Substance report

June 2022

Anilines and Diisocyanates

HBM4EU science and policy for a healthy future

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Authors and Acknowledgements

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First version (January 2020) compiled by project team at RPA consultants based on scoping documents produced by the chemical group leader (CGL) and colleagues.

The EEA has since updated this document to reflect the work developed before the conclusion of HBM4EU, with the support of the CGL and other colleagues.

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Glossary

Abbreviations	
Acute Toxicity (Acute Tox.)	Any adverse effect(s) that results from single or multiple exposures up to 24 hours. By convention, for dermal and oral routes of exposure a 24-hour period is considered while for inhalation exposure a 4-hour period is considered.
AOP	Advanced Outcome Pathway.
Biomarker	The primary chemical or its metabolites used to estimate the extent of exposure of an organism.
bw	by weight
Carcinogenic (Carc.)	A mixture or chemical that induces or increases the risk of cancer.
Carc. 1B	Carcinogenic Category 1B. Substances that are presumed to have carcinogenic potential based on animal data
Carc. 2	Carcinogenic Category 2 - Suspected of causing cancer
CMD	Carcinogens and Mutagens Directive (Directive 2004/37/EC)
CMR	Carcinogenic, Mutagenic, Reproduction
Developmental effects	Effects in the developing offspring from exposure of a parent before conception or during the period of embryonic or fetal development; such effects may include skeletal, soft tissue or functional changes in the offspring and may be observable prenatally, postnatally or at puberty.
Endocrine disruptor (ED)	A chemical that interferes with the normal functioning of the endocrine system such as to result in adverse effects on physical or neurological development, or on the functioning of the reproductive, immune and other body systems.
HBM	Human biomonitoring.
Irritation	Changes or damages after exposure to a substance. Eye Irritation (Eye Irrit.) concerns the production of changes in the eyes after application of a substance to the anterior surface of the eye and, by convention, such effects are classified as irritation if they are reversible within 21 days of exposure. Similarly, skin irritation (Skin Irrit.) is reversible damage of the skin following exposure to the substance of up to four hours.
LC-MS-MS	Liquid Chromatography with tandem mass spectrometry.
MOCA	4,4'-methylenebis[2-chloroaniline] (MOCA).
OEL	Occupational Exposure Limit.

Open one compartment model	This model assumes that the substance can enter and leave by excretion and can be used for substances that distribute rapidly to tissues and fluids.
PBTK	Physiologically based toxicokinetic modelling. These are quantitative descriptions of absorption, distribution, metabolism and excretion.
RCR	Risk Characterisation Ratio. This is the Exposure Estimate/DNEL (Derived No Effect Level) where an RCR <1 is an acceptable risk and a RCR >1 is an unacceptable risk
Reproductive toxicant (Repr.)	A mixture or chemical that has an adverse impact on the sexual function and/or fertility of a parent or on the development or viability of an offspring.
RMM	Risk Management Measure
Specific target organ toxicity (STOT SE-single exposure)	Specific non-lethal organ toxicity resulting from a single exposure to a mixture or substance.
Specific target organ toxicity (STOT RE-repeated exposure)	Specific long-term adverse changes in a specific organ resulting from repeated exposure to a mixture or substance
Substance of very high concern (SVHC)	a chemical (or group of chemical substances) for which it has been proposed that the use within the EU be subject to authorisation under the REACH Regulations due to either its serious hazardous properties and/or because it shows high persistence or accumulation sufficient to meet the criteria of Article 57 of REACH.
TDA	4,4'-Thiodianiline.
4,4’-MDA	4,4'-methylenedianiline.

1 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.

2 Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until 2021. It generates knowledge to inform about the safe management of chemicals, and hence protect human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts to build upon existing evidence bases and improve chemical risk assessment. HBM4EU compares data from across Europe which allows an understanding of regional differences and can help to identify vulnerable groups in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This substance report is based largely on the scoping document for anilines and diisocyanates produced by the EEA in 2017, the short overview report on anilines and diisocyanates produced in 2017, the deliverables produced to date and the presentation titled “Anilines” & Plans for 2020/21 “Diisocyanates” presented at the Joint Meeting of Chemical Substance Group Leaders and Management Board. ECHA information from REACH registrations, information in the C&L Inventory, and opinions and decisions from committees or authorities published in the ECHA website have also been used for this report.

This document summarises known and suspected adverse human health effects of exposure to a range of anilines and diisocyanates and indicates where HBM could be of value in the development of future EU policy, along with defining the remaining challenges to determining human exposure to anilines. Diisocyanates are also discussed as aniline derivatives, such as MDA and TDA are metabolites of respective diisocyanates (like MDI and TDI).

This substance report is intended to inform scientists, policy makers and other interested stakeholders on the potential value of HBM to establish the EU population’s exposure to anilines and diisocyanates.

2.2 Overview of Anilines and Diisocyanates

Aniline is the simplest member of the primary aromatic amines, in which one or more hydrogen atoms of the benzene ring are replaced by an amino group. Derivatives of aniline include a wide variety of different substances. Many aromatic amines are either known or suspected to cause or contribute to a variety of adverse health outcomes in humans, including methemoglobinemia, carcinogenesis, skin sensitization and others. A large number of substances in the aniline group are on the market in the EU. Several aniline derivatives can be found also from the list of substances restricted under REACH. Aniline compounds are also formed as degradation products from azo-colourants, pharmaceuticals and from aromatic isocyanates used for polyurethane polymers, lacquers, foams and adhesives. Hazardous Aniline substances that are produced or imported in the EU at amounts above 1,000 tonnes per year (tpa) according to the European Chemical Agency's (ECHA) include: aniline, o-toluidine, 4,4′-methylenedianiline (MDA), 4,4′-methylenebis[2-chloroaniline] (MOCA), p-toluidine, 1,3-diphenylguanidine, and p-phenylenediamine[1]. The sources of aniline compounds are mainly industrial, since they are used as chemical intermediates in the dying, drugs, plastics, rubber and explosives industries. Anilines can also be formed from the breakdown of certain outdoor air pollutants,and are consider pollutants both in occupational settings and in the environment.

3 Human exposure to Anilines and Diisocyanates

Exposure to anilines and diisocyanates can arise from the air (inhalation), or via ingestion and direct skin contact; the main sources and pathways of exposure are shown in Figure 1. For the general population, these include from black nylon kitchen utensils imported from China, via hair products, medical utensils and smoking (anilines, o-toluidine and p-toluidine). There is also exposure to N-acetyl-4-aminophenol (paracetamol) due to its medical applications. Some aniline compounds are well absorbed through the skin. For example, for MOCA the main exposure route in occupational settings is via skin. Also, exposure to diisocyanates may occur both via the air and skin contact, aerosol ingestion and skin contact. Exposure to o-toluidine from hair waiving products is by inhalation and dermal contact.

There is also concern for anilines that may be present in medical utensils.

[1] https://www.hbm4eu.eu/hbm4eu-substances/aniline-family/

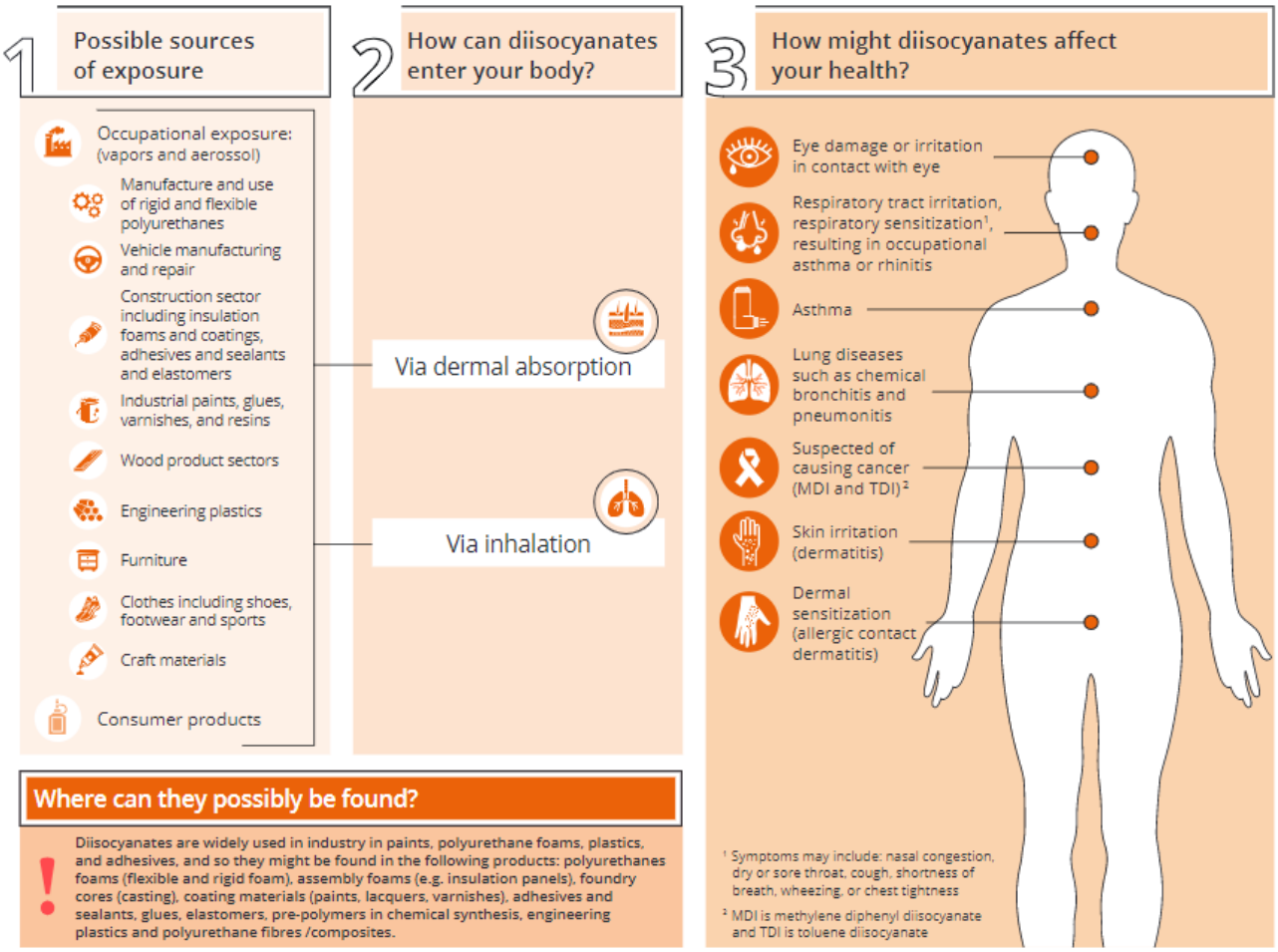

Figure 1 Overview of exposure routes and health effects of Diisocyanates

3.1 Environmental exposure

Anilines are released into the environment from the points and/or facilities where they are produced or used. 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. Generally, exposure to anilines and diisocyanates is more likely to occur in occupational settings, and to a small extent via consumer products, than environmentally.

3.2 Consumer exposure

For the general population, sources of exposure to anilines include black nylon kitchen utensils imported from China (Trier and Granby, n.d.), via hair products, medical utensils and smoking (anilines, o-toluidine and p-toluidine). There is also exposure to N-acetyl-4-aminophenol (paracetamol) due to its medical applications. Specifically, the main exposure to MOCA is via skin; exposure to diisocyanates is via the air and skin contact, aerosol ingestion and skin contact; and exposure to o-toluidine is from hair waiving products by inhalation and dermal contact. Smoking is also a source of exposure to aniline.

3.3 Occupational exposure

A significant proportion of the exposure to anilines and diisocyanates happens in occupational settings. Major use of aniline is as an intermediate in the production of different chemicals, including rubber chemicals, dyes, some pesticides, drugs and polyurethane-based polymers. It is also used in pH regulators and water treatment products and may also be formed in the thermal degradation of MDI-based polyurethane and reactions in rubber industry. MOCA is mainly used as a curing agent of the polyurethane products. It has a low vapour pressure, and it is well absorbed through the skin. Similarly, MDA is used in industrial applications, namely within an epoxy resin hardener containing technical MDA aimed at immobilizing spent ion exchange resins in a high containment matrix and the formulation of MDA mixtures for this use. Diisocyanates are widely used in different applications (e.g. foams, sealants, coatings) throughout the EU. Especially exposure to diisocyanates at small and medium sized enterprises is a concern. There is also concern for anilines that may be present in medical utensils.

4 Health impacts of Anilines and Diisocyanates

4.1 Overview of key health impacts from Anilines and Diisocyanates

Anilines are considered to be a cause of concern with regard to human health because several are known or suspected to be carcinogenic. Indeed, a number of anilines have been classified as carcinogenic to humans (Carc. 1B) or are suspected human carcinogens (Carc. 2). Aniline is also suspected to be mutagenic. Also aromatic diisocyanates, TDI and MDI has been suspected as being carcinogenic (carc cat 2) but the main concern in case of diispcyanates is their ability to cause respiratory and dermal sensitization. Diisocyanate sensitisation may occur at very low exposure levels.

The acute toxicity of anilines and diisocyanates may also be a concern, with a number classified as category three acute toxins (i.e. “classified as toxic”); whilst a number of anilines and diisocyanates are classified as category four toxins which is the mildest category for toxicity and require high exposure levels; for example an adverse effect was observed for dapsone for oral toxicity at 1,200 mg/kg bw (ECHA, 2019).

Long term exposure to aniline and several aniline derivatives can also result in methemoglobinemia and haemolytic anaemia. In addition to diisocyanates, also several aniline compounds are also classified for skin sensitisation with 2,5-TDA having been established as a potent skin sensitizer. Paracetamol (N-acetyl-4-aminophenol) at high exposures can cause sever liver toxicity.

The established or suspected impacts on human health for anilines and aniline derivates are illustrated in Figure 1.

The current EU (ECHA C&L Inventory) and/or IARC classification of selected anilines and diisocyanates is given in Table 1-1.

Table 4-1: Human health classifications		
Aniline	**Human health classifications (CLP)**	**Human health classifications (IARC)**
Aniline	Acute Tox. 3 (swallowed, in contact with skin, inhalation), Muta 2, Carc 2, STOT RE 1	Carc. 3
o-toluidine	Acute Tox 3 (swallowed, inhalation), Eye Irrit 2, Carc 1B	Carc. 1
4,4'-MDA	Skin Sens 1, Muta 2, Carc 1B, STOT SE 1, STOT RE 2	Carc. 2B
p-toluidine	Acute Tox 3 (swallowed, in contact with skin, inhalation), Eye Irrit 2, Skin Sens 1, Carc 2	-
1,3-diphenylguanidine	Acute Tox 4 (swallowed), Skin Irrit 2, Eye Irrit 2, STOT SE 3, Repr 2	-
p-phenylenediamine	Acute Tox 3 (swallowed, in contact with skin, inhalation), Eye Irrit 2, Skin Sens 1	-
MOCA	Acute Tox 4 (swallowed), Carc 1B	Carc. 1
4,4'-Methylenediphenyl diisocyanate	Acute Tox 4, Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, STOT SE 3, Resp. Sens, 1, Carc. 2, STOT RE 2	Carc. 3
4,4-oxodianiline	Acute Tox 3, Muta. 1B, Carc. 1B, Repr 2	Carc. 2B
Dapsone	Acute Tox 4	Carc. 3

Key:

Acute Tox. category 3 – Mild acute toxicity (category 1 is most toxic with category 4 the mildest)

Acute Tox. category 4 – Mild acute toxicity (category 4 is the lowest concern level)

Carc .1B – Substances that are presumed to have carcinogenic potential based on animal data

Carc. 1 (IARC classification) – Substance is carcinogenic to humans

Carc. 2 – Substances that are suspected of causing cancer

Carc. 2B (IARC classification) – Substance is possibly carcinogenic to humans

Carc. 3 (IARC classification) – Not classifiable for its carcinogenicity to humans

Eye Irrit. Category 2/Skin Irrit. 2 – Category 2 substances are classed as irritants with reversible damage

Muta. 2 – May cause mutagenic (genotoxic) damage

Skin Sens. Category 1 - Substances in this category may cause an allergic skin reaction

STOT SE category 1- Toxic to humans after single exposure from animal studies

STOT RE category 1 – Toxic to humans after repeated exposure from studies in experimental animals

STOT RE category 2 – Presumed to be toxic after repeated exposure from studies in experimental animals

Table 2-2 Overview of CLP classifications for Anilines and Diisocyanates

Substance	Properties of concern				Category according to CLP criteria								ECHA info card
	Carcinogenicity (IARC)	Mutagenic	Skin sensitising (SS)	Reproductive Toxicity	Carcinogenicity	Acute Toxicity	Specific target organ tox (repeated exposure)	Reproductive Toxicity	Mutagenic	Eye Damage/ Eye Irritation	Skin Sensitivity	Skin Corrosion/ Irritation	
MOCA / 101-14-4													Link
MDA /101-77-9													Link
MDI /101-68-8													Link
Aniline /62-53-3													Link
o-Toluidine /95-53-4													Link
p-Toluidine /106-49-0													Link
p-PDA /106-50-3													Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.); ** Based on IARC classification. Blank cells denote a lack of classification.

4.2 Vulnerable target groups

The most vulnerable group is workers as they are highly exposed.

4.3 Societal concerns

A citizen survey was conducted across Europe as part of HBM4EU, with over 5,000 valid responses spanning 30 countries. The objective of the survey was to understand citizens awareness and concerns regarding chemical exposure and human biomonitoring.

Regarding citizens' concerns on chemical exposure, in all regions, industrial emissions and pollution were ranked the highest concern of all possible chemical exposures, with Pesticides in food and in the environment ranked second and third for overall answers. Contaminants in drinking water and food were also of high concern, followed by chemicals in drinking water and road traffic (see Figure 2).

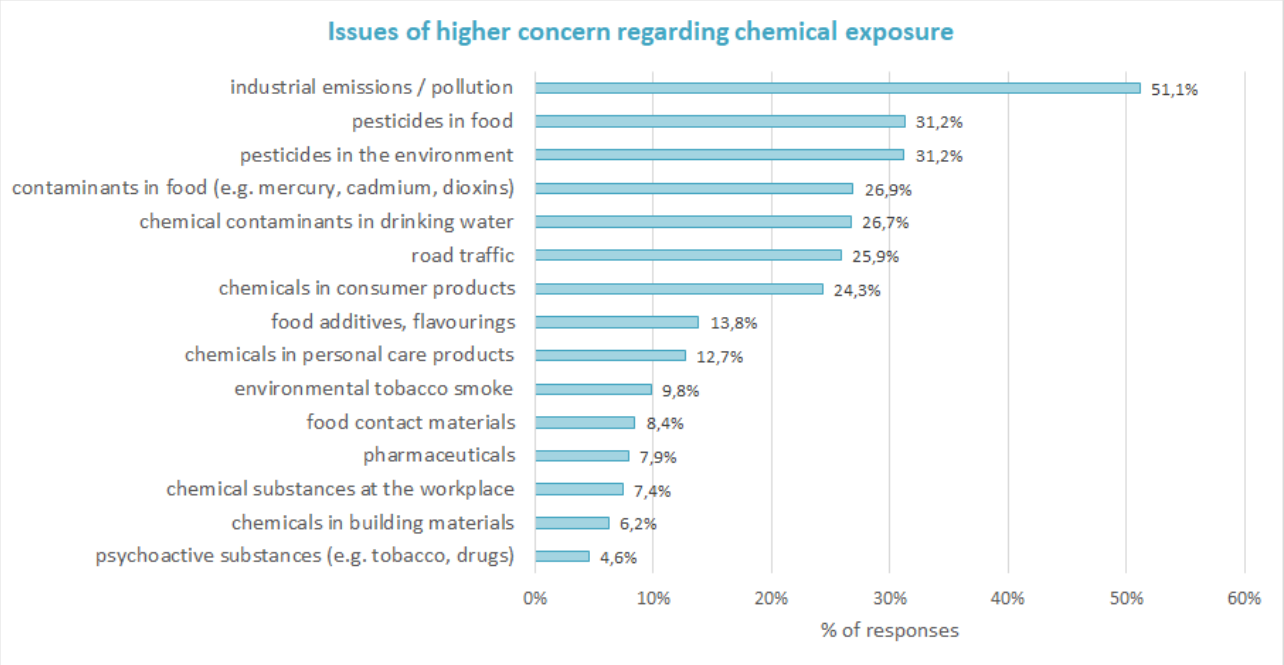

Figure 2 Overall answer distribution on issues of higher concern regarding chemical exposure

While there isn't evidence of specific societal concern directed towards anilines and/or diisocyanates, insofar as they are industrial chemicals and affect the public via industrial pollution, they would be included in the highest concern category. In addition, specific concerns about paracetamol/acetaminophen may be under-recognized (Lau et al., 2016).

Concerning the use of Human Biomonitoring of toxic chemicals, 87 % of the respondents of the HBM4EU citizens' survey supported the use of HBM and said it should be used more, with 50 % saying it should be undertaken as regularly as food and water quality tests, with a stronger coordination at the European level, and near 60 % considered it should be included in the National Health Surveys.

Over 65 % of the respondents strongly supported the importance of HBM studies for the purposes of: evaluating chemical exposure of the population, study the health impacts of chemical exposure, the development of health policy that promote the safe use of chemicals, to support occupational health policies and the safe use of chemicals at work, to raise awareness/understanding the impact

of chemical exposure amongst the population and to raise awareness/understanding of the impact of chemical exposure amongst health professionals and policy makers.

Overwhelmingly, citizens chose food, the environment and drinking water as priority areas of chemical exposure to be addressed by human biomonitoring studies (see Figure 3)

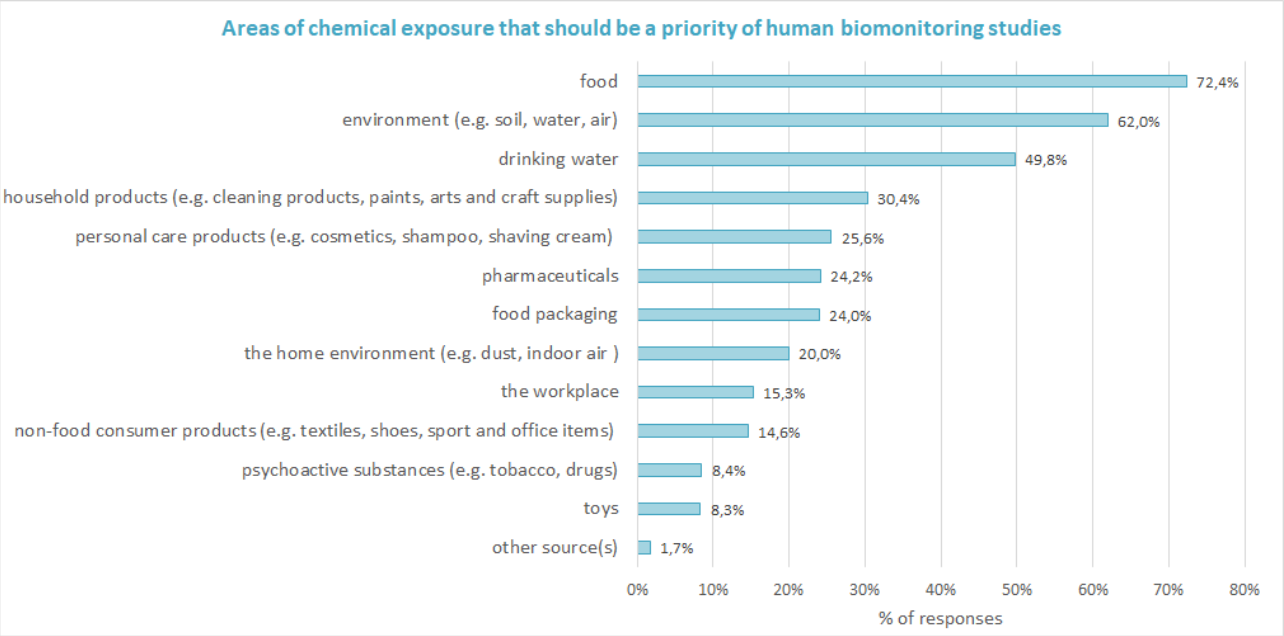

Figure 3 Priority areas in human biomonitoring

It is also noteworthy that, conversely, 13 % of the survey respondents supported the idea that HBM should not be done at all. A round of focus groups in several countries that were also part of the survey provided additional insights. Notably, the level of awareness about human biomonitoring was relatively low across countries and was not related with educational attainment. Moreover, beyond human biomonitoring, the awareness of the potential ill health effects from chemical exposures was also low, underscoring the importance of awareness raising and public education activities and policies.

4.4 Evidence-base on use of human biomonitoring

The evidence base in the literature is sparse, with only eight studies identified for biomonitoring and exposure monitoring of aniline exposure and there appears to be a lack of studies on the aniline group of chemicals as a whole.

Aniline metabolites are biphasic with the unbound portion being excreted rapidly whilst the portion bound to blood protein has a long half-life. LC-MS-MS is available to measure exposure based on urine samples for the various biomarkers.

The development of ICI/EQUAS techniques for aromatic amines (MOCA, MDA, TDA, aniline, o-toluidine) is currently in progress. The current focus for the period 2020-2021 is on diisocyanates (which are listed on the second priority list of HBM substances but are also found within the anilines Priority Substance Group). In this respect, it should be noted that MDA and TDA are metabolites of the diisocyanates.

5 EU policies on Anilines and Diisocyanates

Several policy measures have been introduced in the EU to reduce anilines and diisocyanates exposure. These include measures under REACH and others. 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), meaning it can be subject for authorization at some stage in future.

Diisocyanates (e.g. MDI, TDI, HDI) are planned to be restricted under REACH, 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.HBM4EU Main Findings To Date

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6 Policy questions for Anilines and Diisocyanates

6.1 Introduction

For each of the HBM priority substances stakeholders were asked to identify policy related questions that HBM4EU should address in order to contribute to the strengthening of policy ambitions on Anilines and Diisocyanates. Further background detail on Anilines and Diisocyanates and how the policy questions were selected is available in the scoping document (add hyperlink to the word "scoping document") and the report on stakeholder consultation and mapping of needs. Anilines and Diisocyanates's policy questions are summarised below.

6.2 What is the current occupational exposure to aniline and different aniline derivatives in the EU?

The available data are limited and scattered. However, many anilines are restricted or authorized, which limits exposure. Therefore, no studies to study e.g. MOCA or MDA exposure were planned under HBM4EU. The main exposure to anilines is from the use of anilines in chemical manufacturing. There are some existing studies which have been performed biomonitoring of o-toluidine in general population and workers. A risk assessment performed within HBM4EU suggested a low concern for carcinogenicity related to this exposure (Huuskonen et al., 2022). Occupational exposure to diamine forming diisocyanates were studied in a targeted occupational study in five countries in 2020-2022. The results showed variable exposure levels, which were, however, below the existing biological guidance/limit values. Risk assessment performed within HBM4EU shows however that even these levels may not be without risk since respiratory sensitization to diisocyanates may occur even at very low exposure levels.

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

Single studies performed in Germany and Denmark suggesting wide-spread exposure due to the consumption of paracetamol.

6.4 What are the risks related to these exposures?

A risk assessment has been performed already earlier for MOCA under REACH. This risk assessment used HBM data and provides a good example how HBM can be used to refine the risk assessment. Risk assessment has been performed for o-toluidine under WP5 and for diamine forming diisocyanates under WP5. PBPK model for o-toluidine was created in WP12. AOPs for o-toluidine have been prepared in under WP13. Under WP12 a PBPK model is created for diamine forming diisocyanates. This was used in risk assessment.

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

MOCA and MDA are authorised under REACH resulting in limiting numbers of exposed workers. Based on the existing data from UK and Finland, there has been a decrease in occupational exposure to MOCA. Therefore, MOCA was not considered a good candidate for further research within HBM4EU. Exposure to diamine (MDA, TDA, HDA) forming diisocyanates (MDI, TDI, HDI) was studied under AWP2020-2021 for occupational exposure. However, since REACH restriction concerning diisocyanates is entering in force only 2023, it is too early to assess its impact on occupational exposure to diisocyanates.

6.6 What are the possible uses of Human Biomonitoring for risk assessment?

The potential value of HBM in the risk assessment of aniline was already demonstrated by the first REACH authorisations for MOCA (e.g. ReachLaw Ltd 2016) for which dermal/inhalation modelling techniques resulted in a significant overestimation of exposure when compared to the exposure estimates based on urinary levels of the substance.

Risk assessment performed for o-toluidine provides a model on the use of HBM data in the risk assessment of o-Toluidine for example in future regulatory activities under REACH. A PBPK model used in WP12 can be used to back-calculate urinary levels as external exposure which can be then compared to the external limit values.

Output from the project for diisocyanates could support the implementation of a new binding OEL for diisocyanates under the Chemical Agents Directive (CAD) and also to follow-up the effectiveness of REACH restriction for these substances.

7 Diisocyanate policy questions:

7.1 What is current occupational exposure to diisocyanates?

This new data from HBM4EU diisocyanate study (performed under WP8) 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. Additionally, air levels were in these cases close or below the LOQ. 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.

Also unpublished Finnish HBM data, which was used in the risk assessment of diisocyanates performed under WP5, also indicated low exposure to diisocyanates. In some occupational sectors, the earlier published data estimate higher exposures. Overall, there is still a need to monitor the occupational exposure to diisocyanates because a threshold limit value for BHR cannot be established.

7.2 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.

7.3 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 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.

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

In general, the excess BHR risk estimated from Finnish data was highest for MDI, especially in the construction sector where an excess BHR risk of 3.5 % was estimated. This indicates that for the Finnish construction sector, the expected excess number of BHR cases is 200. Also for HDI and TDI, the construction sector poses the highest risk: 2.9 % and 3.2 % accounting for 165 and 180 excess BHR cases in the Finnish worker population, respectively. For the other sectors (the motor and vehicle repair sector, manufacturing of PUR products and assembling of industrial products) excess risk estimates were between 1.1 – 3.0 %.

8 HBM4EU outputs

8.1 Categorisation

Substances under HBM4EU have been categorised depending on availability of HBM data. The categorisation indicates the information gaps allowing the development of targeted activities to fill the knowledge gaps. Substances will pass from Category E over D, C, B towards Category A as more information becomes available. Fully characterised substances should end up as category A substances.

Table 1-3 HBM4EU categorisation for Anilines and Diisocyanates

Category	Priority substance(s)	Details
A	MOCA / 101-14-4	HBM data are sufficient to provide an overall picture of exposure levels across Europe, and interpretation of biomonitoring results in terms of health risks is possible. Risk management measures have been implemented at national or European level. Improvement of knowledge for these substances will therefore focus on policy-related research questions and evaluation of the effectiveness of existing regulatory measures.
A	MDA /101-77-9	
B	MDI /101-68-8	HBM data exists, but not sufficiently to have a clear picture across Europe. Also, knowledge on the extend of exposure, levels and impact on the human health should be improved, in order to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. Analytical method and capacities to monitor the substances across Europe might have to be improved.
B	Aniline /62-53-3	
B	o-Toluidine /95-53-4	
C	p-Toluidine /106-49-0	HBM data scarcely or doesn't exist. Efforts to develop an analytical method to obtain relevant HBM results need to be done Hazardous properties of the substances are identified, yet greater knowledge on toxicological characteristics and effects on the human health is needed. Interpretation of HBM data is not possible, due to the lack of HBM guidance values.
C	p-PDA /106-50-3	

8.2 Key outputs

Current occupational exposure to aniline and derivatives (including diamine forming diisocyanates) in the EU

The available data on the occupational exposure to relevant aniline compounds have been collected under WP7.1 and summarised under AD8.1 (Report on access to occupational data). According to this analysis, 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. Since biomonitoring is only method to measure occupational exposure to them reliably, in WP9 those laboratories which are able to provide MOCA/MDA biomonitoring were identified. These laboratories performing analysis of different aniline compounds (including MOCA and MDA) have been listed in D9.3 (Database of candidate laboratories for the 1st prioritisation round of substances) and ICI/EQUAS for aromatic amines was performed between 2019-2020.

Occupational exposure to aniline itself is mostly related to its use in chemical manufacturing. Regarding diisocyanates, a systematic review on occupational exposure to diisocyanates were made under HBM4EU. This showed that the recent biomonitoring data on occupational exposure to diisocyanates is limited, especially in some specific uses e.g. in construction sector (Scholten et

al., Ann Work Expo Health. 2020 Jul 1;64(6):569-585). Therefore, an occupational study on the exposure to diisocyanates in specific sectors were designed. Focus was mainly on the use of MDI in different construction uses or in glues and the use of HDI in motor vehicle sector. Results on this study suggest that although measurable levels were detected, the exposure especially to MDI remains rather low, below the proposed limit values for diisocyanates. These low levels require highly sensitive methods for their biomonitoring since the levels are close to the currently used LOQs. However, asthma risk cannot to be excluded even at the relatively low exposure levels, as noted in risk assessment made under WP5.3. Therefore, monitoring of exposure and use and further development of highly sensitive HBM methods is needed. More sensitive methods to detect dermal exposure is also needed since dermal exposure can contribute to the health risk. PBPK models developed under WP 12 help us to convert urinary MDA/TDA levels as external intake allowing the assessment of asthma risk. 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. However, available biomonitoring data on o-toluidine allowed the risk assessment for workers and general population.

Exposure to paracetamol (aniline metabolite) among the general population

There are single studies in Germany and Denmark on the exposure of general population to paracetamol. These has been described in aniline scoping document (D4.2 Scoping documents for 2018). To get a better overview of the paracetamol exposure, inclusion of paracetamol in the studies conducted under WP8 in general population would be needed. The European HBM dashboard has 1 dataset (from Denmark) with paracetamol exposure data integrated. The mixture risk assessment performed under WP15 suggests that paracetamol exposure may have a relevant contribution to the combined risk caused by reprotoxic agents.

Risks related to exposures to the anilines family

WP5.3 deliverable report D5.1 (Human Biomonitoring in risk assessment: analysis of the current practice and 1st examples on the use of HBM in risk assessments of HBM4EU priority chemicals) describes the recent risk assessment of MOCA under REACH, which serves as a good example on the use of biomonitoring in risk assessment.

In 2018 a risk assessment utilising HBM data was performed for o-toluidine under WP5, included in the Deliverable Report D5.5 (Human Biomonitoring in risk assessment: 2nd set of examples on the use of HBM in risk assessments of HBM4EU priority chemicals). In summary, a one-compartment model-based approach was used to estimate the urinary levels corresponding to the external intake levels of o-toluidine or vice versa. This allowed the comparison between available HBM data and existing binding occupational exposure level (OEL) and established cancer risk estimates. A scientific paper on this is in preparation (Huuskonen et al., 2022).

The results suggested that the workers exposed to o-toluidine have a cancer risk below 1:10 000 . 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).

However, the result includes several uncertainties, related especially to the limited amount of HBM data available, and therefore the RA should be seen as an example. In addition, further data on the toxicokinetics of o-toluidine in occupational settings, focusing especially to the correlations between external intake and urinary levels, would strengthen the assessment.

To strengthen risk assessment of o-toluidine, PBPK modelling to calculate external intake based on the urinary o-toluidine levels were performed under WP12. The results of this modelling are

comparable to those obtained earlier by using urinary mass balance-based calculation approach. These results were used to calculate RCRs and were reported in D12.5.

AOPs for anilines and diisocyanates have been developed under to support human health risk assessment.

D5.11 describes the risk assessment of diisocyanates in which the excess BHR risk was estimated based on Finnish biomonitoring data. Bronchial hypersensitivity (BHR) risk was highest for MDI, especially in the construction sector where an excess BHR risk of 3.5 % was estimated. Also for HDI and TDI, the construction sector poses the highest risk: 2.9 % and 3.2 % . For the other sectors (the motor and vehicle repair sector, manufacturing of PUR products and assembling of industrial products) excess risk estimates were between 1.1 – 3.0 %.

Possible impact of REACH on the exposure and risks

WP5.3 deliverable report D5.1 (Human Biomonitoring in risk assessment: analysis of the current practice and 1st examples on the use of HBM in risk assessments of HBM4EU priority chemicals) describes the current situation with MOCA and MDA which are authorised under REACH. Because of the authorisation there are only limited number of exposed workers in EU. Occupational biomonitoring data collected under WP7.1 and summarised under AD8.1 (Report on access to occupational data) describes a decline in the exposure to MOCA observed in UK and in Finland. Therefore, MOCA was not considered as a good candidate for further research under HBM4EU although laboratories performing biomonitoring of MOCA are still needed in EU as long as it is used.

Regarding MDA, AD8.1 describes the potential exposure to MDA (and similar diamine TDA) via the production and use of diisocyanates. A study to collect new data on occupational exposure to diisocyanates was conducted in 5 countries between 2020-2021. Although the results cannot yet inform on the impact of REACH restriction, it will provide baseline data for the future assessment of the impact of REACH restriction/becoming EU OEL for diisocyanates.

8.3 Key data gaps and challenges

HBM4EU is a five-year project, that kicked off in 2017 and finished in June 2022. HBM4EU has helped to identify several specific data gaps that are needed to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. However, some gaps and needs for action will remain after the end of HBM4EU which should be addressed in the future:

The challenges faced in using HBM data to assess human exposure to anilines and diisocyanates are indicated in Figure 4. Analytical measurement of HBM data requires the development of validation data. Exposure estimation is also highly dependent on the particular anilines or diisocyanates in question and the lack of a common methodology with which to measure aniline exposure presents a challenge.

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

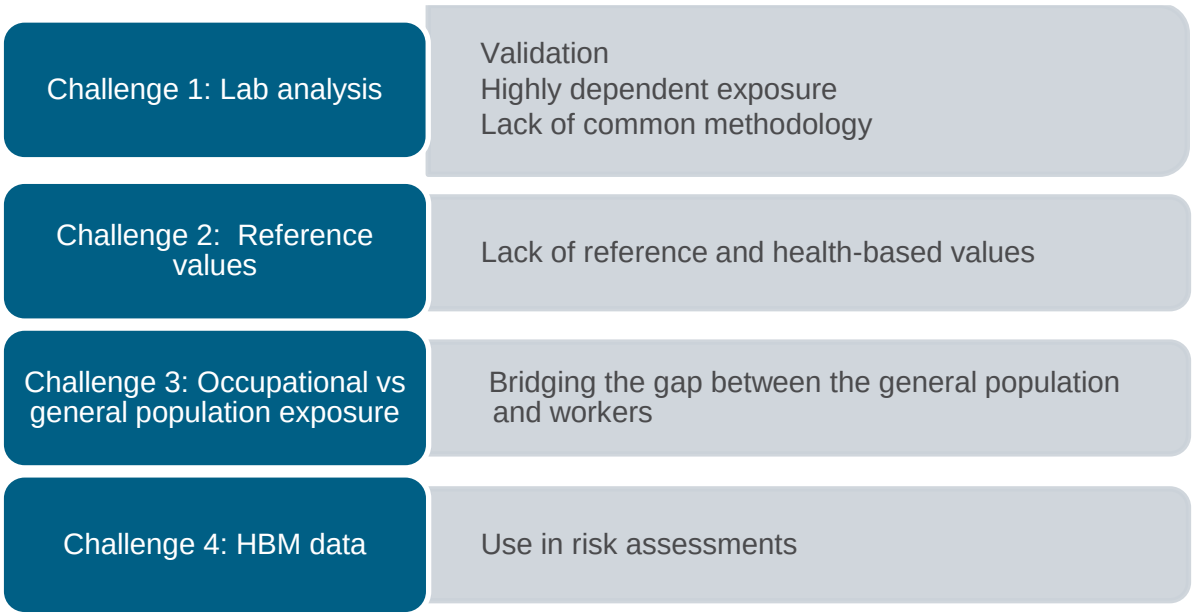

Figure 4 Key data gaps for anilines and diisocyanates

9 Future recommendations

Anilines is a huge group of hazardous substances. Very limited information is available on the exposure of population from different sources. There is a need for further studies on the population exposure to aniline compounds.

There is a need for further follow-up of occupational exposure to diisocyanates to evaluate the impact of the becoming regulatory measures. High sensitivity of the analytical methods is needed for the biomonitoring of diisocyanate exposure.

10 References

Huuskonen et al (2019). Risk assessment for an aniline derivative ortho-toluidine by using human biomonitoring data. Eurotox 9-11.9.2019, Helsinki, Finland.

HBM4EU (2019) CGL meeting Main results “Anilines” & Plans for 2020/21 “Diisocyanates”