isocyanate oligomers is related to asthma with bronchial hyperresponsiveness as a hallmark, but also shows independent chronic obstructive respiratory effects resulting from isocyanate exposure."*	

Table 42: Further studies - cross-sectional studies

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Bruckner et al., 1968)	Cross-sectional n = 26 with multiple	TDI, polymeric isocyanates including	Exposed workers had accumulated exposure from 3 months to 11 years	**Symptoms** (interview, physical examination) Immunologic reactivity to isocyanate antigen conjugates (several tests)	Groups built based on exposure and type of response

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	exposures to diisocyanates n = 18 had never worked with or around isocyanates	MDI, xylylene diisocyanate Research, development and production of isocyanates and other components of urethane plastics	Air samples taken by industrial hygienist, modified Marcali method. Between 3 and 79 samples per year for single years between 1957 and 1967. Median concentration per year: 0-77 ppb	Four groups: - Exposed minimal response (minimal symptoms of mucous membrane irritation) n = 5 - Exposed overdose response (moderate to marked signs and symptoms of chemical irritation of the respiratory tract) n = 16 - Exposed sensitised (signs and symptoms of sensitisation) n = 5: With increasing number of exposure, the time to reaction became shorter and finally bronchospastic symptoms developed within seconds after exposure to minute amounts of isocyanates. All had irritative symptoms before developing symptoms indicative for sensitisation. All had exposures > 20 ppb. - Non-exposed n = 18 n = 6 cases of irritant dermatitis Workers exposed to low levels (not given) of isocyanates developed eye, mouth and throat symptoms. According to the authors concentrations between 20-100 ppb "may predispose some workers to sensitivity to isocyanate compounds"	
(Wegman et al., 1974)	Cross-sectional 1972 Before and after shift on a Monday after three days away from work	TDI Manufacture of PU for matresses and auto seat cushions	Area sampling on the day of lung function testing and on three subsequent days (Marcali method) All job areas were sampled and assigned exposure values and each worker was	**Lung function** (spirometry: FEV_1, FVC; in the morning before work and in the afternoon after eight hours work; only FEV_1 reported): All exposure groups showed significant loss in lung function (FEV_1) during the working day. Dose response relationship suggested (mean change in FEV_1 0.078 L in group A and 0.180 L in group D). Confirmed by regression	Followed up: Age, height, years smoked, cigarettes smoked, duration of exposure was considered for stepwise regression analysis

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 111 (78 males)		categorised according to his or her exposure to a measured mean concentration of TDI. Originally exposure categories were combined to four groups (ppm): A 0.002 - 0.003 B 0.004 C 0.005 D 0.006 – 0.013	analyses. And confirmed by calculation of ratios of those showing no change or increase over those showing decrease per exposure group (ratio increases with exposure group). Greater fall in FEV_1 in workers with symptoms compared to workers without symptoms, n. s. No trend of FEV_1 across subgroups of age, years of smoking or years of employment.	
(Pham et al., 1978)	Cross-sectional Two factories producing mainly plastic foam automobile accessories n = 318 workers (214 men) who had been employed for at least a year	MDI PU foam moulding	Workers used MDI and some TDI for 1 to 10 years. Plant A: MDI consistently < 20 ppb Plant B: MDI peaks up to 87 ppb at foam injection workplaces Group I: Not exposed to any occupational hazard n = 83 (62 men) Group II: Indirect exposure risk due to foam plastics manufacture n = 117 (61 men) Group III: Definite, direct exposure risk due	**Lung function** (single breath carbon monoxide transfer factor test, spirometry): Lower values of VC and diffusion constant in the exposed groups and associated with length of exposure. Possibility of fibrosis in workers with long exposure suggested. Results for men not confirmed by results for women. **Respiratory symptoms** (questionnaire): Higher frequency of bronchitis in exposed groups compared to unexposed group (men and women).	Followed up by Exposure on factory level Men and women analysed separately Exposure to stripping agents, solvents, polyvinyl vapour in exposed groups Exposure to TDI No statistically significant differences between the groups concerning age, height, weight, smoking. More men smoke than women and they are heavier smokers.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			to foam plastics manufacture n = 118 (91 men)		
(Holness et al., 1984)	Cross-sectional, shift, intraday, intraweek 1982 Toronto area Four companies n = 95 isocyanate-exposed workers (70 % males, n = 26 foam-line, 11 injection, 28 finishing, 21 miscellaneous) n = 37 control workers (62 % males; n = 16 plant, 21 Ministry of Labour) (n = 29 were excluded)	TDI Use in foaming operations	Mean length of exposure to isocyanates of 6.5 years Monitoring of TDI and respirable dust during same shift as lung function analysis (area samples; personal samples for 86 workers) Mean exposure concentration for five groups of workers: Area: 0.1 – 1.8 ppb Personal: 0.6 – 2.1 ppb Mean for all exposed: Area: 0.6 ppb Personal: 1.2 ppb Some analyses with three exposure categories: control, ≤1ppb, >1ppb One personal sample > 20 ppb Less than 3 % of the personal or area values > 5 ppb	**Lung function** (spirometer, beginning and end of work shifts on Monday, Wednesday, Friday, sitting position using noseclips): Values of all lung function parameters (Monday morning) lower in the exposed than in the control group (not significant, adjusted for smoking). Significantly larger declines in lung function over the shift in exposed workers. Decline in FVC and FEV_1 over the shift increased over the three exposure categories, but was statistically significant only between controls and exposed groups. No significant relationships observed in regression analysis with continuous exposure. **Respiratory and further symptoms**: Slightly higher frequency of respiratory symptoms in exposed group, n. s..	Respirable dust, mean for all exposed: 0.30 mg/m^3 Significantly lower frequency of family history of asthma, hay fever, bronchitis in exposed group (may be due to screening prior to employment or workers with positive family history may have developed symptoms and left).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Venables et al., 1985)	Cross-sectional (Outbreak of asthma was investigated) 1979 n = 221	TDI Steel coating plant; continuous process, coat was cured by passage through an oven	TDI: 14 ppb at oven entry during normal processing, up to 26 ppb during 5 minute stoppage TWA 1979: 20 ppb	21 workers (9.5 %) with OA symptoms (questionnaire) in 7 years (onset of symptoms after 1971) Symptomatic groups had significantly lower FEV_1 than asymptomatic group. TDI was found to be the cause of the asthma outbreak. It was liberated by a coating modified by a supplier in 1971.	No individual exposure levels Affected individuals may have left the plant
(Alexandersson et al., 1985)	Cross-sectional n = 67 (57 males) n = 56 controls (11 with lung function tests)	TDI, MDI Seven PU foam manufacturing factories (two foam PU blocks, five cast PU in moulds)	Personal sampling on same day as lung function tests Day mean exposure to TDI in foaming of PU blocks: for the whole group: 0.008 mg/m^3 (0.001 ppm) Highest exposure in the group working by foaming machine: 0.023 mg/m^3 (0.008-0.060) Day mean exposure to MDI ≤ 0.001 mg/m^3 during casting in moulds. Highest measurement: TDI 0.275 mg/m^3 MDI 0.139 mg/m^3	**Lung function** (spirometry: FEV_1, FVC, FEV %, MMF; nitrogen washout: Phase III, Closing volume; in the morning prior to work; exposed workers were studied again in the afternoon after work): Lung function of non-exposed group similar to reference values. Lung function of exposed group significantly impaired as compared to reference values, but significant in subgroup of smokers only. No significant changes during work shift. **Symptoms** (standardised questionnaire): Frequency of symptoms significantly higher in exposed non-smokers than in non-exposed non-smokers (nose, throat, dyspnea). No significant difference in symptoms frequency between exposed and non – exposed smokers.	To calculate day exposure figures < detection limit (0.001 mg/m^3) were set to zero. Selection bias (underestimation of acute adverse effects of TDI as sensible individuals may tend to terminate their employment)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Alexandersson et al., 1986)	Two cross-sectional studies 1977: n = 18 1980: n = 8 n = 23 males n = 5 males Employees who had been transferred because of severe symptoms n = 20 controls from the same factory	NDI Rubber plant Manufacture of plastic polymer (component of tires), polymer is hardened in moulds	Measurements in 1980: 8 subjects carried filter pumps, air samples were collected in breathing zone over 15 min during the course of various tasks on the day of the study Mean (range): Moulding 0.007 mg/m^3 (0.001 – 0.036) Preparation of moulds 0.002 mg/m^3 (0.001 – 0.011) Weighing and mixing of substances 0.008 (0.012 – 0.020)	**Lung function** (spirometry: FEV1, FVC, FEV %, MMF; nitrogen washout: Phase III, closing volume): Lung function impairment (of non-acute nature) observed as an increase in CV % (closing volume as percentage of the expired vital capacity) **Symptoms** (standardised questionnaire): Frequency of eye irritation significantly higher in exposed (12/17) than in controls (1/17). Frequency of productive cough, chronic bronchitis and exertion dyspnea higher in the exposed group than in control group, but n.s.	Exposure measurements from only one day, small number of samples High number of exposed subjects with eye irritation Selection bias (study was conducted because of complaints of airway irritation and the necessity to transfer employees to nonexposed work) Silicone oil sprayed in molds (not likely that this caused the irritation)
(Alexandersson et al., 1987)	Cross-sectional and over workweek 15 garages in Stockholm area n = 41 car painters n = 48 car platers (exposed to solvents, grinding dust, welding fumes like car painters,	HDI Monomer and biuret trimer Car painters working with polyurethane paints	Exposure questionnaire Exposure monitoring 278 samples of HDI and HDI-BT Exposure has been individually related to time, use of respiratory protections, working operation, ventilation. Individual exposure determined by industrial hygienist HDI-BT for car painting:	Exposed workers were examined on Monday morning before work and on Friday afternoon Change in **lung function** within the week (spirometry: FEV_1, FVC, maximum mean expiratory flow MMF; Nitrogen washout: Phase III, Closing volume): Car painters did not differ from controls in any of the spirometric variables (before the workweek). Closing volume percent was significantly higher in exposed than in control workers. No significant difference in lung function in car painters before and after a workweek.	Uncertainties in exposure assessment Selection bias (some car painters had been relocated or their employment terminated)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	not to isocyanates n = 70 car mechanics Car painters and car platers were matched against a control by sex (only males), age, height, smoking		mean (range): 115 µg/m^3 (10-385) High short-term peaks up to 13500 µg/m^3 HDI-BT HDI: 1.0 µg/m^3	**Symptoms** (interview by a nurse, standardised questionnaire): Eye, nose throat irritation more frequent in car painters and car platers than in controls, significant for platers only.	
(Wang et al., 1988)	Cross-sectional 1985 Taiwan n = 34, mostly females (38 of 45 workers had complete data, 4 were excluded because of smoking history) Follow-up (5 months after recommendations for improvement of worker protection by the study team)	TDI Velcro-like tape manufacture	Average length of employment 9.2 months Air samples, mean: weaving (n = 3) 12 ppb Packaging/storage (n = 3) 21 ppb Tape processing (n = 15) 47 ppb Highest concentration measured: 236 ppb 5 months after improvement: 7 of 9 air samples < 7 ppb at the processing area	**Lung function** (spirometry in the morning, during a usual working day, after 10 days holiday,5 months after improvement of the workplace): Lung function of n = 21 workers after 10 days holiday: Greatest changes in pre- and post-exposure FEV1 and FVC for workers in the processing areas **Asthma** or asthmatic bronchitis (defined by development of cough for more than 1 month and shortness of breath or wheezing for 1 month after working in the factory): 14 workers met the case definition of asthma or asthmatic bronchitis. Overall prevalence of asthma = 14/34 = 41.2 % Significant trend in asthma frequency across the three exposure areas (0 % asthma cases in weaving, 37.5 % in packaging/storage, 84.6 % in tape processing).	No unexposed control group Difficult to distinguish between irritant and allergic reactions Reversibility may be due to irritant effect and due to short exposure duration. High turnover rate

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Follow up (5 months): No asthmatic symptoms. Lung function significantly improved (FEV_1 and FVC) for 10 workers still employed.	
(Olsen et al., 1989)	Cross-sectional Dow, Texas, USA n = 57 manufacturing workers (85 % participated) n = 89 unexposed workers (89 % participated)	TDI Manufactureoperations	Average TDI plant experience 4.1 years (< 1 – 9 years) Routine industrial hygiene measurements: TWA < 5 ppb, short-term exposure level 20 ppb for routine plant processes Use of self-contained breathing apparatus for breaking into lines for employees. Potential exposure was ranked by an industrial hygienist: None, low, moderate, high	**Lung function** (spirometer, after at least two days away from work, standing or sitting, without the use of nose clips): TDI exposure (classified as current, highest, cumulative, cumulative highest-to-date) not associated with decline in FEV_1 **Respiratory symptoms** (questionnaire): Prevalence of upper respiratory symptoms 68 % in nonexposed group, 34 % in exposed group Prevalence of lower symptoms 33 % in nonexposed group, 17 % in exposed group	No individual exposure levels Age, height, smoking considered in regression analysis Exposure misclassification possible, because rankings were applied to jobs regardless of calendar time
(Parker et al., 1991)	Cross-sectional Minnesota, USA n = 39 randomly selected autobody repair shops (out of 139 contacted shops 59 were eligible)	TDI, MDI Autobody repair	Mean number of years in autobody industry 11.4 ± 9.7 Isocyanate samples from 32 shops 8-h TWA total isocyanates: not detected to 60 ppb, mean 5 ppb	**Lung function** (spirometry at the start and the end of the work day): Abnormal lung function (< 5th percentile) in 8 % (FEV1, FVC) and 23 % (FEV1/FVC) of never smokers. No significant change in lung function between morning and afternoon shifts. Working-years in the autobody industry, nonfunctioning spray booth, smoking were	No individual exposure levels Exposure to dust, solvents

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 162 workers (160 males)		Four percent of workers who spray painted at least one hour/week never used a respirator, 33 % sometimes, 63 % always.	associated with a decrement in FEV1/ FVC (regression analysis). No relationship between shop isocyanate concentration and lung function. **Respiratory symptoms** (self-administered questionnaire): Significant increase of wheezing across categories of respirator use (always, sometimes, never) while spray painting and for coughing and wheezing while sandblasting for non-smokers. No trends for respiratory symptoms and respirator use while sanding.	
(Huang et al., 1991)	Cross-sectional 1988-1989 Asia n = 48 workers (25 males) in three factories: Factory A n = 15 Factory B n = 29 Factory C n = 13 n = 18 controls (9 males)	TDI Furniture manufacture factories; painters exposed to TDI aerosol while brushing PU varnish to the surfaces of wood furniture	Area sampling at five spots Day mean exposure calculated from four measurements taken one, three, five, seven hours after the start of the work shift Marcali method Mean (range): Factory A: 0.79 mg/m^3 (0.49-1.18) Factory B:	**Lung function** parameters (spirometry): Impairment of some lung function parameters significant in workers of factories A and B compared to the control group. **Symptoms** of the respiratory tract, skin, eyes (structured questionnaire administrated by occupational physicians): Prevalence of symptoms was significantly higher in factory A as well as in factory B compared to the control group. No significant difference was detected between workers in factory C compared to the control group. Symptoms of the eyes, nose, throat in all workers in factory A, 60 % in factory B. No	Cited in Diller Exposure measured only on one day and not on an individual level High exposure levels make it difficult to differentiate between irritant and allergic reactions. No information on potential differences in PSA between the factories. Medical history, smoking habits, duration of exposure, weight, height, age was assessed.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			0.31 mg/m^3 (0.22-0.89) Factory C: 0.11 mg/m^3 (0.07-0.24) Aerosol Dermal exposure likely (at least in factories A and B)	symptoms of the eyes in factory C and in the control group, 11 to 15 % reported symptoms of the nose or throat. **Asthma-like symptoms** (dyspnea and wheezing during work): 4 workers (26.7 %) in factory A 3 workers in factory B (15 %) no subject in factory C and of the control group. **Patch test** (0.1 % TDI): Positive patch test in 5 and 2 painters in factories A and B (including three and two workers with contact dermatitis, respectively) and no subject in factory C or the control group. **Mast cell degranulation test**: Significantly higher mast cell degranulation percentage (MCDP) in painters from factories A and B than for the controls (specific to TDI-OA conjugates). No significantly higher MCDP in painters in factory C compared to the control group.	All subjects had no history of respiratory or skin diseases.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Omae et al., 1992)	Cross-sectional (4-year follow up see) 1981 Japan n = 90 workers (male) n = 44 reference workers in the same factories	TDI PU foam manufacture	Working in PU foam factories for 0.5-25 years, mean 13.3 129 personal samples: arithmetic mean: 3.2 ppb geometric mean: ppb 90th percentile: 8.4 ppb maximum: 26 ppb Short-term exposure peaks > 20 ppb in 16/129 samples	**Lung function**, change over working day (3 methods: forced expiratory flow-volume test, respiratory impedance, airway resistance and specific airway conductance): No significant differences in lung function between PU foam workers and referents, except for lower PEF and %PEF in the exposed group. No change of lung function during work shift in both groups. **Symptoms** (questionnaire with interview): Significantly higher prevalence of respiratory symptoms, nasal symptoms, eye symptoms in the exposed workers.	Exposure to tertiary amines, organic tin compounds, polyols, silicon oil, dichloromethane, freons, flame-resisting agents, pigments etc. Possibly a survivor population Current smoking did not affect the results
(Lee and Phoon, 1992)	Cross-sectional n = 26 exposed workers ("mixers") n = 26 controls (workshop maintenance and field staff from government departments), matched by age, race, smoking state	TDI PU foam manufacture	24 personal breathing zone samples: Mean: 0.16 ppm Range: 0.01 – 0.50 ppm	**Lung function**: Mean diurnal variation in PEFR (in one week period): Significantly higher diurnal variation in PEFR in mixers than in controls. FEV_1/FVC significantly lower in exposed (83.0 %) than in controls (89.3 %) Mixers with ten or more years of exposure showed evidence of chronic airways obstruction. **Respiratory symptoms** (questionnaire): About 50 % of mixers had eye irritation or cough during work (significant higher prevalence than in controls). No overt cases of OA	Cited in High exposure level Survivor population

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Bernstein et al., 1993b)	Cross-sectional 1991 n = 243 (n = 175 males) 3-year old plant	MDI Urethane mould plant that had been designed to minimise exposure to MDI	Average duration of employment: 18.2 months (range: 0-32 months) Continuous monitoring of MDI area levels: < 5 ppb Occasional spills reported by workers, but not detected by monitors	Methods: Workers with at least one lower respiratory symptom (questionnaire) and workers with specific antibodies were instructed to perform serial PEFR studies for two weeks (n = 43). PEFR studies were also done in 23 control subjects (no symptoms, no antibodies). Workers with PEFR variability were evaluated by a physician (including methacholine test) for final diagnosis of OA/non-OA. Workers who were assigned final diagnosis of OA/non-OA/work-related urticaria were reevaluated in 1992 (n = 6). Results: PEFR variability detected in 3/9 workers with questionnaire diagnosis of OA, in 2/4 workers with non-OA, in 2/23 control workers without symptoms. Three cases of physician diagnosed OA (3/234, prevalence ca. 1 %) and two cases of physician diagnosed non-OA. Two workers had specific IgE and IgG to MDI-HSA. One of those had urticaria. Cases are considered to be due to intermittent higher than normal exposures to MDI during non-routine working activities.	No unexposed control group

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				Cases were removed from exposure. After 1 year clinical status of OA was described as "inactive".	
(Kim et al., 1997)	Cross-sectional Korea n = 81 workers (41 males)	TDI Spray painters Workshops manufacturing furniture or musical instruments or repairing motor vehicles	Area samples (n = 41) Range 0.5 – 10 ppb Mean 3.5 ± 2.3 ppb Four samples (9.8 %) > 5 ppb	Examinations: Respiratory symptoms (questionnaires and interviews), Chest auscultation, IgE, IgG, FVC, FEV_1 Diagnosis of **TDI OA** was made if there was a decrease of PEFR over 20 % of baseline and if the changing pattern was closely related to workshift. PEFR was recorded in the following cases: Subject complained of sputum, cough, and dyspnea aggravated by work Wheezing audible by auscultation FVC or FEV_{10} < 80 % of the normal Korean reference value Positive IgE RAST for TDI PEFR was checked for 15 workers. Eight workers (9.9 %) were diagnosed with TDI-OA.	Cited in No control group No individual exposure data
(Ulvestad et al., 1999)	Cross-sectional Norway? n = 19 injection workers (previous tunnel workers who were grouped	MDI monomer and prepolymer Sealing work in tunnels	Job-years; mean (range): injection workers: 21 (1-42) tunnel workers: 13 (1-46) MDI monomer (personal sampling, 20 samples):	Examinations: Respiratory symptoms (questionnaire), lung function (spirometry), IgE (TDI, MDI, formaldehyde, eight common allergens), Metacholine provocation test, Clinical examination Higher prevalence of respiratory symptoms, airflow obstruction, BHR, asthma in injection workers compared to other tunnel workers.	No exposure measurements available from the years the "injection department" had existed → most common exposure situations for workers during the last ten years were simulated. No individual exposure data

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	into a department set up for sealing work; exposed to PU and acrylic resins; all the workers employed in this department in 1996 were included) n = 104 other tunnel workers, 6 different sites		mostly below the LOD (< 1 µg/m^3); 1.9 and 3.0 µg/m^3 at 2 occasions where isocyanate resin was spilled during injection work Pre-polymer: n = 4 shift samples: 5.5 – 300 µg/m^3 (median 7.1); n = 18 short-term exposure values: 18-4300 (median 103) µg/m^3 Stationary sampling (n = 6): monomer < 4 µg/m^3, prepolymer < 4 - 31 µg/m^3	Two TDI-HSA-specific IgE positive injection workers (with work-related respiratory symptoms)	Workers had not been informed about health hazards of the chemicals they worked with and did not report any use of airway protection. Exposure to acrylic resins Previous exposure to TDI Underestimation of exposure possible Years in the same job and smoking status were considered in the regression model
(Daftarian et al., 2000)	Cross-sectional United States 114 (39%) of the 290 workers of a plant producing flexible polyurethane foam cushions for automobile seats surveyed by NIOSH in 1999	Monomeric form of a mixture of 2,4- and 2,6-isomers of TDI	Individuals: Total TDI 0.08 – 8.07 µg/m^3 (mean 1.61). By job title: Total TDI means from 0.25 (forklift operators) to 2.75 µg/m^3 (demold workers)	Examinations: Respiratory symptoms (questionnaire), serial PEFR measurement (59 workers), serum TDI specific IgE and IgG, skin patch (TDI, MDI, HDI, IPDI, PPD), TDA in end of shift urine. 22% (25/114) met a questionnaire-based case definition of asthma and 18% (20/114) the case definition of work-related asthma. 42% (25/59) of showed airway hyperrresponsiveness. Of the 100 individuals providing blood for antibody testing, two had an elevated TDI-specific IgG antibody level, and none had an elevated TDI-specific IgE antibody level. Of	Only 39% of workers participated in the survey

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
				the 26 individuals participating in skin patch testing, none developed skin reactions to any of the test allergens either 48 or 96 hours after patch test application. Statistically significant correlations were found between total TDI exposure and both uncorrected (r=0.30, p=0.007) and creatinine-corrected (r=0.35, p=0.002) urine TDA levels.	
(Jang et al., 2000)	Cross-sectional Korea n = 64 randomly selected workers n = 27 controls (23 males)	TDI (n = 44) MDI (n = 20) Petrochem-ical plant Manufacture	60 personal breathing zone samples Sampling during manufacture, sampling time 30-60 min Mean (maximum): TDI 17.4 µg/m^3 (42.9 µg/m^3) MDI µg/m^3 (6.4 µg/m^3)	Airway hyperresponsiveness (AHR) (definition: PC20 FEV_1 < 16 mg/mL of methacholine; continuous index of bronchial responsiveness: BRindex): Prevalence of AHR higher in MDI-exposed workers (4/20; 20 %) than in TDI-exposed workers (2/42; 5 %) and in controls (read from Figure: 2/27; 7 %). Significantly higher BRindex in MDI-exposed workers than in controls, but not significantly higher than in TDI-exposed workers. Differences statistically significant?	No individual exposure measurements Medication, work history, atopy, smoking was assessed by questionnaire
(Schweiger t et al., 2002)	Cross-sectional Ontario, Canada n = 41 (isocyanate exposure, medium solvent category)	HDI (polymeric, < 0.1 % monomeric) Automobile paint manufacture	Four summary exposure categories Personal sampling: HDI monomer: 0.1 – 0.6 ppb Polymeric isocyanate: < 0.01 ppb	**Lung function** (performed at least every 2 years, data taken from medical charts): Significant negative correlation between total years of solvent exposure and FEV_1 and FVC. No correlation of smoking status and FEV_1 and FVC. No differences in lung function between the two isocyanate exposure categories (yes/no)	Survivor effect possible (less physically conditioned workers move to an area where no respirators have to be worn) Smoking status classification may have resulted in a bias towards the null

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	n = 153 (no isocyanate exposure, three categories of solvent exposure: low solvent n = 6 medium solvent n = 92 high solvent n = 55			in the workers with medium solvent exposure. **Respiratory symptoms** were not assessed. However, no respiratory illnesses have been reported.	
(Kakooei et al., 2006)	Cross-sectional Iran n = 39 employees in an automobile manufacturing company n = 117 unexposed employees at other work stations	MDI Window fixation, window glue processes	Personal samples Average concentration of MDI: Window fixation 34.53 µg/m^3 Window glue workplaces 27.37 µg/m^3	**Lung function**: %FEV1/FVC, %PEF significantly smaller in the exposed group than in the control group. **Respiratory symptoms** (questionnaire): Skin, respiratory, eye, mental symptoms significantly more prevalent in the exposed group. Respiratory, eye, mental symptoms significantly more prevalent in workers exposed to higher concentrations compared to lower concentrations than the mean value of 31.22 µg/m^3. Respiratory symptoms increased with the duration of service. However, symptoms not significantly correlated to years or intensity of exposure.	Occupational health and hygiene problems due to missing application of adequate engineering controls and proper safe work practice. This can cause great exposure to air pollutants. Study was conducted in the summer. Higher exposure levels in the winter likely, because windows are kept closed then. No significant differences between the two groups in age, height, duration of service. However, duration of service was shorter in the exposed group. No information on smoking.
(Littorin et al., 2007)	Cross-sectional	TDI or TDI-based PU	Median personal 8h exposure to TDI (ppb):	**Respiratory and eye symptoms** (structured interview, physical examination):	Symptoms may have been caused by combined exposures.

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	Southern Sweden n = 136 exposed to TDI in eleven plants n = 118 unexposed workers from different activities	MDI used in 4/5 moulding plants (low or non-detectable). IPDI used in 1 of these plants. 5 moulding plants, 2 continous-foaming plants, 2 flame-lamination plants, 2 plants with low heating or non-heating processes	continuous-foaming: 0.63-4.0 flame lamination: 0.76-1.5 molding: 0.17-0.64 low heating or nonheating processes: 0.02-0.05 Individual airborne exposure: measured during one shift (n = 79 workers), estimated based on department, task, air measurements (n = 57). Biomonitoring: 2,4-TDA and 2,6-TDA Urine: LOD – 623 and 353 noml/L Plasma: LOD-254 and 509 nmol/L Correlations between air measurements and biomarkers in urine as well as biomarkers in plasma. Biomarkers in urine and plasma also correlated. Skin exposure certainly present	Comparison between exposed and unexposed group: Total symptoms: significant increase in symptoms of the lower airways, nose bleeding (as the only nose symptom investigated), eye symptoms for the exposed group. Work-related symptoms: strong associations with exposure, in particular for attacks of eye symptoms (OR = 10), "wheezing etc" (OR = 21) and dry cough (OR = 11). Continuous measure of exposure within the exposed cohort: Only eye symptoms significantly associated with exposure measures (air, plasma, urine; OR from 1.6 to 4.2) Effect of 2,4-TDI on the eyes was more pronounced compared to 2,6-TDI No clear patterns for other exposure-response relationships.	Coexposures: dusts, other diisocyanates, organic solvents, thermal degradation products of ready-made PU in flame lamination plants (mix of mono-and diisocyanates, aminoisocyanates, amines) High number of workers with airway symptoms is seen as remarkable by authors, because of the selected workforce. However, no dose-response relationship with TDI. Individual airborne exposure was measured for a part of the workers only. Logistic regression model included age, gender, smoking. Atopy was considered. Preemployment health examinations should lead to a selected workforce in the Swedish PU industry (rather healthy concerning airway disease).

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
(Lofstedt et al., 2009)	Cross-sectional, shift 2001 4 Swedish foundries n = 64 foundry workers n = 134 controls n = 10 persons in the exposed group (14 %) declined to participate n = 59 of the invited referents (31 %) declined to participate	Isocyanic acid, methyl isocyanate, formalde-hyde Hot box binder technique (to produce cores for hollow castings)	Individual exposure measured on the same day as lung function ICA and MIC: measured in 4-5 randomly selected intermittent short-term samples (5 min) from the shift Formaldehyde: full shift sample Geometric mean: ICA: 24 µg/m^3 MIC: 4.9 µg/m^3 Formaldehyde: 120 µg/m^3	**Lung function** before and after a day shift: Both groups had reduced lung function before shift compared to reference values. Lung function decrease (VC and FEV1) over shift was significantly greater among exposed workers than in referents. No significant effects of IC, MIC, formaldehyde, smoking during day on lung function change. **Respiratory symptoms** (questionnaire): Higher prevalence of 6 out of 8 symptoms in exposed group than in referents, but for most symptoms difference was not significant. Ocular irritation and coughing without infection significantly more prevalent among exposed workers, especially coremakers.	Follow up: Löfstedt et al. 2011 Coexposures Findings not related to current exposure → other irritants in the foundry might be the cause Swedish legislation is aimed at preventing asthmatics from working in such environments Non-participating rate higher in referents → overrepresentation of referents with symptoms → underestimation of risk Tendency to overreport symptoms possible Selective loss of exposed symptomatic individuals possible
(Pourabedian et al., 2010)	Cross-sectional, shift Iran n = 43 car painters (healthy on enrolment) exclusion criteria: respiratory disorders including asthma, cigarette	HDI Car body paint shop	Mean daily exposure: 15 minutes Mean daily HDI TWA air concentration in the breathing zone: 0.42 ± 0.1 mg/m^3 Mean weekly HDI TWA: 0.13±0.059 mg/m^3	**Lung function**: Variation in PEF (peak flow meter, before and after the shift, over one week): Mean peak flow at the end of the shift on painting day was significantly lower than at the start of the shift 72 % of the workers had >10 % variation in PEF on painting days Effects of exposure remained till the day after painting	High exposure levels No unexposed control group Questions concerning statistical analysis/ reporting of results Organic solutions

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
	smoking, use of respiratory drugs			Significant difference between the two days Significant correlation between HDI and percentage of decrease in peak flow as well as mean peak flow on painting day	
(Hathaway et al., 2014)	Cross-sectional Southern USA n = 73 employed in 2011 in 2 plants (71 males, 1 female, 1 unknown) Participation rate > 80 %	Plant 1: Manufacture of HDI, IPDI, H12MDI and their polyisocyanates Plant 2: Manufacture of HDI polyisocyanates from HDI	Duration of work not determined (12 years on average in previous study) Industrial hygiene monitoring (2007-2012): Airborne HDI monomer, respirator worn (n = 33 samples): Nondetectable n = 14 ≥ 5 ppb n = 3 Airborne HDI monomer, respirator not worn (n = 100 samples): Nondetectable n = 60 all samples < 2 ppb Airborne IPDI and H12MDI: all samples < 2 ppb Authors think it likely that exposure was ≥ 5 ppb for at least some of the reported instances	No cases of **OA** identified (more detailed respiratory medical history questionnaire than in) Accidental unprotected inhalation and skin exposures (questionnaire included questions concerning detection of odor, being in the vicinity of leak or spill, unprotected skin exposure): 15 persons answered one or more of the questions on respiratory symptoms with "yes".	Follow up of No control group No individual exposure assessment Some employees indicated that they noted a characteristic irritation (mostly eye irritation) Detection of odor and skin exposure self-reported and odor subjective Smaller percentage of workers with chronic cough, wheezing and smaller percentage of smokers than in control groups in other studies Healthy worker effect possible (Self-selection)

Reference	Study design and subjects	Isocyanate and use	Exposure	Results	Remarks
			when odors of HDI were reported.		
ctd.			Detection of odor: HDI: n = 68 (93 %) IPDI: n = 32 (76 % of those working with IPDI) Work in vicinity of leak/spill: HDI: n = 62 IPDI: n = 31 Unprotected skin contact reported [more than 15 times]: HDI monomer: n = 39 (53 %) [n = 6] HDI polyisocyanates: n = 27 (37 %) [n = 5] Estimations: Odor: once per 4 years per employee leak/spill: once per 5-6 years unprotected skin exposure: once every 4-5 years		