HBM4EU science and policy for a healthy future

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SCOPING DOCUMENTS

(1st round of prioritization)

Prioritized substance group: Anilines

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1. Introduction

HBM4EU has established Chemical Working Groups during the proposal phase for the nine prioritized substance groups that HBM4EU will work on in 2017 and 2018. Additional substance groups will be identified by late 2018 through the implementation of a refined prioritization strategy.

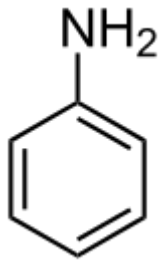
For each substance group, scoping documents are produced under Workpackage 4.4 of HBM4EU. The scoping document will contain a review of the available evidence, will list policy-related questions, identify knowledge gaps and propose research activities. Proposed activities will be fed into the framework of work packages and tasks of HBM4EU in a coordinated and harmonized manner, and will constitute the basis for the annual work plans. The scoping documents are the linkage between policy questions and the research to be undertaken (broken down for single substances) in order to answer those questions. This methodology will optimize work on the different substances, avoid redundancies, ensure coordination and facilitate the calculation of budgets for each WP. The scoping documents do not contain a comprehensive literature review per substance group but are intended to provide information for the WP leaders who will draft the Annual Work Plans.

For the selected substance groups the availability of (toxicology or human biomarker) data is variable. A scheme was therefore developed to classify the compounds within each substance group into categories A, B, C, D and E based on the availability of data to answer research questions (see further). In direct response to the key project goal of exploiting HBM data in policy making to positively impact on human health, the research activities for each substance group will generate knowledge on exposure trends and associated health effects. Throughout the course of the project, we will generate knowledge that will shift substances towards to a higher level of knowledge category.

For further information see www.hbm4eu.eu

2. Background Information

Aniline is the simplest member of the primary aromatic amines, in which one or more hydrogen atoms of the benzene ring are replaced by amino (-NH2) group. Derivatives of aniline include a wide variety of different substances. Some of these (like benzidine and MOCA) are composed of two combined aromatic rings.



Picture 1: Structure of aniline, the simplest member of the aniline group.

Many aromatic amines may cause methemoglobinemia in humans. Aniline and many of its derivatives are known or suspected human carcinogens. Several aniline derivatives can also cause skin sensitization. Classical members of this family are bladder carcinogens 2-naphtylamine and benzidine, which use has been restricted in EU and there is therefore no exposure to these compounds. Aniline compounds are also formed as degradation products from e.g. azo-colourants, pharmaceuticals and from aromatic isocyanates used for polyurethane polymers, lacquers, foams and adhesives. Search from European Chemicals Agency (ECHA) website from authorization list, candidate list of substances of very high concern (SVHC) and registration lists with a search term “aniline” results in more than 2000 search results. Several aniline derivatives can be found also from the list of substances restricted under REACH.

When looking at the aniline substances which are produced or imported in EU areas according to ECHA registration database at amounts above 1000 tonnes per year (tpa) and which have significant health hazards (other than only irritation/corrosion) the following substances can be retrieved:

- aniline, CAS: 62-53-3, harmonized classification in EU; H301, H311, H318, H317, H331, H341, H351, H372, H400
- o-toluidine, CAS: 95-53-4, harmonized classification in EU; H301, H319, H331, H350, H400
- 4,4'-methylenedianiline (4,4’-MDA), CAS: 101-77-9, harmonized classification in EU: H317, H341, H350, H370, H373, H411
- 4,4'-methylenebis[2-chloroaniline] (MOCA), CAS: 101-14-4, Harmonized classification in EU: H302, H350, H400, H410
- p-toluidine, CAS: 106-49-0, harmonized classification in EU: H301, H311, H319, H317, H331, H351, H400
- 1,3-diphenylguanidine, CAS: 102-06-7, harmonized classification in EU; H302, H315, H319, H335, H411, H361f
- p-phenylenediamine, CAS: 106-50-3, harmonized classification in EU; H301, H311, H319, H317, H331, H400, H410

Many anilines have been registered for intermediate use only. These include for example 4-aminoazobenzene, 4-methyl-m-phenylenediamine, 6-methoxy-m-toluidine, 5-nitro-o-toluidine, 4,4’-

methylenedi-o-toluidine. Although also these compounds have serious health hazards, they are not considered further because of the limited exposure due to intermediate use. Below, some anilines are discussed in some detail.

1.1.1. MOCA, MDA and diisocyanates

4,4-methylenebis(2-chloroaniline) (MOCA) and 4,4-methylenedianiline (MDA) are currently authorized under REACH. Both of these chemicals are genotoxic carcinogens to which a threshold for carcinogenic effects cannot be assigned. Both MOCA and MDA are easily absorbed via the skin. Therefore, biomonitoring is the best method for assessing occupational exposure to them. MDA is also a degradation product and a metabolite of MDI, one of the diisocyanates.

MOCA

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. Therefore biomonitoring is the best method to assess occupational exposure to it. Exposure to MOCA can be biomonitored by measuring MOCA excreted into the urine (free and conjugated MOCA). These methods are well established and used in occupational surveillance of workers. ECHA has recently made a dose-response analysis for the carcinogenicity of MOCA and calculated cancer risk levels for different urinary MOCA levels measured as total urinary MOCA in the end of the work-shift in the end of the work week (ECHA, 2015a). Also the EU Scientific Committee on occupational exposure limits (SCOEL) has recommended a biological guidance value (BGV) for MOCA (SCOEL, 2013). There is one application for authorization for MOCA (ECHA, 2016a). It covers up to 89 sites in EU using MOCA as a curing agent in polyurethane production. Estimated number of exposed workers in EU is, however, only about 200. Authorization has been applied for 12 years. There is, however, no European Commission (EC) decision nor ECHA's Risk Assessment Committee (RAC) and Socio-Economic Analysis Committee (SEAC) recommendation on the authorization available yet.

The applicant has used biomonitoring data to assess the workers' exposure to MOCA. In addition, there are established methods available and published studies, especially from UK, on the biomonitoring of MOCA. Since there are substitutes for MOCA available for the use in polyurethane production, the use of MOCA may cease within becoming years when companies are able to move to the substitutes.

Therefore, MOCA might not be a very relevant candidate for further studies under HBM4EU although biomonitoring of MOCA would still be needed in EU as long as there are authorized uses in the EU. Furthermore, biomonitoring in workers should reveal a decrease over time (monitoring policy effectiveness). The general population is not exposed to MOCA, and the levels of MOCA and its metabolites in the urine of the general population are below the detection limits.

4,4'-MDA

Similarly to MOCA, the production and use of 4,4'-MDA is authorized under REACH. Like MOCA, also 4,4'-MDA is well absorbed through the skin and biomonitoring is the best method to assess occupational exposure to it. There are well established methods for the biomonitoring of 4,4'-MDA, which are based on the analysis of total urinary MDA excretion. The risk assessment committee (RAC) of ECHA has derived a dose-response for the carcinogenicity of MDA and calculated cancer risk levels for different urinary 4,4'-MDA levels measured as total urinary 4,4'-MDA in the end of the work-shift in the end of the work week (ECHA, 2015b). There are only two applications for authorization under REACH. They concern 1) the industrial use of an epoxy resin hardener containing technical MDA aimed at immobilizing spent ion exchange resins in a high containment

matrix and 2) the formulation of MDA mixtures for this use. For these uses, there are RAC and SEAC opinions available and a 12 years review period has been proposed for these uses (ECHA, 2017ab). Total number of exposed workers in these uses is 56. The applicant of the authorization provided biomonitoring datasets on the exposure of workers in these uses, and these data were used by RAC in the assessment of excess cancer risk to workers. Due to the limited use (other than intermediate use) and limited number of workers exposed to MDA, occupational exposure to 4,4'-MDA in its industrial use is not a good candidate for further work under HBM4EU.

Diisocyanates

MDA is one of the degradation products and main metabolites of methylene diphenyldiisocyanate (MDI, CAS 101-68-8). Measurement of urinary MDA can be also used to measure the occupational exposure to MDI. Similarly, toluene diamine (2,4-TDA or 2,6-TDA) can be used as a marker for exposure to toluene diisocyanate (TDI, CAS 584-84-9 for 2,4-TDI and 91-08-7 for 2,6-TDI). These diisocyanates are widely used in different applications (e.g. foams, sealants, coatings) throughout the EU, total volume in commerce is 2.5 million tpa (ECHA, 2016b). These diisocyanates (together with non-aromatic hexamethylene diisocyanate, HDI) are important occupational respiratory sensitizers; they are causing several thousand new cases of respiratory allergies (mainly asthma) annually in Europe. 4,4'-MDA (and isomers) is also the major cause of non-compliance of black nylon kitchen utensils imported from China, and the continuous EC testing requirement under the food contact materials legislation EC 10/2011. The source is likely from recycled polyamide (nylon), and from polyamide containing isocyanate lacquers used to coat the glass fibre reinforcement in the utensils. Aromatic isocyanates are also used in adhesives for laminated flexible plastic food packaging. (Mortensen et al. 2005, Trier et al. 2011). Aromatic Polyurethane polymers are also used in medicinal utensils, e.g. for stomi-bags, as nets operated into patients, in blood bags and tubings, as breast implants from where metabolites have been released and measured in the patients' blood causing sensitisation.

The use of the diisocyanates MDI, TDI and HDI has been recently proposed to be restricted in EU unless specific conditions for workers training and risk management measures apply. 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. Diisocyanate sensitization can occur at very low exposure levels, and sensitive methods to assess exposure e.g. by measurement of diamine levels in urine are still needed in the future. There may be a need to study the possibility to improve the sensitivity of the current diisocyanate monitoring methods, and the effectiveness of the possible restriction on the occupational exposure to diisocyanates. Especially exposure to diisocyanates at small and medium sized enterprises is a concern.

There is also a need to better understand the 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.

1.1.2. Aniline and paracetamol

Aniline has been assessed under the existing chemicals regulation in EU (ESR, the pre-REACH EU-wide chemicals legislation). It is currently classified as a suspected carcinogen (carc cat 2) under the Classification, Labelling and Packaging Regulation (CLP) in the EU. In addition to the concerns related to the genotoxicity and carcinogenicity, it can cause methemoglobinemia and haemolytic anaemia after long term exposure. 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. Smoking is also a source of exposure to aniline. The EU risk assessment report from 2008 (based on the ESR) concludes that there is a need to limit the risk especially for workers but also for the general population near the point sources and consumers due to residues in different products. The main cause of concern is its carcinogenicity and genotoxicity (http://echa.europa.eu/documents/10162/d537626b-e5b6-43e9-a7d2-582468edcc24). Toxicity of aniline has been recently assessed also by SCOEL. There are validated biomonitoring methods available for aniline, and e.g. SCOEL has recommended a biological limit value based on the measurement of p-aminophenol in urine (SCOEL, 2016). It is also possible to measure aniline itself from the urine or haemoglobin adducts from blood samples. There are some biomonitoring data available both of the general population and workers exposed to aniline. Aniline has not been currently listed as SVHC substance, nor is it subject of any restrictions under REACH. However, it is listed in the PACT-RMOA list under REACH, which includes substances for which a risk management option analysis (RMOA) or an informal hazard assessment for PBT/vPvB (persistent, bioaccumulative and toxic/very persistent and very bioaccumulative) properties or endocrine disruptor properties is either under development or has been completed since the implementation of the SVHC Roadmap commenced in February 2013. RMOA for aniline was completed in December 2015 and concluded that no action is needed at this time. However, it was noted that the recent exposure data was limited for both workers and for consumers (RIVM, 2015). Further regulatory actions on the aniline could benefit of additional data on both occupational and general population exposure to aniline. A metabolite of aniline, N-acetyl-4-aminophenol, is a commonly used drug, paracetamol, which can cause severe liver toxicity if used at high amounts. Ubiquitous exposure to paracetamol among general population have been demonstrated by Holger Koch's group (Modick et al 2014) who also detected measurable paracetamol levels in the Danish Democophes samples from 2011 (Nielsen et al 2015). The studies from Denmark related self-reported paracetamol intake of the mothers and her reporting of child intake to the biomonitoring of paracetamol among general population, including children and found no clear associations indicating an unknown source (Jensen et al.2014, Nielsen et al 2015, Graungård et al 2016).

o-Toluidine is classified as carcinogenic, cat 1B (May cause cancer; H350). It is manufactured and/or imported in the European Economic Area in 10 000 - 100 000 tpa. SCOEL has recently published a recommendation on o-toluidine, which includes also a recommendation for a biological guidance value (SCOEL, 2016). Although there are published methods for the biomonitoring of o-toluidine, limited biomonitoring data is available. The main uses of o-toluidine include its use as a curing agent in epoxy resins and an intermediate in producing azo dyes and pigments, acid-fast dyestuffs, triarylmethane dyes, sulphur dyes, indigo compounds, photographic dyes and synthetic rubber and rubber vulcanising chemicals. The largest use is, however, as an intermediate in the manufacture of herbicides. Earlier it was used in dyes and pigments. o-Toluidine is banned from cosmetics by the EU Cosmetics Regulation, also the use of azo dyes that release o-toluidine during degradation is not permitted for textiles and other consumer articles in the EU. Still, there are recent reports describing hairdressers exposure to it via the hair waiving products (Johansson et al., 2015). Cherry et al (2011) has estimated that the number of o-toluidine exposed workers in EU is about 5500, mainly in the manufacture of other chemicals.

Taking into account that exposure may still occur via hair waiving products, the actual number may be higher. Also general population is exposed to background levels of o-toluidine.

p-Toluidine (4-aminotoluene) is manufactured and/or imported in the European Economic Area (1 000 - 10 000 tpa). It is classified as suspected carcinogen (H351). Its main use is in the

manufacturing of other chemicals, including dyes, pigments, lubricants and polymer additives. Smoking causes exposure to p-toluidine and it is found in urine in the general population. In hairdressers, no increased exposure to p-toluidine compared to the exposure of general population was seen in a single study (Johansson et al., 2015).

p-PDA

p-Phenylenediamine (CAS 106-50-3) is a common contact allergen present in cosmetics and e.g. in hair dyes and e.g. tattoo inks. It has caused many occupational allergies e.g. among hairdressers exposed due to the contact with hair dyes. It has also been found in black nylon kitchen utensils, like 4,4'-MDA. It has not been regularly biomonitored, although analytical methods for the analysis of it or its metabolites in urine or blood have been published. In these studies exposure of hairdressers to p-PPD has been described. The main hazardous property of p-PDA is its skin sensitizing ability. It has not been listed as SVHC substance, nor is it subject of any restrictions under REACH. However, it has been listed in the PACT-RMOA list under REACH, which includes substances for which a risk management option analysis (RMOA) or an informal hazard assessment for PBT/vPvB (persistent, bioaccumulative and toxic/very persistent and very bioaccumulative) properties or endocrine disruptor properties is either under development or has been completed since the implementation of the SVHC Roadmap commenced in February 2013.

In addition, some of the available studies describe potential exposure to other sensitizing aromatic diamines, like 2,5-TDA, m- and p-aminophenols due to the hair dyes. For example, EU Scientific Committee on Cosmetic Products (SCCP, 2007) has concluded that 2,5-TDA is very potent sensitizer and its use in hair dyes cannot be considered safe based on the available data.

Other high production volume (HPV) aniline compounds

Other substances manufactured/imported in EU >1000 tpa include 1,3-diphenylguanidine (CAS 102-06-7). No biomonitoring studies were found. It is manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tpa. 1,3-diphenylguanidine is used in polymers and manufacturing of rubber and can be released in the environment from many construction, textile, furniture and rubber materials. Few occupational contact allergies have been reported due to 1,3-diphenylguanidine. It is classified as suspected of damaging fertility (H361). It has been subject for substance evaluation under REACH and there are some concerns on its potential genotoxic activity. Another comment raised during the evaluation process relates to the degradation products which may be formed e.g. during rubber manufacturing. These may include e.g. aniline.

Anilines manufactured or imported (in commerce) in EU at amounts of 100-1000 tpa include following substances:

- *N,N-diethylaniline* (CAS 91-66-7), in commerce in the European Economic Area (EEA) in 100 - 1 000 tpa and finds its main uses in the manufacture of other chemicals and in textile treatment products and dyes, rubber and polymers. It is classified as toxic via all routes of exposure and causing organ damage in long term exposure.
- *N-1-naphthylaniline* (CAS 90-30-2); which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses in lubricants and greases, polymers, metal working fluids and hydraulic fluids as well as in the manufacture of rubber products. It is harmful when swallowed and classified as causing damage to organs through prolonged or repeated exposure. It may also cause skin sensitization.
- *N-ethyl-N-[2-[1-(2-methylpropoxy)ethoxy]ethyl]-4-(phenylazo)aniline* (CAS 34432-92-3) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its uses in polishes and waxes, lubricants and greases, adhesives and sealants, washing & cleaning

products, fillers, putties, plasters, modelling clay, inks and toners, leather treatment products, paper chemicals and dyes, polymers and textile treatment products and dyes. It is classified as harmful if swallowed, may cause damage to organs through prolonged or repeated exposure, and may cause skin sensitization.

- *p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline,* (CAS 5026-74-4) and *m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline,* (CAS 71604-74-5) which are manufactured and/or imported in the EEA in 100 - 1 000 tpa per substance. The para-isomer is used in the manufacturing of other substances. There is limited information on the uses of the m-isomer. Both isomers are classified as suspected of causing genetic defects, it may also cause organ damage in long term exposure and skin sensitization.
- *1,1'-(p-tolylimino)dipropan-2-ol* (CAS 38668-48-3) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, non-metal-surface treatment products and polymers. It is classified as fatal if swallowed.
- *dapsone or diaminodiphenyl sulfone* (CAS: 80-08-0) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses in polymers, adhesives and sealants as well as manufacturing of other chemicals, plastics, and rubber. It is also a widely used antibiotic for leprosis and some other diseases. It is classified as harmful.
- *4,4-oxodianiline* (CAS 101-80-4) is an aromatic amine, which is on the candidate list of SVHCs due to its carcinogenic and mutagenic properties. It is manufactured or imported in the EEA in 10-100 tpa and used in the production of polymers.

For these, no systematic data search have been performed but according to the available information only limited/no biomonitoring data exists for these compounds.

3. Categorization of Substances

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

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	MOCA	2,2'-dichloro-4,4'-methylenedianiline	101-14-4	REACH: authorization
	MDA	4,4'- Diaminodiphenylmethane	101-77-9	REACH: authorization
B	o-toluidine	o-toluidine	95-53-4	REACH: candidate for SVHC substance
	aniline	aniline	62-53-3	REACH: PACT-RMOA process completed
	diisocyanates (MDI/TDI)	methylene diphenyldiisocyanate; toluene diisocyanate	101-68-8 584-84-9 91-08-7	REACH, restriction proposal under consideration
	paracetamol	N-acetyl-4-aminophenol	103-90-2	medicines regulations
C	p-PDA	p-phenylenediamine	106-50-3	REACH: PACT-RMOA process ongoing
	p-toluidine	p-toluidine	106-49-0	Registered under REACH, no other current regulatory actions
D		1,3-diphenylguanidine	102-06-7	Registered under REACH, subject for substance evaluation (CoRAP), decision available
		4,4-oxodianiline	101-80-4	REACH, candidate for SVHC
		N,N-diethylaniline	91-66-7	registered under REACH
		N-1-naphthylaniline	90-30-2	registered under REACH
		N-ethyl-N-[2-[1-(2-methylpropoxy)ethoxy]ethyl]-4-(phenylazo)aniline	34432-92-3	registered under REACH
		p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline	5026-74-4 71604-74-5	registered under REACH
		1,1'-(p-tolylimino)dipropan-2-ol	38668-48-3	registered under REACH
		dapsone	80-08-0	registered under REACH
E		other unspecified/unidentified aniline compounds	-	-

4. Policy-related questions

Policy-related questions defined for the priority group “Anilines” are as follows:1. What is the current occupational exposure to aniline and different aniline derivatives (including diamine forming diisocyanates) in the EU?

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

3. What are the risks related to these exposures?

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

5. Research Activities to be undertaken

As explained in this scoping document, “Anilines” is a large group of compounds. Therefore, it is suggested to focus on some priority compounds. These priorities are presented below. These have been selected largely on the basis of regulatory interests. Current information related to MOCA is considered sufficient and further research activities related to MOCA are not considered relevant.

Table 2: Listing of research activities to be carried out to answer the policy questions

Policy question No. (keyword)	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
1, 2	**MOCA**	We have sufficient information on the toxicity and occupational exposure to MOCA. Validated biomonitoring methods are available in EU and information for the use of available biomarkers in occupational risk assessment.	No need for further research actions.
1, 2	**4,4’-MDA**	We have sufficient information on the toxicity and occupational exposure to 4,4’-MDA in the industrial use of this substance. Validated biomonitoring methods are available in EU and information for the use of available biomarkers in the risk assessment of occupational MDA exposure. There are only limited numbers of workers using 4,4’-MDA but exposure to 4,4’-MDA formed from methylene diphenyl diisocyanate may occur among the large group of workers and needs further studies (see below, item “diisocyanates”).	No need for further research actions related to the occupational exposure to 4,4’-MDA in its industrial use. Exposure to MDA in the use of methylene diphenyl diisocyanate (MDI), see below, item “diisocyanates”
1	**aniline**	Methods for the biomonitoring of aniline exist. Toxicity has been evaluated. Some biomonitoring data are available among general population and workers, however, data gaps exists. EU risk assessment concludes concern for workers, general population and consumers.	Risk assessment based on the available biomonitoring data for both workers and general population. Identification of the best biomarker for occupational and general population studies, paracetamol intake as confounder in the biomonitoring of aniline. Setting of reference and health based values. Bridging gaps related to exposure.

Policy question No. (keyword)	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
1	**o-toluidine**	Methods for biomonitoring exist. Toxicity has been evaluated. Limited biomonitoring data among general population and workers.	Bridging gaps related to the exposure of workers and general population. Risk assessment based on biomonitoring data. Setting of reference and health based values.
1	**p-toluidine**	Methods for biomonitoring exist. Toxicity has been evaluated. Only very limited biomonitoring data among general population and workers.	Bridging gaps related to the exposure of workers and general population. Risk assessment based on biomonitoring data. Setting of reference and health based values
1, 2	**diisocyanates**	Important causes of occupational asthma. Biomonitoring methods available but since asthma may occur at very low exposures, sensitivity of the methods should be high. Some occupational biomonitoring studies are available demonstrating exposure.	If/when restriction is going to become in force, there is a need to follow its effectiveness. Appropriateness/sensitivity of methods to detect low level exposures, still relevant for sensitization. This may need further development. Characterization of the all relevant exposure routes. Risk assessment and setting of limit values based on biomonitoring data.
1	**paracetamol**	There are general population biomonitoring data on paracetamol exposure available mainly from Denmark.	What is the general population exposure to paracetamol? Sources of the paracetamol exposure of general population. Paracetamol intake as a confounder in the biomonitoring of aniline. Identification of high exposures and risk assessment of exposure.
1	**p-PPD**	There are publications on the development of a method to measure exposure to p-PPD and testing of this method in hairdressers.	What is the exposure of general population and specific occupational groups, e.g. hairdressers to p-PPD, which is a common constituent of cosmetics and e.g. hair dyes.
1	**anilines in general**	Different aniline compounds may exist in various products or be formed as degradation of other products. Exposure may occur e.g. due to the pigment used in various products like hair dyes.	Screening of aniline exposure of general public and workers (including professionals like hairdressers), identification of compounds and sources of exposure. Identification of new biomarkers for anilines.

6. References

1. Cherrie JW, Gorman Ng M, Shafrir A and Van Tongeren M, Mistry R, Sobey M, Corden C, Rushton L, Hutchings S (2011a) Health, socio-economic and environmental aspects of possible amendments to the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work. o-Toluidine. IOM research project: P937/19, May 2011.
2. ECHA (2015a) Application for authorisation: establishing a reference dose response relationship for carcinogenicity of MOCA. RAC/32/2015/11 rev 1 https://echa.europa.eu/documents/10162/13641/dose-response-carc-moca_en.pdf
3. ECHA (2015b) Application for authorisation: establishing a reference dose response relationship for carcinogenicity of technical MDA. RAC/32/2015/10 rev 1
4. ECHA (2016a) Application for authorization by REACHLaw Ltd in its legal capacity as Only Representative of Suzhou Xiangyuan Special Fine Chemical Co., Ltd for Industrial use of MOCA as a curing agent/chain extender in cast polyurethane elastomer production. https://echa.europa.eu/addressing-chemicals-of-concern/authorisation/applications-for-authorisation-previous-consultations?diss=true&search_criteria_ecnumber=202-918-9&search_criteria_casnumber=101-14-4&search_criteria_name=4%2C4%27-methylenebis%5B2-chloroaniline%5D
5. ECHA (2017a) Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Opinion on an Application for Authorisation for Formulation of an epoxy resin hardener containing technical MDA. 15.3.2017. https://echa.europa.eu/documents/10162/54b6068f-f34e-182e-dae5-47fb5fb05987
6. ECHA (2017b) Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Opinion on an Application for Authorisation for Industrial use of an epoxy resin hardener containing technical MDA aimed at immobilising spent ion exchange resins in a high containment matrix. 15.3.2017. https://echa.europa.eu/documents/10162/54b6068f-f34e-182e-dae5-47fb5fb05987
7. ECHA (2016b) Annex XV restriction report. proposal for restriction. Diisocyanates. v. 2.0. 6.10.2016. https://echa.europa.eu/documents/10162/f210a2bf-bc8f-4a1c-b532-8a8fe3682321
8. Graungaard AH, Siersma V, Lykke K, Ertmann RK, Knudsen LE, Mäkelä M (2016):Maternal pain influences her evaluation of recurrent pain in 6-11 years old healthy children. Acta Paediatr. 105:183-90
9. Jensen JF, Gottschau M, Siersma VD, Graungaard AH, Holstein BE, Knudsen LE. Association of maternal self-medication and over-the-counter analgesics for children. Pediatrics. 2014;133(2):e291-8.
10. Johansson GM, Jönsson BA, Axmon A, Lindh CH, Lind ML, Gustavsson M, Broberg K, Boman A, Meding B, Lidén C, Albin M (2015) Exposure of hairdressers to ortho- and meta-toluidine in hair dyes. Occup Environ Med 72(1):57-63
11. Modick H, Weiss T, Dierkes G, Brüning T, Koch HM (2014) Ubiquitous presence of paracetamol in human urine: sources and implications. 4;147(4):R105-17. doi: 10.1530/REP-13-0527.
12. Mortensen, S. K., Trier, X. T., Foverskov, A., & Petersen, J. H. (2005). Specific determination of 20 primary aromatic amines in aqueous food simulants by liquid chromatography-electrospray ionization-tandem mass spectrometry. Journal of Chromatography A, 1091(1-2), 40–50. http://doi.org/10.1016/j.chroma.2005.07.026
13. Nielsen JKS, Modick H, Mørck TA, Jensen JF, Nielsen F, Koch HM, Knudsen LE. N-acetyl-4-aminophenol (paracetamol) in urine samples of 6-11-year-old Danish school children and their mothers Int J Hyg Environ Health. 2015;218(1):28-33.
14. RIVM (2015) Risk Management Option Analysis Conclusion Document. Substance: Aniline. Authority: Netherlands. December, 2015. https://echa.europa.eu/documents/10162/d47eb986-8a99-b08c-d0ff-48780048c176

15. SCCP (2007) Scientific Committee on Consumer Products opinion on Toluene-2,5-diamine. COLIPA no A5. Available at: https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_108.pdf .
16. SCOEL (2013) SCOEL (2010/2013) Recommendation from the Scientific Committee on Occupational Exposure Limits for 4,4'-Methylene-bis-(2-chloroaniline) [MOCA]. SCOEL/SUM/174 June 2010/Annex March 2013. Available at: ec.europa.eu/social/BlobServlet?docId=6929&langId=en
17. SCOEL (2017) Recommendation 301 from the Scientific Committee on Occupational Exposure Limits for o-toluidine. Available at: https://circabc.europa.eu/sd/a/56b96bab-4963-4cd4-b975-4773743427f0/REC-301%20o-Toluidine%252c%202-methylaniline.pdf
18. Trier, X., Okholm, B., Foverskov, a, Binderup, M.-L., & Petersen, J. H. (2010). Primary aromatic amines (PAAs) in black nylon and other food-contact materials, 2004-2009. Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment, 27(9), 1325–1335. http://doi.org/10.1080/19440049.2010.487500