Di- and triisocyanates

Health-based recommendation on occupational exposure limits

To: the State Secretary of Social Affairs en Employment
No. 2018/20, The Hague, November 28, 2018

Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad een gezondheidskundige advieswaarde afgeleid voor de beroepsmatige blootstelling aan isocyanaten. Dit advies is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de commissie is te vinden achter in dit advies.

Isocyanaten: risico op astma in diverse typen industrie

Diisocyanaten en triisocyanaten (hierna aangeduid als isocyanaten) zijn stoffen die bij inademing kunnen leiden tot allergische klachten aan de luchtwegen, waaronder astma. Isocyanaten zijn uitgangsmaterialen voor polyurethaan (PUR), dat onder meer wordt toegepast in vernissen, lakken, schuim en kleefmiddelen. Deze producten worden onder meer gebruikt in de bouw, de automobielindustrie, de scheepsbouw, de verfindustrie, bij de productie van plastics en bij de productie van elektronica. Werknemers die met dit soort producten werken kunnen te maken krijgen met blootstelling aan isocyanaten, meestal in de vorm van gassen of dampen die ze inademen. Ook kan blootstelling plaatsvinden via de huid.

Gezondheidskundige advieswaarde op basis van 1% extra risico

Aan een allergische reactie op een stof gaat sensibilisatie vooraf: het moment waarop het immuunsysteem in verhoogde staat van paraatheid raakt, maar er nog geen of nauwelijks klachten optreden. Voor allergenen die mensen inademen is het in het algemeen niet mogelijk een concentratie vast te stellen waaronder sensibilisatie niet optreedt. Om voor dergelijke stoffen toch een grenswaarde te kunnen bepalen, heeft de minister van SZW een risiconiveau vastgesteld van 1% extra risico op sensibilisatie door beroepsmatige blootstelling. Dit betekent eenvoudig uitgelegd: als in de algemene bevolking 2 op de 100 mensen gesensibiliseerd zijn, is het streven om het aantal op de werkvloer te beperken tot 3 op de 100. Om tot een gezondheidskundige advieswaarde te komen schat de commissie welke concentratie van de stof in de lucht overeenkomt met het risiconiveau van 1%.

Blootstelling en effecten meten

Er is nog veel onduidelijk over de manier(en) waarop isocyanaten tot allergische klachten van de luchtwegen kunnen leiden. Het is waarschijnlijk dat sensibilisatie niet alleen plaatsvindt na inademing, maar ook na blootstelling van de huid. Duidelijk is dat de reactieve groepen met de chemische formule NCO – die aanwezig zijn in alle isocyanaten – een rol spelen. Dit advies gaat over

isocyanaten met 2 of 3 NCO-groepen (diisocyanaten of triisocyanaten). De concentratie isocyanaat in de lucht wordt in dit advies uitgedrukt in µg NCO per m^3. Er zijn verschillende gevalideerde methoden beschikbaar voor het meten van het gehalte aan NCO in de lucht.

Of mensen zijn blootgesteld aan isocyanaten, kan bepaald worden door het meten van afbraakproducten in het bloed en de urine. Voor de meest gebruikte isocyanaten zijn gevalideerde methoden voor het meten van deze afbraak beschikbaar.

Vaak kan sensibilisatie betrouwbaar vastgesteld worden door het meten van antilichamen die mensen ontwikkelen. Bij veel werknemers die astma hebben gekregen na blootstelling aan isocyanaten, zijn geen specifieke antilichamen gemeten. Voor dit advies heeft de commissie daarom gekeken naar de nadelige effecten op de luchtwegen die na sensibilisatie door isocyanaten kunnen optreden.

Geraadpleegde onderzoeken

Er is onderzoek gedaan naar effecten van isocyanaten na inademing bij dieren en mensen. Voor het afleiden van een gezondheidskundige advieswaarde gebruikt de commissie bij voorkeur onderzoek bij mensen.

Om een gezondheidskundige advieswaarde zo betrouwbaar mogelijk af te leiden heeft de commissie gegevens nodig over het optreden van effecten bij meerdere concentraties. Zo kan er een blootstellingsresponsrelatie worden vastgesteld, op basis waarvan een concentratie kan worden afgeleid die overeenkomt met een extra risico van 1% op het optreden van effecten op de luchtwegen.

Bronchiale hyperreactiviteit (BHR) is een overmatige reactie van de luchtwegen die kenmerkend is voor (beroeps)astma.
De commissie is van mening dat onderzoeken naar BHR voor isocyanaten het meest informatief zijn om het optreden van beroepsastma in te schatten. BHR is in enkele onderzoeken meegenomen. Bij één daarvan, bij autospuiters die zijn blootgesteld aan hexamethyleendi-isocyanaat (HDI), is een blootstellings-responsrelatie beschreven.
Op basis van de gegevens uit dit onderzoek heeft de commissie een concentratie van 0,10 µg NCO/m^3 afgeleid, die overeenkomst met 1% extra risico op het optreden van nadelige effecten op de luchtwegen (in dit geval BHR).

Een ander onderzoek dat een blootstellingsresponsrelatie beschrijft betreft werknemers in productiefaciliteiten voor tolueendi-isocyanaten (TDI) en klachten die

overeenkomen met beroepsastma. Uit die gegevens leidt de commissie af dat een concentratie van 0,14 µg NCO/m^3 overeenkomt met 1% extra risico op het optreden van nadelige effecten op de luchtwegen (in dit geval klachten die overeenkomen met beroepsastma).

Uitgaande van beschikbare onderzoeken bij de mens komt de commissie tot een gezondheids-kundige advieswaarde van 0,1 µg NCO/m^3, als een gemiddelde concentratie over een achturige werkdag.

Notatie voor huidopname

Omdat huidblootstelling ook kan bijdragen aan het ontwikkelen van allergische klachten, adviseert de commissie om een notatie voor huidopname (H-aanduiding) te hanteren.

Advies aan de staatssecretaris

Voor de beroepsmatige blootstelling aan di- en triisocyanaten komt de commissie tot een gezondheidskundige advieswaarde van 0,1 µg NCO/m^3, als een gemiddelde concentratie over een achturige werkdag. Bij deze concentratie hebben werkenden ten opzichte van de algemene bevolking 1% extra risico op het ontwikkelen van BHR, ten gevolge van blootstelling aan isocyanaten. Verder adviseert de commissie voor di- en triisocyanaten een H-aanduiding toe te passen.

executive summary

At the request of the Ministry of Social Affairs and Employment, the Health Council of the Netherlands has derived a health-based advisory value for isocyanates. This advisory report has been prepared by the Dutch Expert Committee on Occupational Safety (DECOS). More information on the tasks of this permanent committee of the Health Council of the Netherlands can be found at www.gezondheidsraad.nl. The members of the Committee are listed on the last page of this report.

Isocyanates: risk of asthma in various types of industry

Diisocyanates and triisocyanates (further referred to as isocyanates) are substances that can cause allergic complaints of the airways when inhaled. Isocyanates are starting materials for polyurethane, which is used in different products including varnishes, lacquers, foams, and adhesives. These products are being used among others in construction work, automobile industry, shipbuilding industry, paints industry, and in the production of plastics and electronics. Workers using these types of products might be exposed to isocyanates, usually as gasses or vapours. Exposure can also occur via the skin.

Advisory value based on 1% extra risk

A chemical-induced allergic reaction is preceded by sensitisation: the moment the immune system is triggered, yet no (significant) complaints occur. For inhaled allergens it is generally not possible to derive a concentration below which no sensitisation occurs. For the purpose of setting an exposure limit for these kind of substances, the Minister of Social Affairs and Employment has set a risk level of 1% extra risk of sensitisation due to occupational exposure. Simply explained, this means: if in the general population 2 out of 100 people are sensitised, the target level is to limit the number in the workplace to 3 out of 100. For its recommendation, the Committee estimates which concentration of the substance corresponds to a risk level of 1%.

Measuring exposure and effects

Much is unclear about the mechanism(s) by which isocyanates cause allergic complaints of the airways. It is likely that sensitisation can not only occur after inhalation, but also after exposure of the skin. It is clear that the reactive NCO-groups – present in all isocyanates – play a role. This advisory report deals with isocyanates with 2 or 3 NCO-groups (diisocyanates or triisocyanates). In this report, the isocyanate concentration in the air is expressed as µg NCO per m^3. Different validated methods are available to determine NCO-levels in the air.

Whether people have been exposed to isocyanates can be determined by measuring breakdown products in the blood or urine. For the most widely used isocyanates, validated

methods for measuring these breakdown products are available.

Often, sensitisation can be reliably determined by measuring antibodies that people produce. In many workers who developed asthma after exposure to isocyanates, however, no specific antibodies were detected. The Commitee has therefore focussed on the adverse effects on the airways that can occur after sensitisation to isocyanates.

Consulted research

Both animal studies and studies relating to humans on the effects of isocyanates after inhalation are available. The Committee prefers the use of data on humans.

To derive an advisory value most reliably, the Committee requires information on the occurrence of effects at multiple exposure concentrations. Then, an exposure-response relationship can be established, which is the basis of deriving a concentration that corresponds with an extra risk of 1% for occurrence of adverse effects of the airways.

Bronchial hyperreactivity (BHR) is an excessive bronchial narrowing that is characteristic for (occupational) asthma. The Committee is of the opinion that studies on BHR are most informative for the estimation of the occurrence of occupational asthma due to exposure to isocyanates. Few studies on occupational exposure to isocyanates have addressed BHR. For one of those studies, on car spray painters who have been exposed to hexamethylene diisocyanate (HDI), an exposure-response relationship has been derived. Based on data from this study, the Committee calculated an exposure concentration of 0.10 µg NCO/m^3, corresponding with a 1% extra risk of adverse effects on the airways (in this case BHR).

Another study that provides information on an exposure-response relationship involves workers in production facilities exposed to toluene di-isocyanate (TDI) and complaints that are consistent with occupational asthma. From these data the Committee derived a concentration of 0.14 µg/m^3, corresponding to a 1% extra risk of adverse effects of the airways (in this case complaints consistent with occupational asthma).

Based on the available data on humans, the Committee recommends a risk-based advisory values of 0.1 µg NCO/m^3, as a mean concentration during an 8h-working day.

Notation for skin absorption

Because skin exposure can contribute to the development of respiratory allergic complaints, the Committee recommends to apply a skin notation.

Advice to the State Secretary

For occupational exposure to di- and triisocyanates, the Committee derives a health-based advisory value of 0.1 µg NCO/m^3, as a mean concentration during an 8-h working day. At this concentration, workers have an extra risk

of 1% of bronchial hyperreactivity (BHR), compared to the general population. Because skin exposure can contribute significantly to the development of respiratory allergic complaints, the Committee recommends to apply a skin notation for di- and triisocyanates.

01 scope

1.1 Background

At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of substances that are used in the workplace. The purpose of these evaluations is to recommend health-based occupational exposure limits, which specify levels of exposure to airborne substances, at or below which it may be reasonably expected that there is no risk of adverse health effects. For respiratory allergens, it is generally not possible to derive a concentration below which no sensitisation occurs. In those cases, the Health Council calculates a risk-based advisory value: the concentration at which the extra risk of sensitisation by occupational exposure is limited to 1%.

This advisory report contains an evaluation of the health hazard of di- and triisocyanates and a derivation of a health-based advisory value.

1.2 Committee and procedure

The present document contains an evaluation of the DECOS, hereafter called the Committee. The members of the Committee are listed at the end of this report.

During preparation and elaboration of this evaluation, scientific exchanges took place with members of the Expert Committee on occupational exposure limits and the Metrology working group of the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). The sections addressing isocyanates to be considered, French existing guidelines and standards, EU classification and labelling, measurement methods, description of the mechanism of action (especially the immunologic effects) and the exposure-response modelling for the risk calculation were reviewed, and commented on, by the ANSES experts.

In 2017, the president of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the report. These comments, and the reply by the Committee can be found on the website of the Health Council.

1.3 Data

The Committee's recommendation for di- and triisocyanates is based on scientific data, which are publicly available. Published literature was retrieved from the on-line databases Medline and Toxline, using a search with the terms ("isocyanat*" and "tox*"). Subsequent searches were performed using the terms ("isocyanat*" and "asthma") and ("isocyanat*" and "lung"). Additional relevant literature was also retrieved using review documents. The relevance of the retrieved literature was subsequently determined based on title and abstract. Only literature was used that includes quantitative data on both isocyanate exposure and the occurrence of respiratory health effects. The final search was carried out in November 2017.

02 identity,properties and monitoring

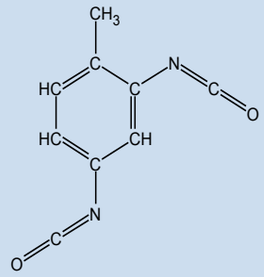
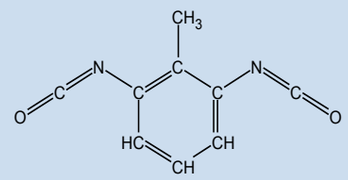
2.1 Identity and physico-chemical properties

Isocyanates are organic compounds that contain one or more functional groups with the molecular formula R–N=C=O. The term polyisocyanate is commonly used when referring to an isocyanate containing multiple isocyanate functional groups. In this document, the Committee applies the general term ‘isocyanate’, and refers to isocyanates that possess either 2 (diisocyanates) or 3 (triisocyanates) functional groups. Monoisocyanates are not subject of this report.

Isocyanates used in the workplace exist in different chemical and physical forms. The most common group of isocyanates are diisocyanates, which are primarily used as monomers for the production of polyurethanes (PUR) and polyisocyanurates (PIR). To reduce the inhalation hazard, prepolymer (isocyanates reacted with polyol) and polyisocyanate (monomeric isocyanates linked either directly or by reacting with alcohols or amines) forms with a lower vapour pressure have been developed.

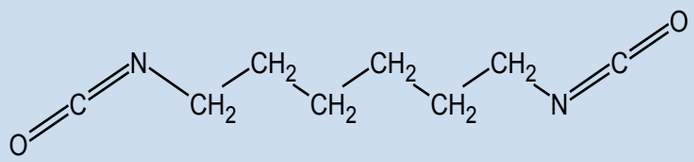
Most data available relate to the group of diisocyanates, in particular its prototype toluene diisocyanate (TDI) (commercially available as mixtures of 2,4- and 2,6-TDI isomers and as pure 2,4-TDI). Other widely used isocyanates are hexamethylene diisocyanate (HDI), methylene diphenyl diisocyanate (MDI), naphthalene diisocyanate (NDI), and isophorone diisocyanate (IPDI).

Toluene diisocyanate (TDI)

Name	:	2,4-Toluene diisocyanate and 2,6-toluene diisocyanate	
CAS number	:	584-84-9 (2,4-isomer) and 91-08-7 (2,6-isomer); most common commercial mixture (80:20): 26471-62-5	
Synonyms	:	TDI; 2,4-TDI and 2,6-TDI; 2,4- and 2,6-diisocyanatotoluene; 4- and 2-methyl-m-phenylene diisocyanate	
Use	:	TDI is an intermediate used in manufacturing flexible polyurethane (PUR) foams, surface coatings, cast elastomers, sealants, and adhesives.	
Molecular weight	:	174.2	
Molecular formula	:	$C_9H_6N_2O_2$	
Physical state	:	Liquid	
Solubility	;	Hydrolytically unstable	
Structure	:	2,4-toluene diisocyanate 	2,6-toluene diisocyanate 
Density	:	1.22 g/cm^3 (25°C)	
Vapour pressure	:	2.7 Pa (25°C)	
		2,4- TDI	80:20 mixture 2,4-TDI and 2,6-TDI
Melting point	:	21°C	12.5-13.5°C
Flash point	:	135°C	132°C
Conversion factor	:	1 ppm = 7.1 mg/m^3	

Hexamethylene diisocyanate (HDI)

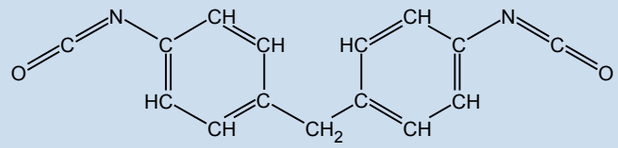
Name	:	Hexamethylene diisocyanate
CAS number	:	822-06-0
EC number	:	212-485-8
Synonyms	:	1,6-diisocyanatohexane (IUPAC); Hexane, 1,6-diisocyanato- (CA-Index name); Hexamethylen-1,6-diisocyanat

Use	:	One of the main uses of HDI is as a polymerising agent in polyurethane spray paint formulations and coatings (e.g., automobile paint). HDI is also used in the preparation of dental materials, contact lenses, and medical adsorbents.
Molecular weight	:	168.2
Molecular formula	:	$C_8H_{12}N_2O_2$
Physical state	:	HDI is a clear, colourless organic liquid with pungent odour
Solubility	:	Hydrolytically unstable
Structure	:	
Density	:	1.05 g/cm³ (20°C)
Vapour pressure	:	0.07 hPa (20°C)
Melting point	:	ca. -67 °C
Flash point	:	130 °C
Conversion factor	:	1 ppm = 6.9 mg/m³

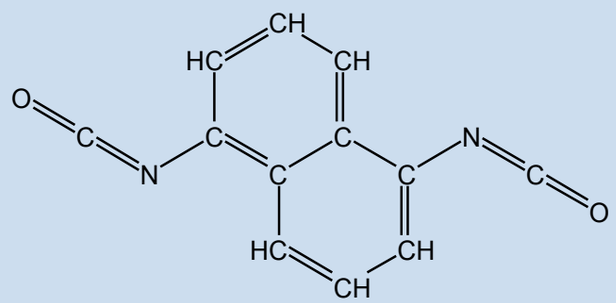
Methylene diphenyl diisocyanate[a] (MDI)

Name	:	4,4'-Methylenediphenyl diisocyanate
CAS number	:	101-68-8
EC number	:	202-966-0
Synonyms	:	1,1'-Methylenebis(4-isocyanatobenzene) (IUPAC)
Use	:	Pure MDI is distilled from the reaction mixture and is mainly used for reaction injection-moulding, thermoplastic elastomers and adhesives. PMDI is primarily to make rigid and semi-rigid polyurethane foams.
Molecular weight	:	250.3
Molecular formula	:	$C_{15}H_{10}N_2O_2$
Physical state	:	Crystalline solid
Solubility	:	Hydrolytically unstable

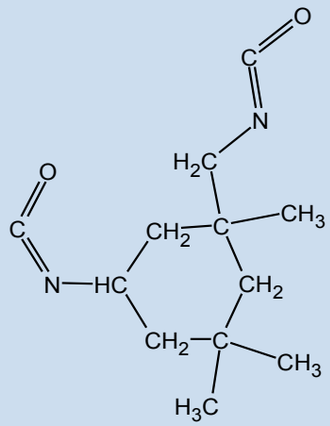
[a] MDI is the generic name of a product used in industrial settings. Polymeric MDI (PMDI), the primary technical/ commercial form of MDI, is actually a mixture that contains 25-80% monomeric 4,4'-MDI as well as oligomers containing 3-6 rings and other minor isomers, such as the 2,2'-isomer (CAS 2536-05-2) and 2,4' ísomer (CAS 5873-54-1).

Name	:	4,4'-Methylenediphenyl diisocyanate
Structure	:	
Density	:	1.23 g/cm³
Vapour pressure	:	0.00049 Pa (20°C)
Melting point	:	The melting range of 4,4'-MDI is 39 - 43°C.
Flash point	:	211°C at 1000 hPa
Conversion factor	:	1 ppm = 10.2 mg/m³

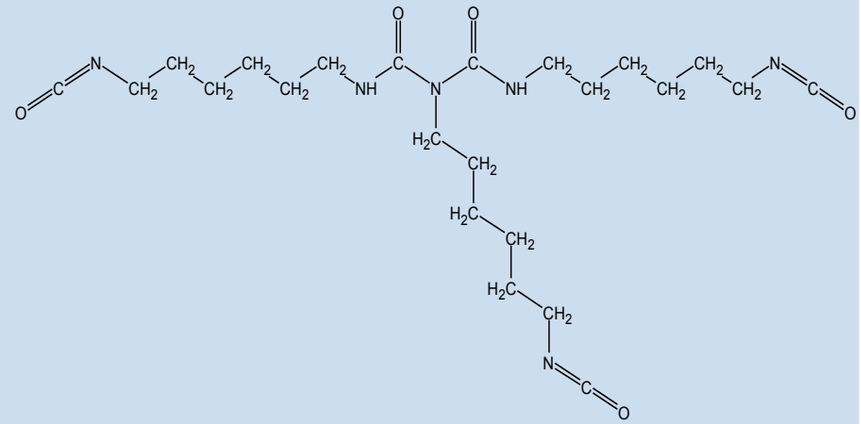
Naphthalene diisocyanate (NDI)

Name	:	1,5-Naphthylene diisocyanate
CAS number	:	3173-72-6
EC number	:	221-641-4
Synonyms	:	1,5-diisocyanatonaphthalene (IUPAC)
Use	:	Mainly used in the automotive industry[1]
Molecular weight	:	210.2
Molecular formula	:	$C_{12}H_6N_2O_2$
Physical state	:	solid
Solubility	:	Hydrolytically unstable
Structure	:	
Density	:	1.42 g/cm³
Vapour pressure	:	0.000008 hPa at 25 °C
Melting point	:	130-132°C
Flash point	:	192°C
Conversion factor	:	1 ppm = 8.6 mg/m³

Isophorone diisocyanate (IPDI)

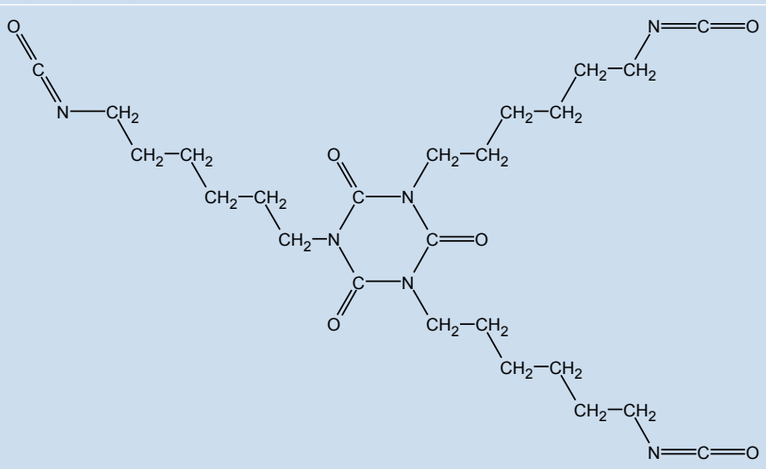
(EC) Name	:	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
CAS number	:	4098-71-9
EC number	:	223-861-6
Synonyms	:	5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane (IUPAC)
Use	:	Yields polyurethanes with high stability, resistance to light discoloration, and chemical resistance; raw material for polyurethane paints, varnishes and elastomers; Industrial coating applications.
Molecular weight	:	222.3
Molecular formula	:	$C_{12}H_{18}N_2O_2$
Physical state	:	Colourless to slightly yellow liquid
Solubility	:	Hydrolytically unstable
Structure	:	
Density	:	1.058 g/cm³ at 20 °C
Vapour pressure	:	0.000635 hPa at 20 °C
Melting point	:	Approximately -60°C
Flash point	:	150.5 °C at 1013 hPa
Conversion factor	:	1 ppm = 9.1 mg/m³

HDI biuret[a]

(EC) Name	:	1,3-Bis(6-isocyanatohexyl)-1-(6-isocyanatohexylcarbamoyl)urea
CAS number	:	4035-89-6
EC number	:	223-718-8
Synonyms	:	HDI-BT, tris(isocyanatohexyl)biuret, tris(6-isocyanatohexyl) biuret, hexamethylene diisocyanate biuret
Use	:	HDI biuret is used as replacement substance for monomeric HDI in coatings.
Molecular weight	:	478.6
Molecular formula	:	$C_{23}H_{38}N_6O_5$
Physical state	:	thick liquid
Solubility	:	Hydrolytically unstable
Structure	:	
Density	:	1.114
Vapour pressure	:	Extremely low
Melting point	:	-19°C
Flash point	:	169.5 °C at 1013 hPa
Conversion factor	:	1 ppm = 19.6 mg/m³

[a] https://www.osha.gov/chemicaldata/; http://www.chemicalregister.com/HEXAMETHYLENE_DIISOCYANATE_BIURET/Suppliers/pid295958.htm [accessed November 8, 2018]

HDI trimer isocyanurate[a]

Name	1,3,5-tris(6-isocyanatohexyl)-1,3,5-triazinane-2,4,6-trione
CAS number	3779-63-3
EC number	223-242-0
Synonyms	(2,4,6-trioxotriazine-1,3,5(2H,4H,6H)-triyl) tris(hexamethylene) isocyanate, 1,3,5-Tris(6-isocyanatohexyl)-1,3,5-triazine- 2,4,6-(1H,3H,5H)-trione; Hexamethylene diisocyanate cyclic trimer; Hexamethylene diisocyanate isocyanurate
Use	HDI trimer isocyanurate is used as replacement substance for monomeric HDI in coatings.
Molecular weight	504,6
Molecular formula	$C_{24}H_{36}N_6O_6$
Physical state	Clear, slightly yellow liquid (lower viscosity grade) Most commercial products contain various amounts of higher oligomers. These products have higher viscosity and also a functionality of >3. Commercial products may also contain asymmetric isocyanurate structures.
Solubility	Hydrolytically unstable
Structure	
Density	1,12 at 25°C
Vapour pressure	Extremely low
Melting point	From -150 °C up to 450 °C no melting point of could be observed.
Flash point	228 °C (HDI oligomers)
Conversion factor	1 ppm = 20.6 mg/m^3

Data on the identities and physico-chemical properties are derived from several sources.[2-5]

[a] http://www.wernerblank.com/polyur/chemistry/isocyanate/cas3779633.htm

Exposure metrics for isocyanates

The common exposure metric for recommendations on occupational exposure limits applied by the Committee is [mg total substance/m^3]. In literature, also the metric [mL/m^3] (reported as parts per million (ppm) or parts per billion (ppb) by volume) is often used for gases and vapours, including isocyanates. Chemically, isocyanates are characterised by the presence of [NCO] groups. These reactive groups have been mechanistically linked to the sensitising properties of isocyanates (see Chapter Mechanism of action). The exposure metric [µg NCO/m^3] has been considered as a practical metric for regulatory purposes for different types of isocyanates, including mixtures.[6] In the UK, Switzerland, and Australia, occupational exposure limits have been established on NCO-mass basis.

In sections relevant for deriving an advisory value, the Committee will specify the exposure levels both as values reported in the literature as well as in the metric [µg NCO/m^3]. For the calculation of the [NCO mass/ volume air] metric the following formulas are used:

µg [isocyanate]/m^3 = ppb (v/v) x [total molecular weight]/24.45[b]

µg [NCO]/m^3 = µg [isocyanate]/m^3 x [molecular weight NCO-groups/[total molecular weight]

[b] The number 24.45 in the equations above is the volume (liters) of a mole (gram molecular weight) of a gas or vapour when the pressure is at 1 atmosphere (760 mm Hg) and at 25°C.

2.2 EU classification and labelling

	TDI (both isomers and mixture)	HDI	MDI	NDI	IPDI
Irritation	Eye Irrit. 2 (H319) Skin Irrit. 2 (H315)	Eye Irrit. 2 (H319) Skin Irrit. 2 (H315)	Eye Irrit. 2 (H319) Skin Irrit. 2 (H315)	Eye Irrit. 2 (H319) Skin Irrit. 2 (H315)	Eye Irrit. 2 (H319) Skin Irrit. 2 (H315)
Acute toxicity	Acute Tox. 2 (H330)	Acute Tox. 3 (H331)	Acute Tox. 4 (H332)	Acute Tox. 4 (H332)	Acute Tox. 3 (H331)
Specific Target Organ Systemic Toxicity	STOT SE 3 (H335)	STOT SE 3 (H335)	STOT SE 3 (H335) STOT RE 2 (H373)	STOT SE 3 (H335)	STOT SE 3 (H335)
Sensitisation	Resp. Sens. 1 (H334) Skin Sens. 1 (H317)	Resp. Sens. 1 (H334) Skin Sens. 1 (H317)	Resp. Sens. 1 (H334) Skin Sens. 1 (H317)	Resp. Sens. 1 (H334)	Resp. Sens. 1 (H334) Skin Sens. 1 (H317)
Carcinogenicity	Carc. 2 (H351)	-	Carc. 2 (H351)	-	
Mutagenicity	-	-	-	-	
Reproduction toxicity	-	-	-	-	

H315: causes skin irritation; H317: May cause an allergic skin reaction; H319: causes serious eye irritation; H330: Fatal if inhaled; H331: Toxic if inhaled; H332: Harmful if inhaled; H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled; H335: may cause respiratory irritation; H351: Suspected of causing cancer; H373: May cause damage to organs through prolonged or repeated exposure.

2.3 Measurement methods

The measurement of isocyanates in air is challenging, with respect to both sampling and analysis. Workers can be exposed to mixtures of (multiple) isocyanate-containing vapours and aerosols, and isocyanate-containing intermediates or by-products. Low molecular weight isocyanates tend to volatilize at room temperature, whereas exposure to prepolymer and polyisocyanate forms primarily occurs after aerosolisation (e.g. spraying) or heating.

For the assessment of the total isocyanate exposure, all these forms should be taken into account. A number of measurement methods and techniques are available for sampling and analysing isocyanates in workplace atmospheres.[7,8] Most of these methods are based on the derivatisation of the reactive NCO-groups to products that can be analysed, usually by some form of chromatography. Given the complexity of accurate sampling and analysis of the total amount of isocyanate groups in air, all existing methods have some limitations. For details on the measurement methods, the Committee refers to the respective guidelines.

Sampling methods

The first critical point for the measurement of isocyanates is the choice of the most appropriate sampler apparatus. Depending on the different conditions of exposure to isocyanates (e.g. temperature, presence of vapours, and aerosols of different sizes), specific sampling methods are preferred.

Impingers are usually efficient to sample aerosols but particles less than 2 µm in diameter can pass through them. Impregnated glass fibre filters are efficient to collect particles of widely varying sizes and vapours:

- The fibre filters impregnated with a derivatising reagent can be used to sample vapours, slow-reacting aerosols (typically aliphatic isocyanate systems), and isocyanate aerosols consisting of particles with a diameter < 2 µm
- The impingers can be used to sample aromatic isocyanates aerosols with particles diameter > 2 µm
- The combination of impinger plus filter can be used to sample vapours and aerosols of aliphatic or aromatic isocyanates with sizes ranging from < 2 µm to > 2 µm in diameter.

However, fast-reacting isocyanate aerosols, such as MDI-based spray foam insulation, should not be collected with an impregnated filter because the necessary derivatisation reaction is inefficient and the measurement of isocyanate will underestimate the actual exposure.

Derivatisation

Upon collection, isocyanates are derivatised to stabilise the compounds, and to improve detection by increasing sensitivity and selectivity. The derivatising agent used depends on the nature of the type of isocyanate to be measured.

Analytical methods

After sampling, filter samples need to be extracted. If the filter was used for collecting isocyanate aerosols, the extraction should take place in the field immediately after sampling. If the filter was used for collecting isocyanate vapours only, the extraction can take place at the laboratory performing the analysis. All samples need to be transferred to an HPLC-compatible solvent. Reversed-phase HPLC is the main separation method. Pure analytical standards are available for monomers, but not for the vast majority of oligomeric isocyanates species, and qualitative standards do not account for isocyanates species generated during process. Various methods for measuring total NCO, NCO monomers and specific isocyanate monomers and oligomers in air are summarised in the tables below.

Methods for the measurement of NCO

Sampler		Derivatising agent	Analysis	Guideline
Impinger + Glass fibre filter impregnated	Impinger: 1,2-methoxyphenyl-piperazine (1,2-mpp) in toluene Glass fibre filter impregnated with 1,2-mpp	1,2 mpp	HPLC/UV or Electrochemical	ISO 16702 (2008) MDHS 25/4 (2011)
	Impinger: Dibutylamine in toluene Glass fibre filter impregnated with dibutylamine	dibutylamine	HPLC/MS	ISO 17734-1 (2013)
	Impinger: 1-(9-anthracenyl-methyl)piperazine (MAP) in butyl benzoate Glass fibre filter impregnated with MAP	MAP	HPLC/UV and fluorescence	ISO 17735 (2009) NIOSH 5525 (2003)
Closed cassette + filter PTFE + glass fiber filter	glass fiber filter impregnated with 9-methylaminomethyl) anthracene (MAMA) The PTFE filter is PLACED in a glass jar containing a solution of 1,2 mpp in toluene immediately after sampling	MAMA + 1,2 mpp	HPLC/UV or fluorescence	ISO 17736 (2010)
Closed cassette + 2 glass fibre filters impreg-nated	2 glass fibre filters impreg-nated with 1,2-mpp	1,2 mpp	HPLC/UV or electrochemical	IFA 7670 (2004)

Methods for the measurement of NCO monomers

Sampler + derivatising agent		Analysis	Guideline
Quartz fibre filter impreg-nated	Quartz fibre filter impregnated with 1-(2-pyridyl)piperazine (1-2PP) or 1,2-mpp	HPLC/UV or fluorescence	INRS MétroPol 004 (2003); OSHA PV 2125, PV 2092, PV 2046, PV 2034, PV 2030; OSHA 42; OSHA 47; MAK Diisocyanate (2006)
Impinger	1,2-mpp in toluene	HPLC/UV or Electrochem-ical	NIOSH 5521 (1994)
	tryptamine in DMSO	HPLC/fluorescence or Electrochemical	NIOSH 5522 (1998)
	1,2-mpp in xylene	HPLC/UV	INRS MétroPol 004 (2003)

Methods for the measurement of specific monomers in air.

Monomer	Sampler + derivatising agent	Analysis	Guideline
TDI	Open cassette + 2 glass fibre filters impregnated with 1-2PP	HPLC/UV and/or Fluorescence	ISO 14382 (2012)
MDI, TDI, HDI	Impinger + 1,2 mpp in toluene	HPLC/UV and/or electrochemical	INSHT MTA/MA-034/ A95 (1995)
MDI, TDI, IPDI, NDI	Bubbler with N[(4-nitro-phenyl)methyl] propylamine in toluene	HPLC/UV	OSHA 18 (1980)
TDI, HDI, MDI, IPDI, NDI	tube with N[(4-nitro-phenyl)methyl] propylamine on glass wool	HPLC/UV	NIOSH 2535 (1994) IFA 7120 (2012?)

03 sources

Isocyanates are the raw materials for all polyurethane products, which are formed if an isocyanate reacts with a polyol (a compound with more than one hydroxyl group). In addition to their use in the manufacturing of polyurethane foam, isocyanates are used in surface coatings (paints), adhesives and textiles. During the use of these products occupational exposure can occur, particularly in processes involving heating and spraying isocyanates.

Worldwide production and consumption of isocyanates continues to increase, predominantly MDI and TDI. In the last 10 years annual isocyanate production has been doubled to $9x10^6$ tonnes, and is expected to increase to $12x10^6$ tonnes in 2020.[9] This increase can be attributed to a great expansion of the Asian-Pacific market, whereas the US and Europe's isocyanate production rates are expected to remain steady.[10]

04 exposure

4.1 General population

People can be exposed to isocyanates indirectly, through the use of products containing isocyanates. The increasing use of isocyanate-containing products have raised awareness of potential health effects in the general population.[9] Exposure to isocyanates can occur during, and after the use of urethane foam for insulating purposes.

4.2 Working population

Isocyanates are used worldwide in a number of important industries, in which occupational exposure can occur. Aliphatic isocyanates (e.g. HDI polymers) are mainly present in external coatings and paints whereas aromatic isocyanates (e.g. MDI and TDI) are used in the production of numerous products such as flexible and rigid foams, adhesives and sealants.[10]

Industries in which isocyanates are used, include:[8]

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

In numerous epidemiological studies the exposure levels in occupational conditions have been assessed. These studies, including the reported exposure levels, are summarised in Chapter 7.

05 kinetics

A number of studies have investigated the uptake, distribution, and excretion of isocyanates, both in experimental animal models and relating to humans exposed under occupational settings. Most of these studies addressed the toxicokinetic behaviour of TDI MDI, or HDI. The Committee provides a concise summary, with an emphasis on inhalation exposure, based on review documents.[10-12]

5.1 Absorption

The Committee notes that with respect to dermal absorption, TDI is reported to penetrate into the outer skin layer, where after it is transformed into conjugates or metabolites.

During inhalation exposure, isocyanates are absorbed via the respiratory tract. In various studies with volunteers and workers, absorption of TDI after inhalation exposure was evident given the occurrence of metabolites in the urine. In a study with 5 volunteers exposed to 40 µg/m^3 of TDI (30:70 mixture of the 2,4- and 2,6-isomer) for 7.5 hours in a test chamber, inhaled doses of approximately 120 µg were estimated, which resulted in TDI plasma levels of 2.2-2.4 µg/L at 8 and 24 hours.

Absorption of isocyanates in animals after inhalation has been determined by radioisotopic tracing studies with ^{14}C-labeled isocyanates. In general, the initial uptake kinetics of isocyanates during exposure appear to be linear. In rats and guinea pigs, a plateau has been reported around 150 min of exposure to TDI. Absorbed fractions of 2-4% of the total TDI dose have been reported in rats, and in guinea pigs exposed to HDI for one hour, maximum blood levels were observed at 2-4 hours after cessation of exposure.

5.2 Distribution

In plasma of exposed workers, TDI is primarily bound to albumin. Binding to macromolecules in the blood and to haemoglobin has also been observed. Clinically, retained HDI has been shown to bind to keratin-18 (in the bronchial epithelium) and albumin (in the fluid that lines the airway epithelium). In a clinical study with both healthy volunteers and asthmatics exposed for HDI for at least 4 minutes, respiratory retention of 60% and 91% was reported.

Inhalation studies in rats and guinea pigs have shown that absorbed MDI and TDI are broadly distributed in the plasma, primarily conjugated with albumin. TDI binds also to other macromolecules in the plasma and to haemoglobin, as found in humans as well. For TDI, fractions of 74-98% and 99.7% of the absorbed radioactivity were found in the blood of rats and guinea pigs, respectively. In rats, the highest concentrations have been found in stomach and small intestine whereas other investigators reported the highest accumulation in the respiratory tract in rats and guinea pigs.

5.3 Metabolism

Isocyanates are very reactive compounds, and it is therefore likely that isocyanates react with tissues with which they come into contact, rather than being absorbed and distributed as free isocyanate molecules. Different metabolites can be generated, dependent on the route of exposure.

The major metabolites of TDI in both animals and humans are toluene diamines (TDA) and their acetylated products. In 11 workers at two flexible foam polyurethane production plants chronically exposed to 0.4-4 µg/m^3 or 10-120 µg/m^3 TDI, varying 2,4- and 2,6-TDA levels (0.4-24 ng/mL in urine; 1-29 ng/mL in plasma) were measured dependent on exposure levels and the time since the last exposure. In workers exposed to an average concentration of 29.8 µg/m^3 TDI, plasma TDA concentrations varied between 1 and 38 µg/L and between 7 and 24 µg/L for the 2,4- and 2,6-isomers. Plasma concentration reached a maximum about 24 hours after the last exposure. The half-time of plasma toluene diamines in the volunteer was about 10 days. Hexamethylene diamine (HDA) has been demonstrated in the urine of persons exposed to HDI.

In a comparative study in rats, 90% of the quantified urine TDI metabolites were conjugates after inhalation exposure, whereas 65% was conjugated after oral exposure. No free TDA and only small amounts of acetylated TDA were detected after inhalation exposure. MDI has been reported to form mono or bis-conjugates with GSH.

5.4 Elimination

Isocyanate metabolites are excreted primarily via the faeces and urine. Urinary elimination has been reported to follow a biphasic pattern. A pool of isocyanate-conjugated albumin persists in the circulatory system.

In volunteers exposed to 40 µg/m^3 of a 30:70 mixture of 2,4- and 2,6-TDI for 7.5 hours, urinary elimination of the toluene diamines showed a biphasic pattern, with rapid first phases (mean half-lives 1.9 and 1.6 h for the 2,4- and 2,6-isomers, respectively). In another study, with 2 volunteers exposed to ca 25, 50 and 70 µg/m^{3,} half-lives of 2-5 hours in the first phase and > 6 days in the second phase were determined. In workers exposed chronically, the half-life in urine ranged from 5.8 to 11 days for 2,4- and 2,6-TDA, respectively. In volunteers first exposed to 0.012, after 2 days to 0.020 and after a further 2 days to 0.022 mg/m^3 HDI (for 2 hours each), an average 39% of the estimated absorbed quantity of HDI was eliminated via the urine within 7 days after the first exposure, based on hexamethylene diamine determination. The elimination half-life of HDA in the urine was determined to be 2.5 hours.

Also in animals, a biphasic elimination has been observed. Excretion following inhalation has been reported to differ from the excretion following exposure by other routes. In rats, 81%, 8% and 4% of the radioactivity was found in the faeces, urine and tissue/carcass/gastrointestinal tract contents, respectively, after an oral dose of 60 mg TDI/kg bw. Following

inhalation exposure of 14.2 mg TDI/m^3, corresponding fractions of 47%, 15% and 34% were recovered.

5.5 Biological monitoring

Biological monitoring of exposure to isocyanates is based on the analysis of isocyanate-derived diamines released by hydrolysis of protein adducts in urine or plasma (reviewed by Cocker, 2011)[13]. The non-invasive measurement in urine is preferred, however, the half-lives of the dominant diamines in urine are relatively short (i.e. in the range of 2-5 hours) and samples should be collected soon after the end of an exposure period and subsequently results mostly reflect exposure on the day of collection. The determination of exposures of longer periods can be done by measuring plasma adducts, as these have longer half-lives (20-25 days).
Biological monitoring methods are available for the most common isocyanates HDI, TDI, IPDI, and MDI.[13] These methods differ in hydrolysis procedures, internal standards, and extraction and derivatisation methods. However, all the isocyanate-derived diamines in urine can be detected in a single gas chromatography-mass spectrometry method. Its limit of detection has been reported to be in the range of 1 nmol/L (equivalent to 0.1 µmol diamine/mol creatinine) with coefficients of variation for within and between day analyses of 5 and 12%, respectively.[14]

Where urine analysis is performed, the following values can be used as a guide for assessing exposure:

Biological Level	Source
1 µmol of isocyanate-derived diamine/mol creatinine in urine	NSW Workcover Biological Occupational Exposure Limit
10 µg methylene dianiline (MDA)/L (~4 µmol MDA/mol creatinine) in urine	German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area Biologischer Leit-Wert (BLW) value

However, it should be noted that biomonitoring methods for isocyanates to date do not provide reliable values.[15] Therefore, it is recommended that for isocyanates biological limit values are only used as biological indicators.

Only in a fraction of workers suffering from isocyanate-induced asthma, sensitisation can be determined by the skin prick test or by in vitro tests for specific IgE antibodies circulating in the blood (biological effect monitoring). This fraction decreases consistent with a half-life of approximately 6 months when exposure is ceased, until serum IgE levels drop to levels which are undetectable by conventional assays.[16] Skin prick tests resulting in a wheal diameter of at least 3 mm larger than the negative control after 15 minutes are usually considered positive for sensitisation. Conventionally, serum concentrations of IgE antibodies to isocyanates are determined by an in vitro immunoassay.[17]

IgG, which has a longer half-life than IgE, has been suggested as a potential biomarker for long-term exposure. It is, however, unclear whether IgG plays a biological role in isocyanate-induced allergy.

06
mechanism of action

Data on the most widely used isocyanates (e.g. TDI, MDI and HDI) indicate that all these substances are irritating and can cause sensitisation in humans. Also, immunological cross-reactivity between isocyanates has been observed.[18] This suggests that isocyanates share at least a common mechanism of action. This chapter is based primarily on data derived from studies on TDI. The Committee considers subsequent implications applicable to the whole group of isocyanates.

In vivo and in vitro studies with TDI vapor show that the majority of inhaled TDI is rapidly detectable in blood and tissues as biomolecular conjugates, by reaction with nucleophilic sites such as the NH_2 group of proteins.[19,20] TDI is one of the main agents responsible for occupational asthma.

TDI-induced asthma appears clinically as classical asthma with inflammation, bronchoconstriction and mucus hypersecretion. As in any occupational asthma, the only effective treatment is the removal from exposure; however even after the withdrawal, people may have persistent asthma symptoms. For example, it has been reported that 6 months after avoidance of exposure to TDI, some patients presented a persistent inflammatory cell infiltrate as well as a non-specific airway hyperreactivity although a decrease of their reticular basement membrane thickening was evident.[21] TDI-induced asthma develops with a variable latency period ranging from a few months to several years after exposure.[22] The asthmatic response may be immediate (<1 hour), delayed (2 to 4 hours later), or both immediate and delayed, and can occur after exposure to low concentrations of isocyanates.[23]

TDI-induced allergic asthma has been reported to occur following exposures to low concentrations of TDI, around 0.36 mg/m^3) and once sensitised, lower levels can trigger asthmatic responses.[24] After exposure to high concentrations, asthma can also be linked to the irritating effects of isocyanates. Indeed, TDI has irritating effects occurring without latency period from 3.6 mg/m^3) (acute toxicity[25]) in the form of non-specific bronchial hyperresponsiveness due to the induction of epithelial cell inflammation by direct tissue injury.[26] Some individuals might become sensitised following a single exposure of this type.[27,28]

The pathogenic mechanisms responsible for the asthmatic response to TDI remain poorly understood; a single mode of action appears unlikely. A number of observations suggests an immunological mechanism for respiratory sensitisation to TDI, i.e. the latency period between the first contact and the occurrence of the asthmatic response, the low incidence compared to the number of exposed subjects (5 to 10% of workers), the similarity of the symptoms observed in TDI-induced asthma with those triggered by inhaled allergens and the presence of IgE in the serum of subjects with pulmonary sensitisation.[29] However, there are differences between classical pulmonary immunological sensitisation mediated by IgE and sensitisation to TDI. For instance, in subjects diagnosed for

TDI-induced asthma, atypical responses to bronchial challenge tests (including delayed responses[30,31]) and an inability to detect specific IgE are observed.[32] The limited success of IgE detection in cases of TDI-induced sensitisation could be due to the lack of information about the structures of the complexes formed.[29] These complexes are not clearly identified (potential binding to albumin, laminin or proteins of the cell membrane), hence there is lack of information about the antibodies formed against these conjugates. Also alternative mechanisms not involving IgE may provide an explanation for the inability to detect specific IgE.[33] Improper diagnosis of sensitisation as a cause for the inability to detect IgE has also been reported: of 75 subjects positively diagnosed by questionnaire, less than half responded to the challenge with high molecular weight allergens.[29]

The mechanistic hypothesis held to explain the pulmonary sensitisation to TDI is the following: TDI behaves as a chemically reactive hapten through its NCO-groups that covalently binds to self-proteins that are captured by immature dendritic airway cells. After maturation, dendritic cells migrate to the nodes to present TDI conjugates to naive T lymphocytes and then polarize them towards suitable Th1 or Th2 differentiation pathway in response to the reactive hapten[18], that initiates immune responses, associated with airway inflammation and asthma. A predominance of Th2 response has been reported with IL-4, IL-5 and IL-13 secretion supporting an humoral immune response leading to the production of specific IgE,[34,35] usually associated with conventional respiratory type I hypersensitivity. The development of delayed reactions and chronic symptoms associated with TDI-induced asthma, and the fact that atopy is not a recognized risk factor for TDI-induced asthma, point at the involvement of other immunologic pathways such as a type IV hypersensitivity reaction. CD8+ T-cells secreting Th1 cytokines such as IFNg has been reported,[36] in addition to CD8+ T-cells producing IL-5.[37] These cytokines are then able to recruit and activate inflammatory cells such as neutrophils and eosinophils[38-41] that secrete in turn inflammatory mediators responsible for the asthmatic response.

Immunologic cross-reactivity has been observed between several isocyanates.[42-45] For example, it is known that all the residues of the albumin targeted by isocyanates to which MDI binds are analogous to those of TDI.[46] However, a recent study reports the absence of cross-reactivity between MDI and TDI in a mouse model of isocyanate-induced asthma.[47] As indicated above, different mechanisms eventually leading to occupational asthmatic responses may be evident simultaneously, i.e. humoral (IgE-dependent) and cellular (delayed-type) responses, respectively. Generally, cellular immune responses dependent on T-cells have a more restricted specificity than humoral responses. The observation that some responses show cross reactivity while other responses do not, underscores that different mechanisms may be operational at the same time. Possibly, these mechanisms may not follow

similar dose-response relationships. It is not known whether putative cellular responses in humans are also more specific as opposed to the cross-reactive humoral responses, nor is it known what is the relative contribution of cellular immune responses to occupational asthma in humans.

Direct pharmacological mechanisms responsible for the TDI-induced asthma have also been reported on the bronchi. Indeed, an inhibitory action of TDI on acetylcholinesterase in the bronchial tissue could play a role in the development of bronchoconstriction[48-50], as well as an effect on the beta adrenergic system.[51] However, the relevance for TDI-induced allergic asthma of these mechanisms, observed at relatively high exposure levels, is unclear. Finally, genetic factors such as genotype of genes involved in the major histocompatibility complex, of glutathione S-transferase or N-acetyltransferase may predispose to the development of isocyanate-induced occupational asthma according to the involved phenotype.[52]

All these mechanisms show that the TDI-induced respiratory sensitisation leading to the development of occupational asthma is the result of more complex mechanisms than those observed in conventional respiratory sensitisation.

The role of dermal exposure to TDI in respiratory allergy is under debate. In workers exposed to products containing TDI, rare cases of skin sensitisation in the form of contact dermatitis or allergic urticaria have been reported.[53] A recent study of the dermal penetration of TDI in rats reports an absorption in the form of protein adducts to less than 1%.[54] In mice, it has been shown that topical application of TDI was responsible for an increased Th2 response with IgE production[55], whereas a Th1 response with an increased IFNg secretion was demonstrated in another dermal exposure model.[56] It has also been shown in mice that TDI dermal application followed by intranasal exposure influences allergic sensitisation to TDI[57] and induces a local and systemic Th2 response[34]. In this mouse model, an important role of B-lymphocytes without major involvement of IgE and without help from T-lymphocytes has also been described.[58,59] In humans, the link between skin sensitisation and the occurrence of TDI-induced respiratory sensitisation remains unresolved. Because of the skin exposure in workplaces where isocyanates are used or produced[60], concerns have been raised about skin exposure as a potential route of allergic sensitisation that could possibly lead to asthma.[61] Pauluhn has proposed that TDI-induced respiratory allergy could involve two sequential mechanisms: dermal exposure leading to systemic sensitisation which, followed by inhalation exposure, would initiate and amplify allergic inflammation and progression to asthma.[54] Another recent study in mice suggests that hair follicles and their associated sebaceous glands could be a reservoir for TDI conjugated to self-proteins and its uptake into immune cells such as local dendritic cells capable of producing allergic sensitisation after presentation to T-cells in the lymph nodes.[62]

07 effects

7.1 Observations in humans

In humans, exposure to isocyanates can result in irritation of the skin, mucous membranes, eyes, and respiratory tract. The most common adverse health ‘effect however, is’ asthma due to sensitisation. Less prevalent are contact dermatitis (both irritant and allergic forms) and hypersensitivity pneumonitis/allergic alveolitis.

In view of the relevance for establishing an advisory value, the Committee will focus on the effects observed after occupational exposure by inhalation. Furthermore, the Committee has limited its review to studies in which exposures were quantified and excluded studies with exposures >100 µg NCO/m^3. These studies with high exposures are likely to report adverse effects, however do not provide a suitable starting point for deriving an advisory value.

7.1.1 Respiratory effects

Numerous studies have been conducted on occupational exposure to isocyanates and respiratory effects. The epidemiological studies are summarised below in chronological order (studies on the same cohort are summarised consecutively), the conclusions of the Committee on the epidemiological data are provided at the end of this section.

Most recently, Collins et al. (2017)[63] reported a surveillance study, for which the exposure assessment was published by Middendorf et al. (2017).[64] In this study, 197 workers in facilities producing TDI were monitored from 2007-2012. 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.[65] 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.[64] Seven cases were identified as consistent with TDI-induced asthma (0.009 per person-years). Two 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).

Collins et al. (2017)[63] provide data on an exposure-response relationship which can be used for a risk calculation. Based on the publication of Collins et al. (2017)[63], the Committee made a risk calculation for cases with (symptoms of) TDI-induced occupational asthma, and exposure to TDI (for details see Annex A). 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%.

Gui et al. (2014) conducted an inception-cohort study with 49 workers during first year of employment at a newly built modern TDI polyurethane foam factory.[66] FEV_1, FVC, asthmatic symptoms and specific IgG were evaluated pre-employment and after 6 and 12 months. Air sampling was done on 7 workers, resulting in measurements mostly below the level of detection of 0.1 ppb (0.3 µg NCO/m^3), and not exceeding 5 ppb (17 µg NCO/m^3) in any sampling period. Seven of 49 developed either new asthma symptoms (N=3), TDI-specific IgG (N=1), new airflow obstruction (N=1) and/or a decline in FEV_1≥ 15% (N=3).

Seventy-three workers in two aliphatic diisocyanate manufacturing or producing plants were surveyed using questionnaires with additional questions on exposure. (Hathaway et al., 2014)[67] At plant 1, HDI monomers and HDI polyisocyanates were the main diisocyanate products. In plant 2, HDI was used to produce HDI polyisocyanates. HDI levels reported were below 2 ppb (7 µg NCO/m^3). Levels of IPDI and H_{12}MDI (only measured in plant 2) were mostly non-detectable or ≤ 0.1 ppb (0.3 µg NCO/m^3). Although skin contact and/or detection of odour was occasionally reported, no cases of occupational asthma were identified.

In a matched retrospective cohort study, Cassidy et al. (2010) studied pulmonary function and prevalence of asthma in 57 workers of two plants manufacturing or producing 1,6-HDI monomer and/or HDI polyisocyanates, which were compared to those of 43 controls during an observation period of 19 years.[68] Air monitoring data ranged from non-detectable to 31 ppb (107 µg NCO/m^3) with a mean value of 0.78 ppb (3 µg NCO/m^3), and from non-detectable to 2 ppb (7 µg NCO/m^3) with a mean level of 0.3 ppb (1 µg NCO/m^3), in plant 1 and 2 respectively. No accelerated annual decline in FEV_1 was observed and no additional cases of adult onset asthma or occupational asthma were noted.

In two publications, Pronk et al. (2007, 2009)[69,70] reported on exposure-response relationships of respiratory symptoms and sensitisation in a large population occupationally exposed to isocyanate oligomers during spray painting. In the first study, 581 spray painters in various industries were assessed for exposure and asthmatic and COPD-like symptoms using questionnaires.[69] Also, serology was performed. Cumulative exposure ranged from 4-66,464 µg NCO/m^3*h*months (mean 3,682 µg NCO/m^3*h*months). Statistically significant associations were found for exposure and asthmatic symptoms, COPD-like symptoms, work-related chest tightness, and work-related conjunctivitis.
In a second study, 229 spray painters were assessed based on BHR, exhaled nitric oxide (eNO), lung function parameters, and serology.[70] Mean exposure was 4,530 µg NCO/m^3*h*months (range 15.4-66,464 µg NCO/m^3*h*months). Workers with higher isocyanate exposure were more often hyperresponsive. A statistically significant exposure-related decreased FEV_1, FEV_1/FVC and flow-volume parameters independent of BHR were found.

The Committee notes that the studies of Pronk et al. (2007, 2009)[69,70] provide detailed information on an exposure-response relationship, which are suitable for risk calculation. Based on the datasets of these studies,the Committee made a risk calculation for exposure to isocyanates and the prevalence of asthma, or BHR (for details see Annex A). An exposure level of 0.10 µg NCO/m^3 for 8 hours was associated with an extra risk of BHR of 1%.

In several plants in Sweden where TDI or TDI-based polyurethane was used in the manufacturing process, 136 workers and 118 unexposed employees were studied by Littorin et al. (2007) using questionnaires and registered symptoms.[71] The average exposure in the ambient air at the workplace of the exposed participants was below 1 ppb (3 µg NCO/m^3). Exposed workers reported more symptoms, particularly work-related symptoms, compared to the controls.

Respiratory symptoms and lung function were assessed in 39 employees exposed to MDI in an automobile factory and 117 controls. (Kakooei et al., 2006)[72] The reported average concentration in the window fixation, and window glue workplaces were 35 and 27 µg MDI/m^3 (12 and 9 µg NCO/m^3), respectively. Respiratory symptoms were increased and lung function was declined in the exposed group compared to the unexposed group.

A 6-year longitudinal study was conducted by Clark et al. (1998) among 780 workers at 12 polyurethane manufacturing plants in the UK, 157 of whom were newly employed and had no prior exposure to TDI.[73] TDI concentrations (8-h TWA) among all production and finishing employees averaged about 1.2 ppb (4 µg NCO/m^3). The majority of the subjects (99.4%) was exposed to concentrations below 5.8 ppb (20 µg NCO/m^3) Baseline FEV_1 was unrelated to TDI exposure group and annual decrease of FEV_1 was not associated with mean daily TDI concentration. Within the newly employed subgroup, there was a statistical association between FEV_1 decline and mean TDI concentration. However, the average annual FEV_1 decline among all new employees was unremarkable.
A cohort of 251 workers from the previous study was re-examined 17 years after the beginning of the study. (Clark et al., 2003)[74] None of the 251 subjects were reported to have been exposed to a mean daily exposure exceeding 5.8 ppb (20 µg NCO/m^3). The annual declines in FEV_1 and FVC were not related to exposure to TDI, and were typical of those measured in other populations not exposed to TDI. Over the study period the cold-foam handling group (n=26) showed an increase in breathlessness and a significant excess decline in FVC; which was not interpreted as a TDI-related effect. The exposed group (n=175) showed an increase in wheezing (mainly smokers), whilst the low-exposure group (n=50) showed a decrease in chest illness. Smoking and an increase in body weight both caused excess declines in FEV_1.

Sweigert et al. (2002) reported a cross-sectional study on workers (n=41) exposed to (primarily polymeric) HDI and non-exposed workers (n=153) in an automobile paint and coating plant.[75] The reported exposure was 0.1-0.6 ppb monomeric and <0.1 ppb polymeric HDI (0.3-2 and <0.2 µg NCO/m^3, respectively). No statistically significant relationship was found for combined isocyanate and solvent exposure and lung function.

In a longitudinal study on the development of respiratory symptoms, 305 TDI production workers of a chemical manufacturing plant in the USA were compared with 581 hydrocarbon producing workers at the same factory, who had never been employed in isocyanate processes. (Bodner et al., 2001)[76] Mean TDI exposures measured 96.9 ppb-months, or 2.3 ppb per job (8 µg NCO/m^3). At the end of the study, there were no differences in self-reported symptoms between the two groups.[76]

Meredith et al. (2000) conducted a case-referent study with cases of occupational asthma from two manufacturing companies in which exposure to either TDI (plant A) or MDI (plant B).[77] Cases mainly attributed to TDI were matched to 51 referents. Seven cases attributed to MDI in two areas of plant B, and 12 non-cases from the same areas were used as referents. Exposures were estimated from existing measurements by job category. From a matched analysis, the OR associated with 8 hour TWA exposures to isocyanates greater than the referent median exposure (1.125 ppb; 4 µg NCO/m^3) was 3.2 (95% CI 0.96 to 10.6; p=0.06).

Morgan et al. (2000) surveyed 181 workers employed in assembling and spray painting new cars using annual spirometry and questionnaires.[78] Exposure was reported not to have exceeded the exposure limit but was not further specified. According to the authors, there was no indication reported for adverse effects, as the annual decline in the FEV_1 was similar to that found in other studies.

In a cross-sectional study by Jang et al. (2000), 64 randomly selected workers at a petrochemical industrial complex exposed to TDI or MDI were compared to 27 controls using questionnaires, allergic skin test and BHR measurement.[79] Reported mean air levels were 17.4 µg TDI/m^3 and 1.3 µg MDI/m^3 (8.4 and 0.4 µg NCO/m^3, respectively). The prevalence of airway hyperresponsiveness was higher in MDI-exposed workers than in TDI-exposed workers, whereas MDI-exposed workers had higher BR-index (defined as log (% fall in FEV_1)/log (final concentration of methacholine 10)) compared to controls.

In a relatively large longitudinal survey (including 313 workers assigned to a TDI production unit and 158 matched referents), mean exposure estimates ranged from 0.5 ppb (recent) and 9.9 ppb (historical) (2 and 34 NCO/m^3, respectively). (Ott et al., 2000)[80] Annual periodic examination results were assessed in relation to these industrial hygiene estimates. Neither cross-sectional nor longitudinal analyses of FVC and FEV_1 a showed statistically significant exposure-response relationship.

One hundred fourteen workers at a foam production plant were studied using medical questionnaires, airway hyperresponsiveness, and antibody production. (Daftarian et al., 2000)[81] TDI levels were measured up to 2.75 µg/m^3 (mean) (1.3 µg NCO/m^3). Twenty-five cases of asthma were diagnosed, 20 met the definition of occupational asthma. Twenty-nine of 59 suitable peak flow participants were considered hyperresponsive; 8 of 29 had a work-related pattern.

Ulvestad et al. (1999) studied the prevalence of asthma among 19 tunnel workers exposed to synthetic resins and compared it with the prevalence in 104 non-exposed workers.[82] Levels of monomeric MDI were mostly below level of detection. Exposure of total prepolymeric MDI was estimated to be 5.5-300 µg/m^3 (median 7.1) (1.7-93 µg NCO/m^3 (median 2.2)). Exposed (injection) workers reported more respiratory symptoms and had higher BHR, asthma symptoms and airflow limitation.

Hathaway et al. (1999) matched 32 workers in a HDI biuret and trimer production plant exposed to HDI to non-exposed controls to compared lung function.[83] Mean exposure to HDI was 0.5 ppb (1.3 µg NCO/m^3); work without respirator was reported to occur for 2 hours/day. No significant exposure to HDI biuret and HDI trimer was reported. No accelerated decline in FVC or FEV_1 was observed.

Tarlo et al. (1997) identified cases of isocyanate-induced occupational asthma cases and the companies at which they worked.[84] Within a database maintained by The Ontario Ministry of Labour, these authors compared isocyanate concentrations measured at 20 case companies (with compensated claims) with 203 non-case companies, based on air samples collected during the same 4-year period during which the occupational asthma claims arose. The proportion of case companies that were ever recorded as having a measured ambient isocyanate concentration of ≥ 5 ppb (17 µg NCO/m^3) was greater than for non-case companies.

In a study reported by Kim et al. (1997), 81 spray painting workers received self-administrative questionnaires and direct interviews on respiratory symptoms.[85] Serology was also performed. TDI concentrations in the air of the workshops ranged from 0.5 to 10 ppb (2-34 µg NCO/m^3), and the mean was 3.5 ppb (12 µg NCO/m^3). PEFR results of 8 (9.9%) workers corresponded to the diagnostic criteria of TDI-related occupational asthma. A correlation was found with increased IgE and IgG levels.

Akbar-Khanzade et al. (1996) reported a short term study (5-7 urethane mould operators and 5-8 non-exposed controls) and a long term study (65 painters and mould operators 68 non-exposed workers with a 2.5 year follow up).[86] Exposures reported for the short-term study were 1.55 ppb

MDI (5 µg NCO/m^3) and 90 µg polymeric MDI/m^3 (30 µg NCO/m^3); amounting to a total NCO exposure of 35 µg NCO/m^3. No daily or weekly reduction in the subjects' pulmonary function was observed. Exposures reported for the long-term study were 1 ppb MDI (3 µg NCO/m^3), 290 µg polymeric MDI/m^3 (97 µg NCO/m^3) and 0.45 ppb MDI (1.55 µg NCO/m^3); amounting to a total NCO exposure of 102 µg NCO/m^3. These isocyanate/solvent-exposed subjects showed significant long-term reduction in their FVC and FEV_1.

Alexandersson et al. (1987) compared the lung function and asthmatic symptoms of 41 car painters exposed to isocyanates (HDI and HDI-BT) to those of 70 car mechanics and 48 car platers not exposed.[87] The estimated mean exposure of the car painters was 1 µg HDI/m^3 (0.5 µg NCO/m^3) and 115 µg HDI-BT/m^3 (25 µg NCO/m^3) (total exposure 26 µg NCO/m^3). No statistically significant differences in asthmatic symptoms and lung functions were observed between isocyanate exposed car painters and non-exposed groups. Closing volume in relation to vital capacity was increased in car painters.

In a follow up study, Tornling et al. (1990) studied 36 car painters and 115 controls.[88] The mean exposure for the car painters was 1.5 µg/m^3 HDI (1 µg NCO/m^3) and 90 µg/m^3 HDI-BT (20 µg NCO/m^3) (total exposure 21 µg NCO/m^3), frequently peak exposures were noted. A yearly reduction in FVC, FEV_1, and VC in smoking car painters vs smoking controls was reported. No differences were found for non-smoking car painters compared with their non-smoking controls.

In a reanalysis by Dahlqvist et al. (1995), the lung function was assessed from 20 workers also included previously.[89] Average exposure estimates reported were 1.4 µg/m^3 HDI and 90 µg/m^3 HDI-BT, resulting in a similar total NCO exposure. Ten out of 20 showed a decline in FVC within the week. A correlation was found between the change in FVC in a week and the long term (6-y) change.

Bernstein et al. (1993) studied 244 workers exposed to MDI in a urethane mould plant in a surveillance type of approach.[90] Exposure was monitored continuously and levels were below 5 ppb (17 µg NCO/m^3). Cases of occupational asthma were assessed and spirometry was performed for 2 weeks in 43 workers with and in 23 workers without lower respiratory symptoms. Serial peak expiratory flow rate was abnormal in 3 (33%) of 9 workers with occupational asthma, in 2 (50%) of 4 with non-occupational asthma, and in 2 (9%) of 23 case control subjects. Physician diagnosed occupational asthma in three cases, one non-exposed.

When conducting a 4 year cohort study, Omae et al. (1992) first published the results of a cross-sectional study.[91] The study population included 90 male workers who had been working in polyurethane foam factories and 44 reference workers from the same factories. The mean exposure concentration of TDI calculated from 129 personal samples was 3.2 ppb

(11 µg NCO/m^3). Pulmonary function and its change during the working day as assessed by examining the forced expiratory flow-volume curve, respiratory impedance, and airway resistance and specific airway conductance in exposed workers were not different from those in controls.

In the 4-year longitudinal study in 7 Japanese polyurethane foam manufacturing plants, Omae et al. (1992) examined pulmonary function in 57 foam workers (duration of employment 4-29 years) and 24 referents in relation to TDI exposure over a 4-year period.[92] No significant differences were observed in the average annual decline of pulmonary function between 28 workers exposed to 0.1 ppb (0.3 µg NCO/m^3; AM TWA over study period), 29 workers exposed to 5.7 ppb (AM, 20 µg NCO/m^3) and the 24 unexposed referents. However, a significantly larger decline of pulmonary function (MMF, FEV_1/FVC, FEF_{25}, FEF_{75} and PEF was found in a group of 15 workers, exposed to a mean TDI-concentration of 8.2 ppb (28 µg NCO/m^3) and those who had peak exposure excursions to ≥ 30 ppb (≥ 103 µg NCO/m^3).[91,92]

Lee and Phoon (1992) studied the diurnal variation in PEFR in 26 TDI-exposed mixers from eight factories making polyurethane foam, and 26 unexposed controls.[93] A relatively high mean exposure level of 16 ppb (55 µg NCO/m^3) was reported. The mean diurnal variation in PEFR of the mixers was significantly higher than in controls. No cases of asthma, but a high prevalence of irritative symptoms such as cough and eye irritation was reported.

Jones et al. (1992) reported a study with 394 (at the start) workers in two polyurethane foam production plants.[94] Mean TDI levels ranged from 2.37-4.11 ppb (8-14 µg NCO/m^3); 9% of measurements exceeded 5 ppb (17 µg NCO/m^3). Multiple regression analysis showed significant adverse effects of cumulative TDI exposure on initial level of FVC and FEV_1 (of current smokers), and an effect at on FEF25-75 over all smoking categories. TDI exposure however, had no significant effect on FEV slopes. Logistic regression showed that chronic bronchitis was more prevalent among those with higher cumulative exposures, after controlling for smoking, age, and sex. BHR was associated with reduced airway function.

Huang et al. (1991) studied asthmatic symptoms and lung function of painters handling polyurethane varnish in three furniture manufacturing factories with TDI exposure (48 painters and 18 referents).[95] Average air concentrations of 790, 310 and 110 µg/m^3 (381, 150, 53 µg NCO/m^3), respectively, were measured. In the two factories with the highest exposures, 26.3% and 15% of the subjects, respectively, displayed asthmatic symptoms, lung function loss, and an increment in mast cell degranulation percentage specific to TDI. No increase in these parameters was observed in the third factory.

Parker et al. (1991) surveyed 152 white male workers from 39 autobody repair shops exposed to TDI.[96] The reported concentrations for total isocyanate ranged from non-detectable to 60 ppb (206 µg NCO/m^3), a mean exposure level of 5 ppb (17 µg NCO/m^3) was noted. Abnormal lung function was noted in automobile repair shop workers, but no significant change in pulmonary function was seen between the morning and afternoon shifts. In addition, no relationship was seen between shop isocyanate levels and pulmonary function.

In a cross-sectional study by Olsen et al. (1989) among workers (n=57) in an unspecified number of TDI manufacturing plants in the USA, exposed to concentrations that were stated to have been below 5 ppb (17 µg NCO/m^3) (8-h TWA) and 20 ppb (69 µg NCO/m^3) (STEL), FEV_1 measurements were made over a 3-week period and analysed for associations with past and current exposure.[97] Comparison with the findings in a reference group of 89 unexposed workers revealed no differences. It was concluded that the routine exposure level in the plants was not associated with a decline in forced expiratory volume.

In a cross-sectional study (Wang et al., 1988) among employees of a Korean facility using a TDI-based adhesive in tape production, the overall prevalence of occupational asthma was 41% (14/34).[98] Four workers with smoking history had been excluded from analysis. The prevalence rate was 0% in a work area with a mean TDI concentration of 12 ppb (41 µg NCO/m^3), 38% in a work area with a mean concentration of 21 ppb (72 µg NCO/m^3), and 85% among employees assigned to an area with a mean concentration of 47 ppb (161 µg NCO/m^3).

Alexandersson et al. (1986) reported two separately conducted studies (1977 and 1980) with a total of 23 workers in a rubber plant exposed to NDI.[99] Control group consisted of 20 male non-exposed workers at the same factory. Mean exposure range reported was 2-7 µg/m^3 (1-3 µg NCO/m^3), most samples were taken during moulding for which a mean exposure of 7 µg/m^3 (3 µg NCO/m^3) was reported. Asthmatic symptoms were more common in exposed individuals and closing volume (% of vital capacity) was higher than in the control group. Other lung functions variables were comparable.

Musk et al. (1982) followed 107 workers in a polyurethane plastic manufacturing plant over a five-year period with measurements of FEV_1, and questionnaires on respiratory symptoms and smoking habits.[100] The majority (>90%) of the exposure measurements of TDI and MDI were below 5 ppb (17 µg NCO/m^3). The geometric mean of TDI was 1-1.5 ppb (3-5 µg NCO/m^3); MDI levels were reported to be in the range of 0.3-0.6 ppb (1-2 µg NCO/m^3) (total mean NCO exposure amounting to 6 µg/m^3). The five-year change in FEV_1 did not exceed that expected from aging. No acute change in FEV_1 could be demonstrated over the course of a Monday either before or after a two-week vacation.

In a re-evaluation, the authors confirmed their previous results.[101]
Using the same cohort, Gee and Morgan (1985) reported on the ventilatory capacity of 68 workers (42 previously also included) continuously exposed to TDI (initially) and, gradually to MDI only.[102] Twelve blue-collar workers served as controls. TDI levels ranged from 3 ppb (10 µg NCO/m^3) to 1 ppb (3 µg NCO/m^3) later in the study. The MDI concentration was estimated to be approximately 1 ppb (3 µg NCO/m^3). No significant shift decrement was noted.

Venables et al. (1985) reported a cross-sectional study on 221 workers exposed to TDI in a steel coating plant who were surveyed using questionnaires and lung function and skin prick tests.[103] Various levels were measured up to 26 ppb (89 µg NCO/m^3) during normal processing levels were measured up to 14 ppb (48 µg NCO/m^3). 9.5% of the workers had symptoms of occupational asthma. All occupationally exposed groups had lower mean FEV_1 values.

Sixty-seven workers in 7 polyurethane foam producing factories exposed to TDI and MDI, and 56 non-exposed workers were surveyed using questionnaires and lung function testing. (Alexandersson et al., 1985)[104] The reported exposures were 8 µg TDI/m^3 (4 µg NCO/m^3; mean for the whole group); and 5 µg TDI/m^3 (2 µg NCO/m^3) and 1 µg MDI/m^3 (0.3 µg NCO/m^3) (mean during casting in moulds). An increased frequency of symptoms from the airways in non-smokers was found, no association between isocyanate exposure and lung function was found.

Respiratory parameters of 95 workers from four companies exposed to TDI in foaming operations and 37 controls were compared by Holness et al. (1984)[105] Mean exposure reported was 1.54 ppb (5 µg NCO/m^3) (area) and 2.50 (9 µg NCO/m^3) (personal). Exposed workers had a slightly higher frequency of respiratory symptoms, and slightly lower baseline lung function and significantly larger decline in lung function cross-shift.

In a longitudinal study by Omae et al. (1984) among 55 production workers and 21 unexposed referents in TDI manufacturing plants, no relation was found between lung function and exposure to TDI (0.7-1 ppb) (2-3 µg NCO/m^3).[106] Prevalence rate of work-related irritation of eyes and throat was higher among workers exposed to TDI compared to the referent group, which the authors explained by co-exposure to other chemicals, e.g. phosgene.

A total of 111 workers exposed to TDI were examined for their ventilatory capacity during a work shift. (Peters et al., 1975)[107,108] Workers were divided into four groups over an exposure range of 3 ppb to 13 ppb (10-45 µg NCO/m^3). All four groups demonstrated significant declines in FEV_1, with the magnitude of decrease correlating with level of exposure.

This cohort, reduced to 63 workers, was restudied two years later. (Wegman et al., 1977)[109] Of these workers, 57 could be assigned reliable personal exposure levels for the two-year study period. Pulmonary function measurements were made again before and after work on the first day of the working week. The 57 workers were divided into three exposure subgroups (< 0-1.5; 2.0-3.0; > 3.5 ppb) (< 0-5; 7-10; > 12 µg NCO/m^3), for which a dose-response relationship was observed for FEV_1. Only those in the lowest exposure subgroup showed normal two-year declines.

Also a subsequent 4-year longitudinal of ventilatory function in the remaining cohort (n=48) revealed a dose-response relationship between average exposure to TDI and change in FEV_1. (Wegman et al., 1982)[23] Workers with mean exposure in excess of 12 µg NCO/m^3 showed a greater rate of decline of FEV_1 over the 4-year period than that expected from aging.

The respiratory health of 277 workers in a new TDI manufacturing plant was studied prospectively during 5 years of exposure. (Diem et al., 1982)[110] Longitudinal change in pulmonary function was assessed in 223 men for whom individual slopes of annual change could be constructed. Cumulative TDI exposure was dichotomised at 68.2 ppb (234 µg NCO/m^3 *months). After adjusting for pack·years of smoking, the 74 men in the high cumulative TDI exposure category had significantly larger declines in FEV, %FEV, and FEF_{25-75} than did the 149 men in the low exposure category. When stratified based on smoking habits, in never smokers, average annual decline was greater in those with higher cumulative TDI exposure. This effect was not observed in current and previous cigarette smokers.

Respiratory and immunological effects of isocyanate exposure were studied by Weil et al. (1979) in 168 workers at a TDI manufacturing facility, using questionnaires and spirometry.[111] Follow up visits and tests continued periodically for over 5 years. Mean TDI levels were categorised in ‘high’, ‘moderate’, and ‘low’, of which the moderate mean was reported to be 3.2 ppb (11 µg NCO/m^3). The values of the parameters of lung function declined, and some of the workers in the study group had evidence of sensitisation to TDI.

Butcher et al. (1977) performed a longitudinal study in a TDI manufacturing plant with a total of 113 exposed workers and 53 referents, including health questionnaire, pulmonary function, environmental monitoring, and immunological testing.[112] Personal measurements amounted up to 25 ppb. There was a significant proportion of workers who reported onset of lower respiratory symptoms after beginning work in the TDI areas. No exposure-related decline of pulmonary function was observed.

Adams (1975) conducted a 9-year prospective study of workers involved in TDI manufacturing.[113] Annual lung function tests were carried out on 180 asymptomatic workers, who were potentially exposed to TDI levels that were decreasing over time (1962: 58%; 1970: 1-2% of the samples above 20 ppb (96 µg NCO/m^3)). The relationship of the FEV_1 and FVC to the height, age, and duration of exposure was examined by linear regression analysis. No evidence was found that exposure accelerated the rate of decline.

Forty-four workers involved in the research, development and production of isocyanates were studied clinically and immunologically. (Bruckner et al., 1968)[114] Twenty-six had multiple exposures to diisocyanates, whereas 18 had never worked with or around isocyanates. Median exposure levels ranged from 1 to 77 ppb (3-265 µg NCO/m^3). Various exposed to low levels (not further specified) developed eye, mouth and throat symptoms. The authors noted an exposure range of 20-100 ppb (69-344 µg NCO/m^3) as an overall range that would result in predisposition for isocyanate sensitivity.

Evaluation of epidemiological studies

Only two studies provide data on an exposure-response relationship that can be used for a risk calculation. These studies, by Pronk et al. (2007, 2009)[69,70] and Collins et al. (2017)[63], will be further discussed in Chapter 9 'Hazard assessment'.

The majority of the remaining epidemiological studies involves measurements of lung function. The Committee notes that the timing of lung function testing is critical for obtaining reliable results on isocyanate-induced effects, as isocyanate-induced asthma involves temporary and both acute as well as delayed changes in lung function. Longitudinal analyses usually involve routine (annual) tests over several years. For a reliable assessment of chronic decline in lung function (FEV_1, FVC) a follow-up of 5-8 years is needed, given the inherent parameter variability.[115-117] Also, a relatively large population needs to be studied to be able to distinguish subtle reductions in function[118] and a linear decrease is only apparent from the age of around 30 years onwards. In this context, it is noteworthy that most studies (>70%) on chronic lung function decline with a follow-up of ≥1 year (references[68,73-76,78,80,83,92,94,100-102,106,111-113]) did not report significant adverse effects.

The epidemiological studies on isocyanate exposure and lung function have several limitations. In general, in studies on sensitising agents selection bias cannot be excluded given the likelihood that individuals that develop occupational asthma will be lost to follow-up, leading to an underestimation of risk. Also, dermal exposure and subsequent sensitisation via the skin can generally not be excluded. Other limitations relate to exposure assessment, which is challenging and should have been performed according to a proper design, with an acceptable measurement method and reported in sufficient detail. Additional

uncertainty on exposure levels is introduced by the use of respiratory protection. The available epidemiological data consist of results derived from heterogeneous studies that differ in design, exposure assessment methods, occupational setting, outcome definition, data analysis and reporting of effect estimates, which preclude conducting a meta-analysis. Also, multiple analyses that have been published were based on the same populations and can therefore not be considered independent investigations. For the comparison of results for different types of isocyanates, the Committee has taken a pragmatic approach by determining an effect level or no-effect level when possible, based on exposure levels and effects reported in studies for different isocyanates (Figure A). It must be noted that most studies are underpowered because of a limited number of individuals. Therefore, especially the no-effect levels should be interpreted with caution.

The Committee further notes that the (no) effect levels cannot be directly compared, as in these studies different strategies were applied for exposure assessment (i.e. personal versus stationary measurements, peak measurements versus full shift measurements). Also, reported effects have been associated with different measures of exposure (e.g. mean and median exposure levels, or use of exposure categories). Nonetheless, Figure A provides a rough indication of the exposure range in which effect levels have been reported.

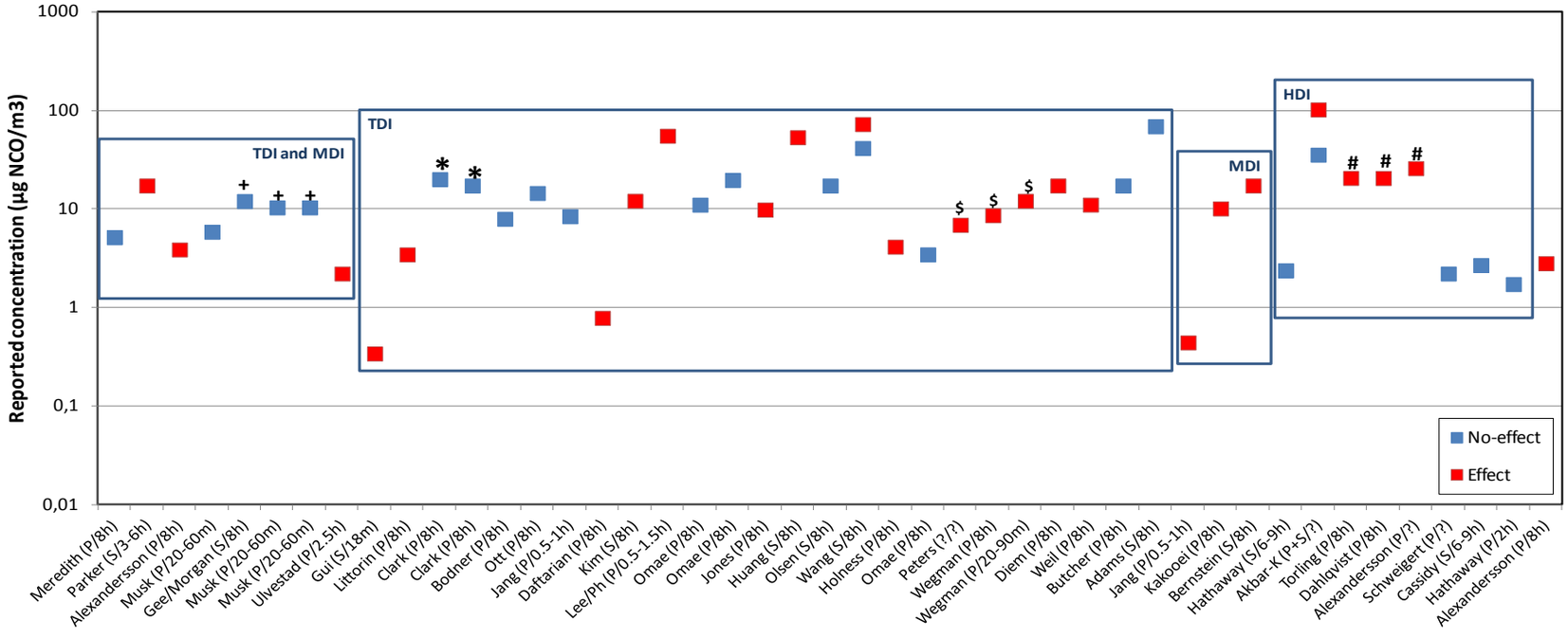


Figure *A. Distribution of (no) effect levels stratified on isocyanate type*

Overview of epidemiological studies with exposures quantified <100 µg NCO/m^3, reporting respiratory effects and studies reporting absence thereof. The studies are stratified based on isocyanate type. Represented are either effect levels or no-effect levels reported in the studies (name of first author) specified on the x-axis. In addition, it is specified whether exposure was assessed using personal (P) or stationary (S) measurements, and whether the concentration represents a short-time measurement or an 8h-value. Studies on the same populations of workers have been marked (*, #, +, $).

The Committee concludes that overall, effect levels have been reported in a broad range from 100 (the upper cut-off level of the evaluation) down to < 1 µg NCO/m^3. Noteworthy, when stratified according to isocyanate type used, no apparent differences in potency between TDI, HDI and MDI can be distinguished.

Conclusion

The Committee concludes that all available epidemiological studies have several limitations. The studies of Pronk et al. (2007, 2009)[69,70] (on BHR and asthma symptoms) and Collins et al. (2017)[63] (on 'TDI-consistent' cases of occupational asthma) are the only studies that provide sufficient data on an exposure-response relationship that can be used for risk quantification. These studies are further addressed in section 9.2 (Hazard quantification).

In the majority of the remaining epidemiological publications, lung function parameters have been studied in cross-sectional design. The Committee notes that these studies show a high heterogeneity and inconsistent results, with reported effect levels as well as no-effect levels over a large concentration range. This concentration range does not appear to differ between TDI, HDI and MDI.

7.1.2 Other effects

Acute and short-term toxicity

At relatively high concentrations, all isocyanates are irritating to the mucous membranes of the eyes and nose. Some people may develop bronchial sensitivity to isocyanates after peak exposures. These people, when later exposed to even very low concentrations of isocyanates, which may be below the exposure standard, may react by developing asthma-like symptoms, such as chest tightness, cough, wheeze and shortness of breath.

Non-respiratory effects due to repeated exposure

No studies are available on adverse effects in humans on other organ systems than the respiratory system or skin due to repeated exposure to isocyanates.

Genotoxicity

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. In a controlled atmosphere chamber, five workers (TDI-exposure history 2.5-12.5 years) were exposed during 4 times 30 minutes to increasing concentrations of TDI (0.036-0.22 mg/m^3; 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).[119]

Carcinogenicity

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.[12] After the IARC review, updates have been published for all three cohorts. The Committee concludes that the results of these updates are in line with the initial IARC conclusion.

In the Swedish cohort, non-significant increases in rectal cancer and non-Hodgkin's lymphoma (NHL) were observed in the first analysis.[120] In an update with 11 more years of follow up, fewer total cancer cases than expected were observed, although the lung cancer incidence was enhanced in women.[121] 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, slight increases in pancreatic cancer (standardized 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.[122] 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.[123]

In the USA 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, 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.[124] This cohort was updated with an extended follow-up of 18 years.[125] 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 however, was observed for these cancers. Mortality from breast, intestine, and brain cancers and NHL were slightly increased, although not significantly, and associated with exposure duration or cumulative TDI exposure.

Reproductive toxicity

No studies are available on human reproductive toxicity from exposure to isocyanates.

7.2 Animal studies

Animal studies are valuable in clarifying the modes of action of isocyanate-induced allergenic effects. For instance, exposure via the skin was shown to be a highly effective way to sensitise the respiratory tract in a number of animal species.[61] However, the Committee considers the animal toxicity data on isocyanates of limited value for establishing an advisory value. At present, there are limited data on respiratory sensitisation in animals and no validated animal models are available. Also, there is a lack of data on potential differences between modes of action in humans and animals. Furthermore, animal studies are usually performed at relatively high exposure concentrations of monomeric isocyanates, whereas workers are exposed to more diverse isocyanate exposures (i.e. different types and forms). Only a short summary is provided based on online databases.[2,3] Additional references are noted separately.

Genotoxicity

Inconsistent results have been observed in in vitro genotoxicity assay. Negative as well as positive findings have been reported for TDI and MDI, for which the positive findings have been attributed to the formation of mutagenic MDA when using DMSO as vehicle. Also the induction of chromosomal aberration has been observed for TDI and MDI. HDI was tested negative for mutagenicity in bacteria and in mammalian cells. NDI was negative in the Ames test but positive in the hypoxanthine-guanine phosphoribosyl transferase forward mutation assay in V79 cell cultures. NDI was also positive in a chromosomal aberration assay. IPDI was negative both in the Ames test as well as in the CHO/HPRT forward mutation assay. HDI trimer isocyanurate was negative in the Ames test.

In vivo, TDI was considered negative in micronucleus tests in rats and mice and in an UDS test in rats. HDI and MDI were negative in micronucleus assays in rats and mice, respectively. NDI was negative in a chromosomal aberration assay in mice and an UDS test in rats. IPDI was found to be non-clastogenic in a micronucleus assay in mice.

Carcinogenicity

Carcinogenicity data are available for TDI, HDI, and MDI.

A combined chronic toxicity and oncogenicity study in Fischer 344 revealed no carcinogenic potential of HDI after 2-year inhalation with vapour concentrations up to and including 0.164 ppm. A Maximum Tolerated Dose (MTD) was established at the highest concentration tested.[2]

Extensive reviews have been published on the carcinogenicity of TDI[12,126] and MDI[126]. Animal studies with TDI show inconsistent results. Intragastric administration of a mixture of 2,4- and 2,6-TDI was found to be carcinogenic in male and female rats and male mice, but after inhalation exposure no evidence for carcinogenicity was found. The pattern of multiple tumour induction observed for TDI after oral administration has been noted to be very similar to that found in experimental studies carried out with the carcinogen 2,4-TDA.[126]

Two carcinogenicity studies are available for MDI, in which Wistar rats have been exposed by inhalation. At the highest concentration used, severe olfactory epithelium degeneration was observed in the nose and of the lining epithelium of the lung in both sexes. Also at the highest dosage, pulmonary adenomas were observed in males and females, and a pulmonary adenocarcinoma in males.

IARC concluded that for TDI, there is sufficient evidence for carcinogenicity in experimental animals[a]. For a mixture containing monomeric and polymeric MDI, IARC concluded that there is limited evidence in experimental animals for carcinogenicity[b].

[a] Furthermore, IARC concluded that there is inadequate evidence for the carcinogenicity of TDI in humans. Overall, IARC concluded that TDIs are possibly carcinogenic to humans (Group 2B).

[b] IARC also concluded that there is inadequate evidence for the carcinogenicity of MDI and polymeric MDI in humans. Overall, IARC concluded that MDI (industrial preparation) is not classifiable as to its carcinogenicity to humans (Group 3).

Sensitisation

All extensively tested isocyanates (TDI, MDI, HDI) show a skin sensitising potential, in guinea pigs and/or mice.[127]

Various studies have been published for several isocyanates on the determination of the elicitation threshold in the Brown Norway rat model, both after dermal sensitisation[54,128,129] and after sensitisation by inhalation.[130] When comparing skin-sensitised animals with animals sensitised by inhalation exposure, the authors concluded that the elicitation thresholds did not demonstrate essential differences.[130]

Reproduction

No effect of exposure to TDI up to 2.1 mg/m^3 was found on any of the reproduction parameters evaluated in a 2-generation reproduction toxicity study in rats. In a prenatal developmental toxicity study in rats no embryotoxicity or teratogenicity was observed at any exposure concentration up to 3.6 mg TDI/m^3). A combined reproduction, neonatal development, and neurotoxicity study with HDI tested up to 2.1 mg/m^3 in the rat revealed no effects on for reproduction (including neonatal development). For HDI and MDI, no developmental toxicity was observed in prenatal developmental toxicity study in rats for exposures up to 2.1 mg/m^3. In a prenatal developmental toxicity study in rats with MDI, no embryotoxicity or teratogenicity was observed at any exposure concentration up to 9 mg/m^3. In a prenatal developmental toxicity study

with rats, concentrations of 12 mg/m³ polymeric MDI induced clear signs of developmental (embryo-/foeto-) toxicity in the form of reduced placental and foetal body weights and an increased occurrence of foetal skeletal (and overall) variations and retardation. However, these findings were associated with clear signs of maternal toxicity including mortality. In a prenatal developmental toxicity study with rats exposed to IPDI at a concentration of 4 mg/m^3, animals showed indications of delayed foetal development, however only in the presence of maternal toxicity.[2]

7.3 Summary

In humans, exposure to isocyanates may result in sensory irritation, decreased lung function, and may cause or exacerbate asthma. Most human data relate to isocyanate exposure and adverse effects on lung function, and display a high variability in the occurrence of health effects and in the exposure levels at which these are observed. Human data on the genotoxic and carcinogenic properties, and the reproduction toxicity of isocyanates are inadequate.

All extensively tested isocyanates are potent sensitisers in animal models. Animal data suggest that isocyanates are non-genotoxic, and that under some conditions TDI and MDI can be carcinogenic. The data available on reproduction toxicity indicate that isocyanates are not toxic to fertility and development.

08
existing guidelines, standards and evaluation

8.1 General population

Not available.

8.2 Occupational population

For several isocyanates, exposure limits were applied in the Netherlands until a new OEL system was introduced in January 2007[a]. Currently, no legally binding exposure limits exist for isocyanates. Occupational exposure limits for other countries are presented in Table 8.1.[6,131,132]

Table 8.1 Occupational exposure limits for isocyanates in several countries (mg/m^3) [6,131,132]

country (organisation)	NL	Fr[1 a]	USA (OSHA)	USA (NIOSH)	USA (ACGIH)	Germany (AGS)	UK (HSE)
TDI	-	0.080 8h 0.160 5m	0.200	-	0.036	0.035	-
HDI	-	0.075 8h 0.150 5m		0.035 0.140	0.034	0.035	-
MDI	-	0.100 8h 0.200 5m	0.200	0.050 0.200	0.051	0.050	-
NDI	-	0.095 8h 0.190 5m		0.040 0.170	-	0.050	-
IPDI	-	0.090 8h 0.180 5m		0.045 0.180	0.045	0.046	-
HDI prepolymers	-	1 15m					
Polyisocyanate	-						0.020 8h 0.070 15m [NCO]

[a] The French limits are indicative and non-regulatory values, set in 1986 (and for the HDI prepolymers in 1993).

[a] TDI, HDI, NDI: 0.04 mg/m^3; MDI, IPDI: 0.05 mg/m^3

09
hazard assessment

9.1 Hazard Identification

9.1.1 Hazard identification of allergens

The classification of work-related asthma comprises a broad spectrum of conditions that can be either induced or triggered at the workplace. Work-related asthma includes two main phenotypes, i.e. occupational asthma caused by the workplace and asthma that is exacerbated by the workplace. Occupational asthma can develop either with a latency period (allergic asthma), or without a latency period (non-allergic asthma; irritant induced asthma). The latter can in turn, arise in an acute form (Reactive Airways Dysfunction Syndrome (RADS)) or a form with a delayed onset ('not so sudden' RADS) which is associated with lower exposures.[133] For the aim of deriving an occupational exposure limit for isocyanates, the Committee focuses on asthma caused by the workplace (occupational asthma). In line with the definition specified in the fourth edition of Asthma in the Workplace, the Committee defines isocyanate-induced occupational asthma as 'a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to exposure to isocyanates at the workplace'.[133]

The critical event in the development of occupational asthma with an allergic mechanism is the induction of sensitisation. The Committee considers the induction of sensitisation also critical from the viewpoint of protecting occupational health, as preventing this process will also prevent the development of asthmatic symptoms. The induction of allergic asthma by high-molecular weight agents is mediated by the production of specific IgE antibodies. In those cases serological tests can serve as specific markers for the development of occupational asthma. The Committee has previously used the endpoint sensitisation as a basis for deriving an advisory value, for instance the number of sensitised workers in a bakery for fungal α-amylase.[134] As is explained below, for isocyanates other effects have been considered by the Committee.

9.1.2 Hazard identification of isocyanates

Exposure to isocyanates can lead to a spectrum of diseases which include, in addition to acute toxicity and allergic asthma, hypersensitivity pneumonitis, irritant-induced asthma, and persistent nonspecific airways hyperresponsiveness.[10] Although chemically, isocyanates belong to the group of low-molecular weight allergens, isocyanate-induced asthma also has striking similarities with 'allergic' asthma observed after exposure to high-molecular weight allergens. Isocyanate-induced asthma is characterised by variable airflow obstruction in which IgE-dependent and IgE independent mechanisms appear to play a role.[18,135] Most studies however, show a poor correlation between bronchial responses after exposure to isocyanates and the presence of specific IgE antibodies.[10] It has further been reported that the majority of individuals with isocyanate-induced asthma do not have allergen-specific IgE.[18,33] On the other hand, likely all occupational asthma cases with isocyanate-specific IgE can be

attributed to isocyanate exposure. The Committee therefore concludes that IgE is a very specific, but insensitive biomarker for isocyanate-induced disease. Consequently, the Committee considers serological test results on IgE-production not a reliable basis for deriving an advisory value. Recently, it has been postulated that IgG might be a useful biomarker for exposure in surveillance of isocyanate-exposed workers.[136] However, currently insufficient data are available for further exploration of this parameter for the use in risk assessment.

As isocyanate-induced sensitisation detected by IgE production does not provide a means to establish an advisory value, the Committee subsequently considered respiratory effects that occur following sensitisation. Numerous studies have been published on several adverse effects that have been linked to isocyanate-related asthma, i.e. the occurrence of clinical symptoms (respiratory irritation, rhinitis, wheezing, etc.) accelerated lung function decline, and bronchial hyper-responsiveness (usually defined by the concentration methacholine inducing a 20% fall in FEV_1 after inhalation challenge). None of these effects are specific for asthma.

Historically, lung function decline (usually measured as FEV_1 and FVC) has been the primary effect studied in relation to isocyanate exposure. Lung function is a parameter with a high intrinsic variability which is associated with the presence of asthma, but the association is not particularly strong. Occupational asthma is characterised by airway obstruction variable over a working day. Many patients – especially at a younger age – have unaffected lung function during symptom-free episodes. The Committee concludes therefore that lung function decline has a limited predictive value for asthma, in particular if measured in longitudinal studies.

Also BHR, although it is considered a hallmark of asthma, is not specific for allergenic asthma. BHR is consistent with allergenic and irritation-induced asthma, but also with other respiratory diseases, like COPD. Also, BHR may normalise after several days or, in rare cases, be absent in sensitised workers.[137] However, BHR is the only effect parameter that takes into account the variability of asthma-related airway obstruction. The Committee therefore considers BHR the most relevant surrogate endpoint for isocyanate-induced occupational asthma in epidemiological studies.[138] Unfortunately, only few studies have addressed BHR related to exposure to isocyanates.

9.1.3 Group approach

Most (historical) epidemiological data are available for the isocyanate prototype TDI. In the last decades, other isocyanates such as HDI and MDI are being applied in dimer-, trimer-, and polymer form which have inherently lower vapor pressure and volatility, and subsequently an assumed reduced inhalation hazard. Also, it is suggested that different

types of isocyanates possess different sensitisation potencies and it has been argued that oligomers are less potent than diisocyanates.[139] The Committee acknowledges that the contribution of different modes of action to isocyanate-induced toxicity can differ between isocyanates, and potentially lead to potency differences (see Chapter 6). The Committee notes, however, that data on potency of different isocyanate forms are limited to results from non-validated animal models[139,140] and primarily relate to the irritant potency[139]. The Committee concludes that available data (either epidemiological or mechanistic) do not allow a definite conclusion on, or the quantification of, these potential differences in sensitisation potency.

In practice, mixtures of different types and different forms of isocyanates are used. For most of these isocyanates, insufficient data are available for a quantitative hazard assessment. From the epidemiological data available for different isocyanates (TDI, HDI, and MDI) no consistent difference in potency is apparent. In this context, it is notable that a risk calculation for the association between HDI exposure and BHR in spray painters leads to a similar result as a risk calculation based on TDI exposure and cases consistent with occupational asthma. The Committee, overall, considers a group approach for all (currently used) di- and triisocyanates appropriate.

9.2 Hazard quantification

If possible, the Committee derives a health-based advisory value which represents an exposure level at which no adverse effects are anticipated (i.e. the application of a threshold approach). Although it is generally believed that a threshold exists for both sensitisation as well as elicitation, in practice, such thresholds have been shown to be difficult to determine based on the available information. For allergens, the Health Council therefore applies a risk-based approach for the derivation of an advisory value.[141] Generally, in this approach an extra sensitisation risk of 1% is taken into account (i.e. a 1% increase in sensitised individuals who are occupationally exposed, in addition to the cases present in the general population). As IgE is not a suitable effect parameter in case of isocyanate-induced respiratory allergy, other effect parameters have been considered for the hazard quantification.

Risk-based approach for isocyanates

Currently, only two studies provide sufficient data on the exposure-response relationship of respiratory health effects and exposure to isocyanates by inhalation, namely the study by Pronk et al. (2007, 2009)[69,70] and more recently, the study by Collins et al. (2017)[63]. The Committee notes that also the studies by Pronk et al. (2007, 2009)[69,70] and Collins et al. (2017)[63] have limitations. The studies of Pronk et al. (2007, 2009)[69,70] for instance, suffer from potential bias due to the healthy worker effect, and due to the selection of companies on voluntary basis. Also, the

study was limited to car body repair shop workers and industrial spray painters, the latter using personal protection. However, the Committee is of the opinion that it is a suitable basis for hazard quantification. In this study, exposure as well as multiple health endpoints were well characterised. Also, all associations were adjusted for current smoking, age, sex and atopy and the results of the different endpoints studied were consistent. Importantly, Pronk et al. (2007, 2009)[69,70] included BHR in their analyses, which the Committee considers most predictive for the development of occupational asthma.

In the surveillance study of Collins et al. (2017)[63], cases of asthma were not formally clinically diagnosed by the consulting pulmonologist and the length of exposure was based on worker reports collected from questionnaires. Therefore, it is not excluded that results of this study may be biased by misclassification of either exposure status, or outcome status, or both.

Pronk et al. (2007, 2009)[69,70] studied the association of HDI exposure and BHR as single parameter, and combined with the occurrence of asthma-like symptoms. The Committee has applied a logistic regression analysis on the individual data, and confirmed the robustness of this analysis with subsequent categorical analyses (for details see Annex A). All analyses resulted in comparable results, i.e. an exposure level of 0.10 µg NCO/m^3 corresponding with a 1% increase in BHR prevalence.

Collins et al. (2017)[63] performed a logistic regression analysis with data on cumulative exposure to TDI and the number of cases “consistent with TDI-induced asthma”. The Committee used the exposure-response relationship reported by Collins et al. (2017)[63], to calculate the exposure level corresponding to a 1% extra risk of being a case “consistent with TDI-induced asthma” (for details see Annex A). An exposure concentration of 0.14 µg NCO/m^3 was derived for a corresponding extra risk of 1%, which notably, is comparable with the result of the risk calculation based on the study of Pronk et al.

9.2.1 Risk-based recommended occupational exposure level

For di- and triisocyanates, the Committee derives a risk-based advisory value of 0.1 µg NCO/m^3. This value corresponds to an extra risk of BHR of 1%. This value is based on non-chronic exposures, but will also limit potential effects due to chronic exposure.

9.2.2 Health-based short-term exposure limit (STEL; 15-minutes TWA)

Short-time exposure to peak levels of isocyanates might result in relatively high risks for the development of isocyanate-induced occupational asthma. The Committee notes that there are no quantitative data available on this relationship. Therefore, the Committee cannot derive a health-based short-term exposure limit.

9.3 Conclusions and recommendation

The Committee is of the opinion that a threshold for isocyanate-induced sensitisation and subsequent development of asthma cannot be determined based on the available literature. The Committee therefore applied a risk-based approach, and derived an advisory of 0.1 µg NCO/m^3. At this concentration, workers have an extra risk of 1% of bronchial hyperreactivity (BHR), compared to the general population.

9.4 Skin notation

A skin notation for a substance is recommended when data indicate a substantial contribution from dermal exposure on systemic adverse health effects, on which a health-based advisory value is based. To decide on a skin notation, generally the Committee uses the quantitative approach described by ECETOC.[142] In this approach, a skin notation is considered necessary when the amount absorbed by both arms and forearms in 1 hour could amount to more than 10% of the amount that can be absorbed via the lungs on exposure to the advisory value for 8 hours. As noted in Section 5.1, isocyanates penetrate the skin and are conjugated or metabolised rather than absorbed. As a consequence, the ECETOC criterion for recommending a skin notation is not met. However, there is growing evidence that suggests that skin contact with isocyanates can cause sensitisation leading to allergic asthma.[61,127] Due to this significant contribution from dermal exposure, the Committee recommends to apply a skin notation for isocyanates.

9.5 Groups at extra risk

Several groups of workers have or may have an increased risk when exposed to isocyanates. First, isocyanate-sensitised workers (either via the inhalatory or the dermal route) are at higher risk to develop symptoms after exposure to – even very – low airborne levels. Second, workers with pre-existing asthma or those with more general respiratory symptoms may also have an increased risk to develop symptoms most likely because of non-specific irritation.

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annexes

A risk calculations

Risk calculation based on Pronk et al. (2007, 2009)69,70

For the risk assessment data published earlier by Pronk et al. (2007, 2009)[69,70] were obtained with permission from the authors. The original study involved 581 individuals from car spray paint shops and industrial scale spray paint facilities (airplanes, ships). These individuals were mainly exposed to isocyanate oligomers. Specific IgE and IgG to HDI were assessed in serum using various assays, an evaluation of respiratory symptoms by questionnaire was also available.

A subsample of 229 individuals underwent a more detailed medical survey consisting of isocyanate specific sensitisation, bronchial hyper-responsiveness (BHR), baseline spirometry and exhaled nitric oxide (eNO). BHR was tested using a methacholine challenge. From 14 workers BHR and baseline spirometry were not determined; one person stopped during challenge because of health complaints. Personal exposure was estimated by combining personal task-based inhalatory exposure measurements and time-activity information as described in the original publications.

The original data were reanalysed considering BHR20 (20% change in FEV_1 at a maximal dose of methacholine of 2.5 mg (~10 µmol)) and asthma as the endpoints of interest. Asthma was defined as the presence of bronchial hyper-responsiveness on the basis of the BHR20 and the wheezing over at least a period of a week over the last year. Exposure-response relationship were based on a categorical analysis in which controls were considered separately and exposed were categorized in tertiles (by approximation). Controls consisted of 20 office workers, and 28 other workers with no or negligible exposure (e.g. foremen responsible for planning; workers not physically present during spraying). The internal controls were used for obtaining a baseline prevalence for asthma and BHR. In the original papers the exposure was expressed as total NCO concentration in different tasks multiplied by the number of working hours exposed over the period of a month and expressed in log µg/m^3 * working hours / months (with on average 161 working hours/month). First, exposure-response analyses were performed using the original exposure metrics from the publications. Then, exposure was rescaled by taking the antilog and calculating exposure for a day average exposure (8 working hours).

Several approaches have been used:

1. Exposure-response analysis using exposure data on the individual level. This approach makes optimal use of the data and stays close to the original publications. Analyses using splines showed that the logistic model had the best fit. The exposure response relationship had a regression coefficient of 0.0775 for BHR and 0.0467 for asthma (BHR and wheeze) in a logistic regression analysis. These slopes lead to

exposure levels at which the extra risk is 1% of respectively 0.10 and 0.20 µg/m^3.

2. Exposure-response analysis using exposure data after categorisation. The exposure response relationship was also calculated using a simple Poisson regression analysis to model an exposure-response relationship through the origin (no intercept, at zero exposure risk equals risk in controls) relative to the baseline prevalence of BHR20 or asthma in non-exposed using the below given information. Calculations were performed by using SAS software.

Average NCO concentration (s.d.), expressed in log µg/m^3 * working hours / months (average 161 working hours/month)	Number of individuals in exposure category	Individuals with BHR20	Individuals with asthma
Controls	48	3 (6.3%)	2 (4.2%)
1.721 (1.182)	54	7 (13.0%)	2 (3.7%)
6.423 (0.909)	56	10 (17.9%)	5 (8.9%)
9.094 (0.835)	56	13 (23.2%)	9 (23.2%)

On the basis of the available data exposure response slopes have been calculated. These slope factors were used to calculate the point where the exposure is associated with a 1%, 2%, 3% and 5% extra risk, relative to the background risk for either asthma/BHR or BHR using internal controls from the studies by Pronk et al. A sensitivity analysis was performed, comparing Poisson models with logistic models. Hardly any differences were observed, with a somewhat better fit for the Poisson model.

Endpoint	Reference category	Slope (K)	P	extra risk, RR and exposure at extra risk (µg/m^3 over 8 working hours)							
				1%		2%		3%		5%	
				RR	Exp	RR	Exp	RR	Exp	RR	Exp
Asthma (BHR20 and wheeze)	2/48 (4.2%)	0.24	0.098	1.24	**0.13**	1.48	**0.36**	1.71	**0.97**	2.19	**7.09**
BHR20	3/48 (6.3%)	0.31	0.039	1.16	**0.10**	1.32	**0.19**	1.48	**0.37**	1.80	**1.39**

RR is the relative risk; Exp is the exposure (in µg NCO/m^3) over an 8 hour working day corresponding with the benchmarked risk level.

Risk calculation based on Collins et al. (2017)[63]

Collins et al. (2017)[63] report a logistic regression analysis for the association between TDI-induced asthma and cumulative TDI exposure (criteria for diagnosis are described in Cassidy et al. (2017)[63] exposure assessment was reported by Middendorf et al. (2017)[64]. In this study, also peak exposures (based on 95th percentile) and other respiratory parameters were studied.

In the present analysis, the Committee has calculated the exposure level that corresponds to an extra 1% of 'predicted probability of being a case', based on the association between (log) cumulative exposure and TDI-induced asthma. For the extrapolation from cumulative exposure to 8h-TWA exposures it is assumed that exposure duration does not influence the shape of the exposure-response curve.

The predicted probabilities (for a 42-y old) were derived from Table 3 of the publication by Collins et al. (2017)[63], which contains a selected number of relatively high exposures (5-20 ppb-years; total range 0.04-21.6 ppb-years).

Data as presented in Table 3 of Collins et al. (2017)[63]. Predicted probability for being a case for median age of 42 and some selected levels of cumulative exposure

Model 1	5 ppb-years	10 ppb-years	15 ppb-years	20 ppb-years
TDI-induced asthma (7 cases)	0.053	0.085	0.111	0.134
TDI-induced asthma or indeterminate asthma (9 cases)	0.061	0.081	0.096	0.107
FEV1 decline (19 cases)	0.147	0.177	0.198	0.213
Symptoms of asthma (23 cases)	0.143	0.160	0.170	0.178

From these predicted probabilities, the log odds were derived (odds = P/(1-P), log odds = LN(odds)):

Exposure (ppb-years)	LN exposure	Predicted probability	Odds	Log odds
5	1.609	0.053	0.056	-2.883
10	2.303	0.085	0.093	-2.376
15	2.708	0.111	0.125	-2.081
20	2.996	0.134	0.155	-1.866

There is a linear relationship between the log odds and the log exposure (LN ppb-years). The coefficient for exposure of the linear regression line (β=0.7328) corresponds to the coefficient of the logistic regression model (β=0.7301) reported by Collins et al. (2017)[63].

With this model, the Committee has derived the cumulative exposures corresponding with a range of predicted probabilities, and subsequently calculated an 8h-TWA assuming a mean exposure duration of 11.8 years (mean exposure years).

Predicted probability	Extra risk (%)	Cumulative exposure (ppb-years)	8h-TWA (ppb)	8h-TWA (µg NCO/m³)
0.01	1%	0.48	0.04	0.14
0.02	2%	1.26	0.11	0.38
0.03	3%	2.23	0.19	0.65
0.05	5%	4.60	0.39	1.34

B list of abbreviations

BHR (%)	Bronchial hyperresponsiveness (% of fall in FEV1 which is considered as hyperresponsive)
COPD	Chronic obstructive pulmonary disease
FEF (%-%)	Forced expiratory flow (interval, % of FVC)
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HDI	Hexamethylene diisocyanate
HDI-BT	Hexamethylene diisocyanate biuret
IPDI	Isophorone diisocyanate
MMF	Maximum midexpiratory flow
MDI	Methylene diphenyl diisocyanate
NDI	Naphthalene diisocyanate
PEV1	Passive expiratory volume in 1 second
PEF(R)	Peak expiratory flow (rate)
TDI	Toluene diisocyanate

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