HBM4EU science and policy for a healthy future

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

HBM4EU

POLICY BRIEF

JUNE 2022

European Human Biomonitoring Initiative

Anilines and Diisocyanates

This policy brief summarizes the adverse human health effects of anilines and diisocyanates, their main exposure pathways for humans, and how human biomonitoring could be of value in the development of EU policy.

KEY MESSAGES

- Exposure to anilines and diisocyanates, both acute and chronic, can result in or contribute to a range of adverse health effects.
- The contribution of anilines to cancer is of particular concern, especially for exposed workers.
- In the case of diisocyanates, the main concern is occupational asthma and skin allergy.
- Workers in the rubber, chemicals, dyes, some pesticides, drugs and polyurethane polymer industries are particularly exposed to anilines.
- Workers in the polyurethane, car painting and construction sectors are particularly exposed to diisocyanates.
- General population is exposed to anilines via smoking and consumer products, and to a lesser extent from ambient air pollution.
- Paracetamol is an aniline derivative with widespread general population exposure due to its medical use.
- Exposure of general population to diisocyanates is limited, but may occur via certain specific products used e.g. in renovation.
- European citizens are concerned about industrial chemicals (such as anilines and diisocyanates) and largely support the use of HBM for risk assessment and policy, though awareness is still low.

BACKGROUND: HBM4EU

The European Human Biomonitoring Initiative, HBM4EU, running from 2017 to June 2022, is a joint effort of 28 countries, the European Environment Agency and the European Commission, and co-funded under Horizon 2020. The main aim of the initiative is to coordinate and advance human biomonitoring in Europe. HBM4EU has provided a wealth of improved evidence of the actual exposure of citizens to chemicals and their possible health effects. Human biomonitoring allows us to measure our exposure to chemicals by measuring either the substances themselves, their metabolites or markers of subsequent health effects in body fluids or tissues. Information on human exposure can be linked to data on sources and epidemiological surveys to inform research, prevention, and policy with the objective of addressing knowledge gaps and promoting innovative approaches. If you would like to read more about the project itself, please visit the HBM4EU website.

HBM4EU RESULTS

The main outputs from the HBM4EU to date include the following:

In order to further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach to study planning and implementation in Europe. An analysis of the current practice concerning HBM for anilines and diisocyanates: HBM (urinary) data have been employed by ECHA to establish a reference dose response relationship for the carcinogenicity of MOCA (ECHA, 2015). The intention of this was to encourage the use of HBM data in applications for authorisation of MOCA. This has resulted in the use of HBM data to assess occupational exposure in authorization context and has showed that HBM can give a more accurate estimate on exposure than other means to assess occupational exposure to MOCA.

A risk assessment was performed for o-toluidine (OT) based on published human exposure data, where workers occupationally exposed to o-toluidine were estimated to have a cancer risk of 1:20 000 in a worst-case scenario. The approach used in this risk assessment can be used in the following regulatory risk assessments of o-toluidine.

A PBPK model has been developed for OT. Mean daily intake of ortho-toluidine was estimated for both the general population and for occupational exposure and used for the risk assessment. It was estimated that workers exposed to OT have a cancer risk of 60 to 90 per 10^6 in the worst-case scenario. The exposure levels and cancer risk of OT in the general population were orders of magnitude lower when compared to workers (Huusken *et al.*2022).

HBM4EU found that the availability of exposure data for many aniline substances is limited. Although there are regulatory measures (including e.g. REACH restrictions and authorisations) already established for the use of many aniline compounds, it is suspected that occupational exposure to some of them may be more widespread. For example, hairdressers may be exposed to some aniline substances since they may be present in hair waving products and hair dyes. Exposure to the aniline metabolite N-acetyl-4-aminophenol (i.e. paracetamol) is widespread from its use as a drug and may contribute to the reproductive effects of combined chemical exposures.

Data on the current exposures to diisocyanates especially from the construction sector, large vehicle manufacturing and repair and from the use of MDI based glues was identified as limited. The new data from HBM4EU diisocyanate study suggested, however, low but still measurable exposure to MDI and HDI in these sectors. However, even these low levels may present an asthma risk. A PBPK model developed within HBM4EU was used to estimate the excess asthma cases related to certain diisocyanate biomarker levels.

Measurement of a prioritised list of biomarkers for many aniline compounds and diisocyanates is possible, mainly in urine and involving LC-MS-MS techniques. The measurement of some aniline compounds and diisocyanates exposure in blood via protein adducts is also possible, but this approach has not been thoroughly investigated.

HBM4EU conducted an External Quality Assurance Scheme (EQUAS) and an Inter-laboratory Comparison Investigation (ICI) for the analysis of anilines and diisocyanates and found the results roughly comparable with each other and achieved via robust methods and quality controls.

Adverse outcome pathways (AOPs) relevant for anilines (e.g., o-toluidine) have been identified regarding haematotoxicity. However, AOPs related to carcinogenicity (urinary bladder cancer) of anilines are currently missing. AOPs regarding skin and respiratory sensitising properties of diisocyanates were identified. In addition, AOPs regarding other diisocyanate-caused adverse respiratory outcomes (e.g., pulmonary irritation mechanisms) were also identified.

HBM4EU also laid the foundations for a European HBM Network to monitor human exposure to priority chemicals, including anilines and diisocyanates.

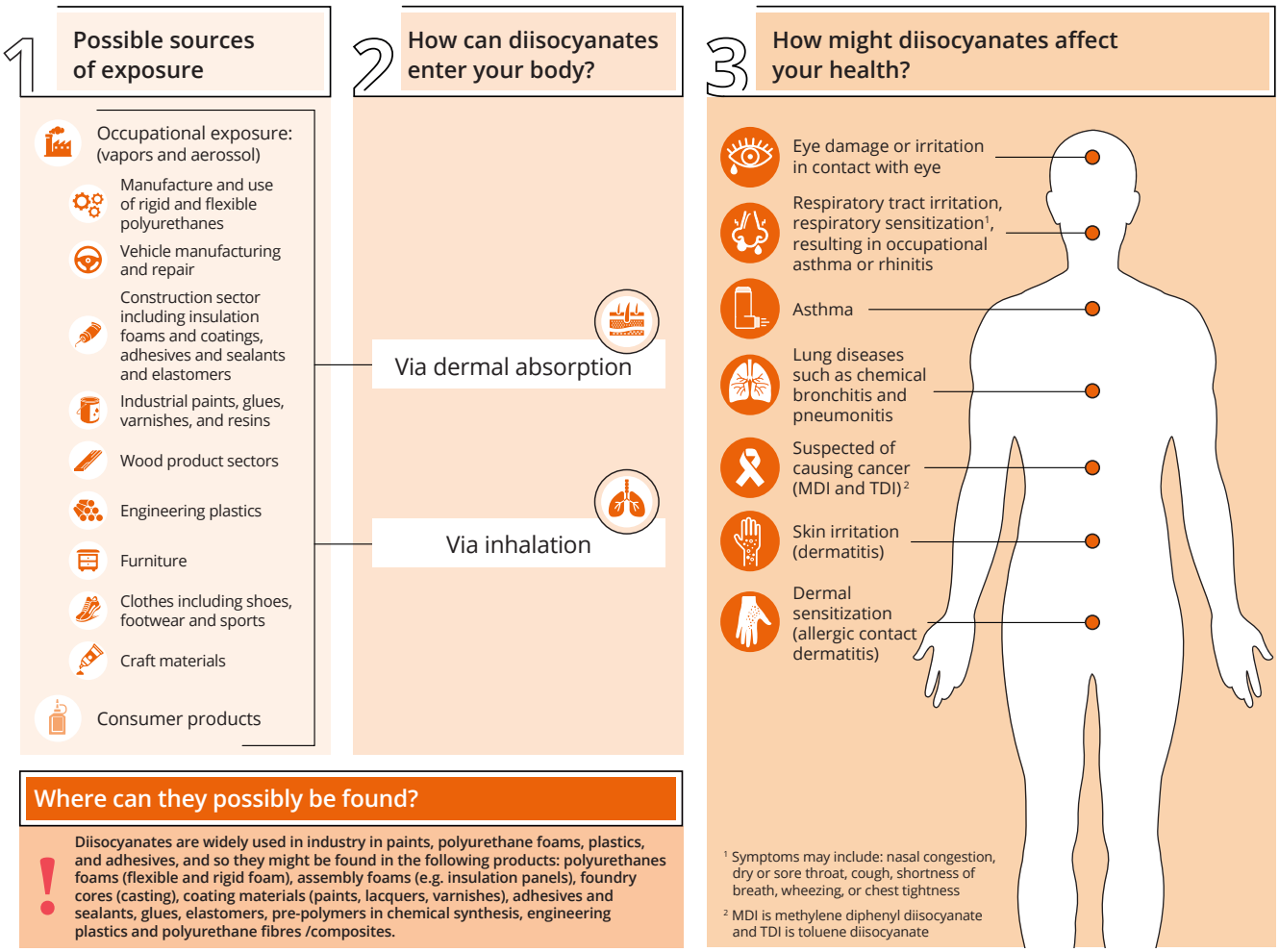
EXPOSURE & HEALTH EFFECTS

The main source, pathways of human exposure and health effects of anilines and diisocyanates are shown in Figure 1.

Anilines are released into the environment from the points and/or facilities where they are produced or used. For most of the general public, environmental exposure may occur by breathing in contaminated air or from second hand cigarette smoke, though exposure to very small amounts of anilines may also occur through contaminated food or drinking water. Exposure via skin contact can also occur and is in fact the main route for some types of anilines. Exposure to anilines and diisocyanates is more likely to occur in occupational settings, and to a small extent via consumer products.

In terms of health effects, both anilines and diisocyanates can cause acute effects. Long-term exposure to anilines can also result in blood conditions like methemoglobinemia and haemolytic anaemia, and some anilines are also known to cause skin sensitisation even at low exposure levels. The derivatives of aniline are also of concern. For example, several derivatives are skin sensitizers whilst paracetamol (N-acetyl-4-aminophenol) at high exposures can be severely toxic for the liver.

Figure 1. Overview of exposure sources, pathways and health effects associated with diisocyanates



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results on anilines have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan. These are available in the HBM4EU Science to Policy section.

Several policy measures have been already introduced in the EU to reduce anilines exposure. These include authorisation under REACH for MOCA and MDA. o-Toluidine is prohibited from use in cosmetics under the EU Cosmetics Regulation whilst azo dyes which could potentially release o-toluidine are prohibited for use in textiles and other consumer articles. o-Toluidine is currently listed in the candidate list as a SVHC (substance of very high concern). Diisocyanates (e.g. MDI, TDI, HDI) will become restricted under REACH from 24 August 2023, unless specific conditions regarding the training of workers and the use of RMMs are applied where there are concentrations of 0.1% or above for the diisocyanates. In addition, there is a binding occupational exposure limit value under preparation under the EU chemicals agents' directive (CAD (Directive 98/24/EC)) for diisocyanates.

POLICY QUESTIONS

The answers below are summarised. For more details, please consult the substance report available on the dedicated substance page of the HBM4EU website.

1 What is the current occupational exposure to aniline and different aniline derivatives (including diamine forming diisocyanates) in the EU?

We do not have a good general answer to that question. The data are scattered, and its coverage is limited. Many aniline compounds are nowadays restricted, which limits occupational exposure to them. Use of MOCA and technical MDA is authorised under REACH and exposure to them is rather limited in terms of number of workers. Occupational exposure to aniline itself is mostly related to its use in chemical manufacturing.

Occupational exposure to diisocyanates, and effects for regulatory measures on the exposure to these substances, especially in small and medium sized companies, needs further data. Although some studies exist, the data is still limited and not very recent.

There are also some data on the occupational exposure to specific anilines (carcinogen o-toluidine and sensitiser PDA) through e.g. hair dyes but the biomonitoring data on these exposures, which may concern large number of workers, is still limited.

2 What is the exposure to paracetamol (aniline metabolite) among the general population?

We do not have European wide data on that. There are studies in Germany and Denmark on the exposure of general population to anilines, including paracetamol, measured through HBM and they found it to be ubiquitous in both cases. In a Danish Study (Nielsen et al., 2015), metabolites of paracetamol were detected in the urine of all but one of 145 schoolchildren aged 6-11 and of all of their mothers in urban and rural settings. The average concentration of the metabolite in the mothers' urine was about three times that of their children. A large German study with over 2000 samples also found ubiquitous body burden of anilines metabolites (Modick et al., 2014). Possible sources of these metabolites are direct intake of paracetamol (most common), occupational exposure to aniline, ubiquitous exposure to environmental sources including food, and cigarette smoke which contains anilines. The HBM4EU dashboard has 1 dataset with paracetamol exposure data integrated.

3 What are the risks related to these exposures?

Many anilines are carcinogenic, meaning they cause or contribute to cancer in humans. For example, HBM4EU calculated that workers exposed to the aniline o-toluidine have a cancer risk of 1:20 000 in the worst-case exposure scenario (0.5 mg/L in urine). The exposure levels calculated based on HBM data were below the binding occupational exposure level set under the EU Carcinogens and Mutagens Directive (BOELV, 0.44 mg/m3 corresponding to 2.2 mg/L as urinary total o-toluidine). This risk assessment demonstrates how HBM data can be used to support the RA of o-toluidine.

Paracetamol may contribute to the reproductive effects in combination with environmental exposure to other reproductive toxicants.

4 What is the possible impact of REACH on the exposure and risks?

We do not have enough evidence to answer that yet. Because of the REACH authorisation there are limited number of exposed workers to MOCA and MDA in the EU. Occupational biomonitoring data collected in HBM4EU describes a decline in the exposure to MOCA observed in UK.

5 What is current occupational exposure to diisocyanates?

The new data from HBM4EU diisocyanate study suggests low, but still measurable exposure to MDI and HDI in construction sector, in use of MDI glues, adhesives or sealants and in the motor vehicle sector. Highest exposures were observed in activities involving either polyurethane foam or HDI paint spraying. In many cases, however, levels remained below or close to LOQ, especially when MDI glues, adhesives or sealants were used. In polyurethane foam spraying or in HDI paint spraying high air levels may be measured but the use of RPE limits the exposure of workers. Therefore, air levels alone cannot inform us on the real exposure of workers, but biomonitoring data is needed to assess the exposure and confirm the proper functioning of personal protection. Therefore, we emphasise the role of biomonitoring in the control of occupational exposure to diisocyanates. The dermal wipe samples tested in this study were often unable to detect exposure. This further emphasises the role of biomonitoring in the assessment of all routes of exposure to diisocyanates.

6 What are the best markers to identify hazardous exposures to diisocyanates?

Urinary diamines are the most commonly used biomarker for the monitoring of exposure to diisocyanates. Hb adduct analyses can also be used but require blood sampling. Further analysis of the HBM4EU diisocyanate data will bring more information on their comparability. Since current exposures were often below or close to the LOQs of the urinary diamine methods increasing the sensitivity of the method may need to be considered. Urinary lysine adducts may provide a good alternative for U-MDA in case of MDI exposure. Diisocyanate IgG measurement does not necessarily provide advantages over U-diamine analysis. Further analyses of HBM4EU diisocyanate study data will give us more information on the usability of IgG and urinary lysine adduct analyses in the biomonitoring of diisocyanate exposure.

7 What is the likely impact of forthcoming REACH restriction/possible EU wide OEL of disocyanates?

Since the REACH restriction on diisocyanates due to be implemented in 2023, it is too early to evaluate the possible impact of this restriction. The HBM4EU diisocyanate study (together with the systematic review by Scholten et al., 2020), however, provides baseline data for future assessment of the impact of the restriction. Since there is a binding limit value for diisocyanates also under preparation in the EU, this is also likely to impact on the exposure. However, based on the results of this study, in many cases MDI and HDI levels were already low suggesting compliance with the BOELV in the studied activities. The main challenges are related to the activities involving spraying of diisocyanate products or where dermal exposure may be significant.

8 What are the health risks and human health impacts of the current occupational diisocyanate exposures?

Risk assessment based on the existing published and additional Finnish biomonitoring data was performed. In general, an excess bronchial hyperreactivity (BHR) risk calculated from Finnish data varied between 1.1-3.5% in construction and motor and vehicle repair sectors and for the manufacturing of PUR products. These estimates include, however, large uncertainties.

KNOWLEDGE GAPS

HBM4EU has helped to identify a number of specific data gaps and challenges that must be addressed to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. Biomonitoring of anilines is dependent on the particular aniline compound in question and there are not established methods for all potentially relevant anilines or diisocyanates.

Considering that diisocyanates may increase the asthma risk even at very low exposure levels, highly sensitive methods are needed.

HBM4EU coordinator:
German Environment Agency hbm4eu@uba.de

Knowledge Hub coordinator:
European Environment Agency hbm4eu@eea.europa.eu

www.hbm4eu.eu

HBM4EU science and policy for a healthy future

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.