1 Prioritised substance group: Diisocyanates

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1.1 Background Information

1.1.1 Hazardous properties

Diisocyanates are a group of chemicals containing two isocyanate functional groups (R–N=C=O) in otherwise varied structures. Due to the functional groups, all diisocyanates induce similar health effects, and are potent skin and respiratory tract sensitisers. In addition, carcinogenicity is a concern.

The two major diisocyanates in the European market are 4,4'-methylenediphenyl diisocyanate (MDI), m-tolylidene diisocyanate (TDI), both of which have several isomers. A third diisocyanate with wide-spread use, especially in car paints, is hexamethylene diisocyanate (HDI). Information on the amounts of their manufacture and/or import in the European Economic Area, as well as their current harmonised health hazard classifications under the CLP regulation, is presented in Table 1. In addition to these three compounds, there are several other diisocyanates in the European market that are manufactured and/or imported in smaller yet notable amounts. Five of them, abbreviated as NDI, XDI, TMXDI, TRIDI and TODI (Table 1) are currently under evaluation for harmonised hazard classification under the CLP regulation in the Risk assessment committee (RAC) of the European Chemicals Agency (ECHA). For these five diisocyanates, there is little information available, and their proposed harmonised classifications are mostly based on read-across from MDI, TDI and HDI. At workplaces, diisocyanates, like MDI, can occur also as oligomers or prepolymers in various products. The chain endings of the oligomers and prepolymers contain, however, free isocyanate groups. In addition, these may also contain traces of monomeric diisocyanates.

The respective degradation products and metabolites of MDI and TDI, 4,4-methylene dianiline (MDA; CAS 101-77-9; 10 000 – 100 000 tonnes per year) and 2,4-toluene diamine (2,4-TDA; CAS 95-80-7; no tonnage information available) are also a concern. They both have harmonised classifications for Skin Sens. 1, Muta. 2 and Carc. 1B, and 2,4-TDA in addition as Repr. 2 (suspected of damaging fertility). Moreover, both MDA and TDA have been listed as substances of very high concern (SVHC) under REACH.

Mixture effects appear highly possible for diisocyanates, particularly concerning the sensitising properties. This is based on their shared mode of action that is a consequence of the protein reactivity of the isocyanate groups, although differences in potency among diisocyanates are likely.

Table 1-1: Selected diisocyanates in the European market (Source: European Chemicals Agency, http://echa.europa.eu/)

Abbrev.	Chemical Name	CAS No.	Manufacture and/or import in the European Economic Area (amount, tonnes per year)	Harmonised health hazard Classification under the CLP regulation (Annex VI of Regulation (EC) No 1272/2008)
MDI	4,4'-methylenediphenyl diisocyanate + other isomers	101-68-8	100 000 – 1 000 000	Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Acute Tox. 4 *, STOT SE 3, Resp. Sens. 1, Carc. 2, STOT RE 2 *
TDI	4-methyl-m-phenylene diisocyanate + other isomers	584-84-9	100 000 – 1 000 000	Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Acute Tox. 2 *, STOT SE 3, Resp. Sens. 1, Carc. 2
HDI	hexamethylene diisocyanate	822-06-0	10 000 – 100 000	Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Acute Tox. 3 *, STOT SE 3, Resp. Sens. 1
IPDI	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate + other isomers	4098-71-9	10 000 – 100 000	Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Acute Tox. 3 *, STOT SE 3, Resp. Sens. 1
HDMI	4,4'-methylenedicyclohexyl diisocyanate	5124-30-1	10 000 – 100 000	Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Acute Tox. 3 *, STOT SE 3, Resp. Sens. 1
NDI	1,5-naphthylene diisocyanate	3173-72-6	1000 – 10 000	Skin Irrit. 2, Eye Irrit. 2, Acute Tox. 4 *, STOT SE 3, Resp. Sens. 1 + Addition of Skin Sens 1A and modification of Acute Tox 4 * to Acute Tox 2 under evaluation
XDI	1,3-bis(isocyanatomethyl)benzene	3634-83-1	1000 – 10 000	n/a Skin Sens. 1A and Resp. Sens. 1 under evaluation
TMXDI	1,3-bis(1-isocyanato-1-methylethyl)benzene	2778-42-9	100 – 1000	n/a Skin Sens. 1A and Resp. Sens. 1 under evaluation
TRIDI	2,4,6-triisopropyl-m-phenylene diisocyanate	2162-73-4	100 – 1000	n/a Skin Sens. 1 and Resp. Sens. 1 under evaluation
TODI	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate	91-97-4	10 – 100	n/a Skin Sens. 1A and Resp. Sens. 1 under evaluation

** Indicates that manufacturers or importers must apply at least this minimum classification, but must classify in a more severe hazard category in the event that further information is available which shows that the hazard(s) meet the criteria for classification in the more severe category (See Annex VI, Section 1.2.1 of the CLP Regulation)*

1.1.2 Exposure characteristics

Diisocyanates are widely used in different applications in industry, most notably in the manufacturing of polyurethanes (that are used for various purposes) and as hardeners in industrial paints, glues, varnishes and resins. Total amounts used in the EU are 2.5 million tonnes per year and MDI, TDI and HDI account for more than 95% of this total volume. Since there are no suitable alternatives for the majority of the uses, the use is not expected to decline in near future.

Also consumers may be exposed to diisocyanates from products containing diisocyanates, particularly glues. In addition, consumers may be exposed from use of large amounts of polyurethane foams in do-it-yourself applications, and from on-site-construction activities in public and private buildings. Occupational diisocyanate exposure occurs primarily via inhalation and skin, but also through the gastro-intestinal tract. TDI and HDI are relatively volatile, and their air concentrations can, therefore, be significant at room temperature. Also other diisocyanates, such as MDI, can reach high air concentrations in certain conditions of use, for instance during spray painting. Furthermore, heating of products containing polyurethans can produce diisocyanate monomers (relevant e.g. in welding, soldering, flame cutting and sawing).

For the major diisocyanates, particularly MDI and TDI, there are HBM data available from polyurethane manufacturing, and also some data from the construction sector. Most of the studies are, however, mainly focused on large companies such as polyurethanes industries or paint factories in which the protective personal equipment (PPE) and the safety procedure are often well established. Less data is available from small/medium companies (SMEs) or micro-sized companies (car painting shops, construction painters, etc.) where the exposure of workers can be more relevant due to reduced attention of workers regarding the safety procedures and the correct use of PPE (Geens et al., 2016; Johansson et al,. 2015). Limited biomonitoring data are available on exposure to HDI or NDI.

For IPDI, XDI, TMXDI, TRIDI and TODI, there does not appear to be published biomonitoring data from the past ten years. In addition, health based guidance values have not been determined for diisocyanates, as according to the current view, a threshold value for the sensitising effects does not exist.

1.1.3 Policy relevance

Due to the sensitising properties, the three MDI isomers are restricted under the REACH regulation, and shall not be placed on the market as a constituent of mixtures in concentrations ≥ 0.1% by weight for supply to the general public, unless the packaging contains protective gloves and is marked properly (Entry 56 in Annex XVII of Regulation (EC) No 1907/2006).

In addition, the use of MDI, TDI and HDI has been recently proposed to be restricted in the EU unless specific conditions for workers training and risk management measures apply (RAC/SEAC, 2017/2018). The aim of the restriction is not, however, to ban the use of diisocyanates but rather to improve the control of diisocyanate use by obligatory training for good working practices and risk management. This is the first time that this type of restriction has been proposed at the EU level and there is an interest to follow-up on the effectiveness of the restriction. If the restriction proposal on diisocyanates is going to come in force, it should have an impact on the exposure to diisocyanates, but the SMEs may still pose a challenge. Therefore, a follow-up on the effectivity especially in SMEs is of high interest.

Also an MDI metabolite, MDA, has been placed in the list of authorised chemicals due to its classification for carcinogenicity (Entry No 02 in Annex XIV of Regulation (EC) No 1907/2006).

1.1.4 Technical aspects

For Human Biomonitoring, diisocyanate metabolites (diamines) can be measured in urine (for instance, MDA for biomonitoring of MDI, and similarly TDA for TDI). After the hydrolysis of urine, the released amines can be analysed using different methods (LC-ECD, GC-MS, LC-MS/MS). Cocker and Jones (2017) have published a method that allows the simultaneous determination of the metabolites of hexamethylene diisocyanate (HDI), 2,4-toluene diisocyanate and 2,6-toluene diisocyanate (TDI), isophorone diisocyanate (IPDI) and methylene diphenyl diisocyanate (MDI) in human urine. However, challenges have been faced e.g. in the case of workers' co-exposure to both aromatic amines and diisocyanates (Gries et al., 2013, Sabbioni et al., 2000; Cocker, 2011; Jones et al.,2017).Urinary metabolites of MDA reflect both the exposure to MDA and MDI (Tinnerberg et al., 2008; Cocker, 2011; Sabbioni et al., 2010; Jones et al.,2017), which may be an issue in some sectors in which co-exposure may occur(Six and Richter, 2003). Therefore, the relevance of non-isocyanate sources for MDA exposure at the workplace should be clarified before selecting biomonitoring parameters. When using urinary metabolites for the biomonitoring of diisocyanate exposure, also elimination kinetics, which may differ between the different diisocyanates, needs to be considered (Budnik et al., 2011). Wrong timing of the sampling may lead to the underestimation of the exposure. In addition, occasional and lower level exposures, which might still lead to sensitisation, are challenging to be detected.

The timing issue is not anymore so important if another approach for diisocyanate biomonitoring, i.e. adduct analysis is used. Either albumin or haemoglobin adducts has been used for the biomonitoring of diisocyanates. The adducts analysis provides several advantages, among which the most relevant is that their half-life is ranging from about 20 days for albumin adducts up to 120 days for hemoglobin adducts, thus reflecting a chronic constant exposure over a longer period of time than urinary concentrations (Sabbioni et al., 2010). This advantage may, however, apply mainly to workplaces with a continuos exposure pattern. The ability of adducts to detect occasional exposures to sensitising isocyanate concentrations still remains to be established. Disadvantage of the adduct analysis is the need for blood sampling and that they usually need a significant amount of material to work with and involve usually a complex sample preparation. There are specific adducts identified for diisocyanates (e.g. MDI-Lys, AcMDI-Lys) whereas arylamine adducts can be formed both due to the exposure to aromatic amines and isocyanates (e.g. MDA-Val-Hyd, AcMDA-Val-Gly-Gly) (Gries et al., 2013; Sabbioni et al., 2000 & 2010 & 2016). These diamine based DNA adducts are often considered as a first step for genotoxic and carcinogenic effects (Sabbioni et al., 2010; Lindberg et al., 2011).

1.1.5 Societal concern

Diisocyanate-induced skin and respiratory sensitisation have been common occupational conditions, although appear to be declining due to improvements in occupational hygiene. Still, diisocyanate asthma and skin sensitisation are big concerns in occupational health, and are diagnosed in different countries each year. It has been estimated that the incidence of diisocyanate induced asthma is between 16-70 cases per 10000 exposed workers annually, meaning a total of 470-2350 new asthma cases in the EU each year (RAC/SEAC, 2017/2018). They are included in trade union priority list of substances of concern. Although there are occupational exposure limit values for some diisocyanates set in different countries, EU wide values do not exist, and these national values are generally not fully protective from sensitisation.

The effectiveness of the diisocyanate restriction and authorisation requirements under REACH should be monitored, especially concerning occupational exposure. Exposure to diisocyanates at small and medium sized enterprises is a particular concern.

There is also a need to better understand the occupational exposure routes of isocyanates, e.g. via air, direct skin contact, or via ingestion of aerosols in order to target risk management measures correctly.

In addition, sensitive biomonitoring methods, together with air and skin monitoring methods, are needed for the assessment of the effectiveness of the personal protective equipment.

Furthermore, as diisocyanates can cause occupational asthma and skin sensitisation at very low exposure levels, and the appropriateness and the sensitivity of HBM methods to detect low level exposures may need further development. In addition, it would be important to study exposure to the less known diisocyanates.

1.2 Categorisation of Substances

Table 1-2: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, substances (see general introduction)

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
B	-MDI			Proposed: Annex XVII of REACH
	-TDI			
C	HDI			
	IPDI			
	NDI			
D	XDI			
	TODI			
	HDMI			
	TMXDI			
	TRIDI			

1.3 Policy-related questions

1. What is the current occupational exposure to diisocyanates?
2. What are the best markers to identify hazardous exposures to diisocyanates?
3. What is the likely impact of the forthcoming REACH restriction of diisocyanates?
4. What are the health risks and human health impacts of the current occupational diisocyanate exposures?

1.4 Research Activities to be undertaken

Table 1-3: Listing of research activities to be carried out to answer the policy questions

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
1	All diisocyanates	Sporadic information on exposures available, not very recent	Action: Review of the available data on diisocyanates, identification of data gaps (sectors with limited data)
1,2,3	All group a and b diisocyanates	Sporadic information on exposures available, not very recent. Different approaches for biomonitoring available.	Gaps: Exposure in SMEs using diisocyanates for different purposes? Sensitivity of the HBM methods at low exposure levels? Action: Occupational survey focused on sectors with limited data available. This provides a base-line to study the effects of the restriction and should include also testing of different biomarkers for their sensitivity at low exposure levels.
4	MDI, TDI, (HDI)	Sensitisation capacity of diisocyanates known. Also some diisocyanates possibly carcinogenic.	Gaps: What are the risks at current exposure levels. Is there a cancer risk due to formation of respective diamines? Action: Risk assessment based on biomonitoring data taking into account both asthma and cancer risks. This may need also PBPK modelling data.

1.5 References

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