Substance report

June 2022

Aprotic Solvents

HBM4EU science and policy for a healthy future

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Authors and Acknowledgements

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First version (March 2021) compiled by project team at Wood: Dr. Ian Keyte, Neil Patton and Dr. Robert Whiting based on scoping documents produced by the chemical group leader (CGL) and colleagues: Caspar Corden, Kristina Flexman. 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	
AMCC	N-acetyl-S-(N-methylcarbamoyl)cysteine
BLV	Biological Limit Values
C&L	Classification & Labelling
CAS	Chemical Abstracts Service
CLP	Classification, Labelling, Packaging
DMAC	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
ECHA	European Chemicals Agency
HBM	Human Biomonitoring
HBM-GV	Human Biomonitoring Guidance Value
IARC	International Agency for Research on Cancer
NEP	N-ethyl-2-pyrrolidone
NMP	N-methyl-2-pyrrolidone
OEHHA)	Office of Environmental Health Hazard Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
UN	United Nations
UNEP	United Nations Environment Programme
C&L Classification Names	
Carc	Carcinogenicity
Acute Tox	Acute Toxicity
Repr	Reproductive Toxicity
Muta	Mutagenicity
STOT RE	Specific target organ toxicity - repeated exposure
STOT SE	Specific target organ toxicity- single exposure
Eye Dam/ Irrit.	Eye Damage / Eye Irritation
Resp Sens.	Respiratory Sensitivity
Skin Corr / Irrit.	Skin Corrosion/Irritation
Skin Sens.	Skin Sensitivity
Properties of concern	
Reprotox	Toxic to Reproduction
ED	Endocrine Disrupting
PBT	Persistent, Bioaccumulative and Toxic

1. Key Messages

- HBM4EU has produced toxicological information, available biomarkers, analytical methods, and the most significant exposure routes.
- The high percentage of values above the limit of quantification in the two studies from Germany, and the newly analysed samples for the DMF metabolite, clearly show that the investigated population was exposed to NMP, NEP and DMF.
- Nevertheless, a comparison of the exposure data with the newly derived HBM-GV_{GenPop} showed that exposure for adults, children and adolescents is well below the guidance values for all substances tested. However, some gaps still remain in exposure levels for the general population and the geographic distribution of exposure.

2. Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until June 2022. It generates knowledge to inform about the safe management of chemicals and hence, protect human health and the environment in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts and to 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 document provides a summary of the known and suspected adverse human health effects of aprotic solvents and describes the main exposure pathways for humans. It also indicates where HBM could be of value in the development of EU policy, along with the remaining challenges in determining human exposure. This brief is intended to inform policy makers and other stakeholders involved in policy making, implementation and enforcement, on the value of HBM to establish the EU population's exposure to four key aprotic solvents.

This policy brief is based largely on the scoping document for aprotic solvents, first draft produced in 2019 and regularly updated, as well as the accompanying reports on legislative mapping, and the summary of HBM4EU results in relation to the key policy questions. Additional information from ECHA documents including the C&L Inventory, and legislative text for relevant EU policy areas, have been used to supplement the data for this brief.

2.2 Overview of aprotic solvents

Solvents can exist as either polar or non-polar compounds. Furthermore, polar solvents can be further disaggregated into two main classes 'protic' (hydrogen-donating) and 'aprotic' (non-hydrogen-donating).

Both the protic and aprotic solvent groups include a wide array of substances, used in a wide range of applications. The HBM4EU prioritisation process identified a sub-set of key aprotic solvents, all of which have reproductive toxicity as "reprotoxic aprotic solvents". In this document the term 'aprotic solvents' is taken to include the following four substances covered by the prioritisation process under HBM4EU:

- NMP (1-methyl-2-pyrrolidone) (CAS 872-50-4)

- NEP (1-ethylpyrrolidin-2-one) (CAS 2687-91-4)
- DMAC (N,N-dimethylacetamide) (CAS 127-19-5)
- DMF (N,N-dimethylformamide) (CAS 68-12-2).

All four are classified in the EU as reproductive toxicants (category 1B), raising particular concerns for vulnerable groups such as children and pregnant women.

Key human exposure routes are through use of various consumer products (such as paints, detergents, and fragrances), as well as through industrial and professional use.

3 Human exposure to aprotic solvents

3.1 Environmental exposure

Use of the four aprotic solvents in Europe is very high, with quantities registered under the REACH regulation of 10 000 to 100 000 tonnes per year for NMP, DMF and DMAC, and 1000 to 10 000 tonnes for NEP[1]. As well as similar hazard properties, they also have similar patterns of use (ECHA, 2018).

While information on environmental concentrations is lacking (Scoping document), they are likely to be released via e.g., washing machine liquids/detergents, automotive care products, paints, adhesives, fragrances, and air fresheners, as well as from industrial uses.

3.2 Occupational exposure

Aprotic solvents are utilised both within professional use products and consumer use products (see consumer exposure below). For professional use, aprotic solvents are also used in the workplace, such as in graffiti remover, cleaning formulations, pH-regulators, precipitants, neutralisation agents and laboratory chemicals (scoping document).

While all exposure routes are important, dermal exposure is particularly relevant, given their low volatility and potential to be absorbed via the skin. This and inhalation exposure are the most important exposure routes in the workplace (Scoping document).

3.3 Consumer exposure

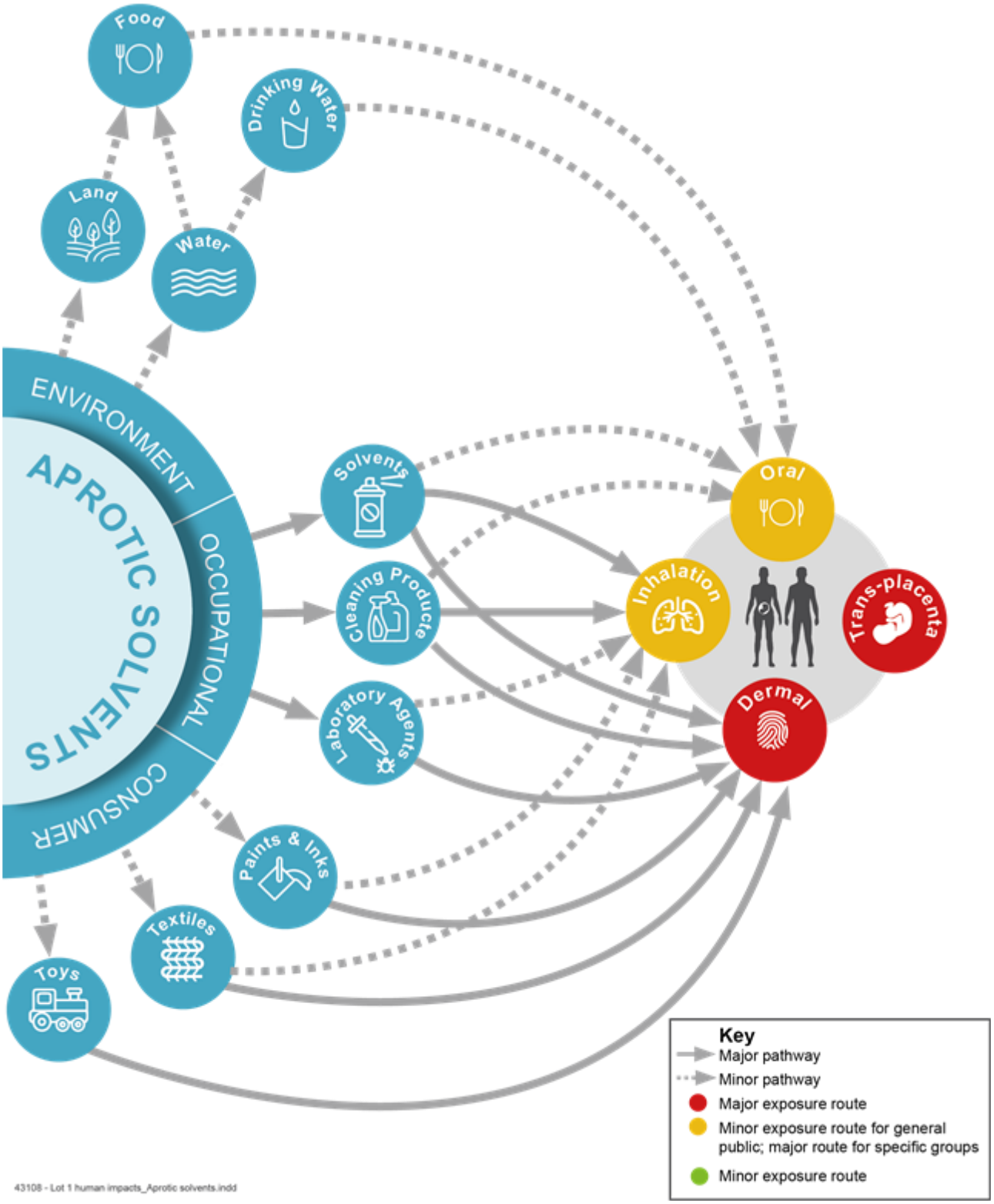
Exposure of the general population has been confirmed since 1991 (Ulrich et al, 2018). While exposure of workers is the main concern (ECHA, 2018), there are important consumer uses such as paints, children's toys, textiles, carpets, inks, and printer toner (Scoping document) as well as other uses mentioned in 3.1 above. They have also been used in some cosmetic products, though use of DMAC and DMF NMP has been banned in the EU since 2010 but NMP and NEP – since 2020 (EC 1223/2009 Regulation on cosmetic products).

Dermal exposure is a particularly significant route, as the solvents are absorbed through the skin. Indoor exposure is also important through inhalation to emissions from consumer products and articles.

Figure 3.1 provides a diagram to further illustrate these pathways to exposure.

[1] Scoping document (version from September 2020- see link

Figure 3.1 Overview of exposure route and pathways for aprotic solvents



4 Health impacts of aprotic solvents

4.1 Overview of key health impacts

The key concern in a regulatory sense for the aprotic solvents is their reproductive toxicity. All four have ‘harmonised’ classification under the CLP regulation as Category 1B reproductive toxicants (Repr. 1B, H360D, may damage the unborn child). Some of the group also have harmonised EU classification for acute toxicity and for skin and/or eye irritation (scoping document). Skin and eye irritation has been directly demonstrated for people in the workplace (e.g., for NMP), while likely reproductive effects in humans have been demonstrated for all of the substances in laboratory (in vivo) experiments in animals, supplemented with some evidence of relevant effects due to occupational exposure of humans.

An overview of current EU (ECHA C&L Inventory) harmonised classification of the four aprotic solvents is provided in the table below (see the Authors and Acknowledgements

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Glossary for full list of terms/classifications):

Table 4.1 Overview of CLP classifications for aprotic solvents

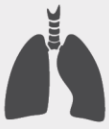
Substance	Properties of concern				Category according to CLP criteria									ECHA info card
	Toxic to Reproduction (R)	Endocrine Disrupting (ED)	Skin sensitising (SS)	Persistent,Bioaccumulative and Toxic (PBT)	Carcinogenicity	Acute Toxicity	Reproductive Toxicity	Mutagenicity	Specific target organ tox (repeated exposure)	Specific target organ tox (single exposure)	Eye Damage/ Eye Irritation	Respiratory Sensitivity	Skin Corrosion/ Irritation	Skin Sensitivity	
NMP							1B*			3*	2*		2*		Link
NEP							1B *			3	1, 2		2		Link
DMAC						4*	1B*				2				Link
DMF						4*	1B*	2	1,2	1	2*				Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.).

An overview of health effects associated with exposure to aprotic solvents is provided in **Error! Reference source not found.**.[2]

Figure 4.1 Overview of health effects associated with exposure to aprotic solvents[3]

[2] An explanation of the categorisation of the strength of evidence for the health effects presented in Figure 4.1 is provided in Appendix 2.
[3] All four aprotic solvents identified by HBM are classified as Repr.1B – H360D, where 'D' means developmental effects. Fertility is unaffected. (i.e., none of the HBM aprotic solvents are classified H360F).

Target organ of the body	Effects	Relevant Substances	Adults (men)	Adults (women)	Infants / Foetuses
Reproductive organs 	Reproductive toxicity	NMP, NEP, DMAC, DMF	●	●	●
Unborn child 	Developmental toxicity	NMP, NEP, DMAC, DMF	○	○	●
Liver 	Hepatitis, other liver injuries	DMAC, DMF	●	●	●
Skin 	Skin irritation	NMP	●	●	●
		NEP	●	●	●
Eyes 	Eye irritation	NMP, DMF	●	●	●
		NEP, DMAC	●	●	●
Lungs 	Respiratory irritation	NMP	●	●	●
		NEP	●	●	●

Key: ● Strong evidence ● Suspected ● Evidence lacking ○ Not applicable

4.2 Vulnerable target groups

Pregnant women and young children are particularly vulnerable groups of the population, as are professional and industrial workers (scoping document).

4.3 Societal concerns

All four of the aprotic solvents are included on the ‚substitute it now' list (SIN list) developed by CHEMSEC, reflecting wider societal concern with their use. NMP, DMAC and DMF are also on the Trade Union Priority List for REACH authorisation (scoping document).

5 EU Policies on aprotic solvents

Aprotic solvents are an example of the EU's move towards considering substances in groups, in order to avoid 'regrettable substitution'. Following previous substance-specific action on these solvents, the European Commission and ECHA have more recently considered risk management for the most used three substances in the group (NMP, DMAC and DMF) (ECHA, 2018). This approach is designed to improve regulatory consistency and will lead to reduced occupational exposure to DMAC and DMF (and potentially NEP) in the same way that NMP is already restricted under REACH (Ulrich et al, 2018).

Specifically, Italy has proposed a restriction in the form of an EU-wide occupational exposure limit (DNEL) for DMF, which has led to a recent proposal for an amendment to the REACH regulation by the Commission (Regulation EC 1907/2006). The Netherlands plans to submit a similar proposal for a restriction on DMAC and NEP (ECHA, 2019).

NMP, DMF and DMAC are also identified as substances of very high concern under the REACH regulation. Both DMF and DMAC are included in Annex II of the cosmetic products regulation (i.e., substances prohibited from being used in cosmetic products)

An overview of these regulatory measures at EU level is provided in Figure 5.1.

Figure 5.1 Overview of EU policy measures relating to aprotic solvents

Chemicals	• All four aprotic solvents are classified as category 1B reproductive toxicants (may damage the unborn child) under Regulation (EC) No 1272/2008 on classification, labelling and packaging (the CLP Regulation) • Three of the aprotic solvents (NMP, DMAC and DMF) are also identified as substances of very high concern under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). This is on the basis of their classification as reproductive toxicants. • Under REACH, marketing and use of NMP is restricted for most uses above concentrations above 0.3% unless industry introduces measures to ensure that exposure is limited to 14.4 mg/m^3 for inhalation exposure and 4.8 mg/kg/day for dermal exposure. For coating of wires, this restriction only comes into effect in May 2024. Similar restrictions are planned for NEP, DMAC and DMF. • The International Agency for Research on Cancer categorise DMAC as a probable human carcinogen (category 2A).	• As a result of their classification under the CLP regulation, the four solvents may not be sold to the general public on their own or in mixtures at a concentration of 0.3% or more. This is under Annex XVII, entry 30 of the REACH Regulation. • DMAC, DMF, NMP and NEP are now prohibited from use in cosmetics under the EU's Regulation 1223/2009 on cosmetic products. • NMP, DMAC and DMF are used in production of medicinal products, controlled under directive Directive 2001/83/EC on medicinal products for human use and Directive 2001/82/EC on veterinary medicinal products	**Consumer**
Environmental	• Under the EU's industrial emissions directive (2010/75/EU), the CLP Regulation classification means that all four aprotic solvents must be replaced as far as possible by less harmful substances or mixtures within the shortest possible time (at regulated industrial installations).	• Under Directive 98/24/EC - risks related to chemical agents at work (the Chemical Agents Directive), employers must eliminate risks in the workplace or reduce them to a minimum, with a preference for substitution. This is a general requirement for all chemicals. • There are also binding Occupational Exposure Limits under the Chemical Agents Directive, for NMP, DMAC and DMF. These co-exist with the restriction setting exposure limits under REACH as well as with national occupational exposure limits in some Member States.	**Occupational**

6 Policy questions

6.1 Introduction

Embedded in the substance prioritisation, stakeholders were asked to identify policy related questions that HBM4EU should address in order to contribute to the strengthening of policy ambitions on aprotic solvents. Further background detail on aprotic solvents and how the policy questions were selected is available in the scoping document and the report on stakeholder consultation and mapping of needs.

6.2 What is the current internal exposure of the workers in EU to reprotoxic aprotic solvents, especially with respect to female workers at reproductive age, and do they exceed Guidance values (reference and HBM values), where they are available? What data gaps exist?

There are quite a lot of internal exposure data of workers in the EU, however they are not always specifically analysed with respect to female workers at reproductive age. Due to assumptions that the workers are in general more protected than the general population and due to limited resources of project partners involved this issue was not covered within HBM4EU in detail. Human biomonitoring values for workers have been derived both for DMF and DMAC within HBM4EU (D.5.9.).

Existing data gaps:

- For NEP, information on occupational environments is scarce at all, for other aprotic solvents it is lacking in relation to vulnerable population groups, such as females of reproductive age, mothers, and their young children is missing.
- HBM-$GV_{Workers}$ for NMP and NEP are lacking.

6.3 What is the current exposure of the general EU population to reprotoxic aprotic solvents, especially with respect to females at reproductive age as well as mothers and their young children, and do they exceed Guidance values (reference and HBM values), where they are available? What data gaps exist?

A literature search was carried out and revealed that exposure data for aprotic solvents are scare for the general population in Europe. Data for the general population for NMP and NEP are available from Germany for children and adolescents (Schmied-Tobies et al., 2021), as well as young adults (Ulrich et al., 2018). Data from the German Environmental Specimen Bank (ESB) are also available for young adults for the DMF metabolite AMCC (data unpublished).

The high percentage of values above the limit of quantification clearly shows that the investigated German population was exposed to NMP, NEP and DMF.

The analysis of time trends of NMP and NEP exposure (years 1991-2014) revealed a continuous exposure to both NMP and NEP over the investigated time span. For DMF (years 2000-2021), a > 50% decrease in AMCC concentrations could be observed.

HBM-GVs have been derived for the general population regarding NMP and NEP, available in D5.9 3rd substance specific derivation of EU-wide health-based guidance values. The HBM-GVs for NMP and NEP have been published (David et al., 2021).

For children, this value is 10 mg/L for both NMP and NEP. For adolescents and adults, an HBM-GV_{GenPop} of 15 mg/L has been derived both for NMP and NEP. For DMF, a provisional HBM-$GV_{Workers}$ of 10 mg/g creatinine has been derived for the metabolite AMCC. For the purpose of this

risk assessment, this value was adjusted to a provisional HBM-GV_{GenPop} of 1 mg/g creatinine for a comparison with the data from the Environmental Specimen Bank (ESB).

A risk assessment of NMP, NEP and DMF regarding reproductive toxicity has been based on this data for the general population and on the newly derived HBM-GV_{GenPop}. The assessment showed that exposure for adults, children and adolescents is below the guidance values both for NMP and NEP as well as for DMF. Maximum values of the studies were a factor of 4.7 to 10 lower than the corresponding HBM-GV_{GenPop} values. The maximum value found in the data from ESB for the DMF metabolite AMCC was a factor of 2.5 lower than the provisional HBM-GV_{GenPop} of 1 mg/g creatinine.

Even when considering the combined exposure to NMP and NEP, the values are not exceeded. The calculated hazard index (HI) was well below 1 in all cases considered (i.e., children, adolescents and adults) with maximum HI values of 0.3, indicating that there was no exceedance of the HBM-GVs. For young adults, the HI was calculated for the combined exposure to NMP, NEP and DMF resulting in a maximum HI value of 0.6. However, a possible combined exposure with other reprotoxic substances present in the environment should be considered in “real-life-situations”, since these might increase the risk for common effects (Kortenkamp and Faust, 2018).

Data gaps:

HBM-GV_{GenPop} for DMAC and DMF are lacking (a provisional HBM-GV for the DMF metabolite AMCC was derived).

The results of the literature search clearly indicate a data gap for exposure in the whole of Europe towards the investigated aprotic solvents (i.e., NMP, NEP, DMAC and DMF). A picture of internal exposure burden could only be attained for NMP and NEP for the German population (aged 3-17) and students in Germany (aged 20-30) and for DMF for students in Germany (aged 20-30).

6.4 Are there geographical differences and differences caused by industrial sector in the exposure of workers in EU to reprotoxic aprotic solvents?

There is currently only very limited data available to answer this question.

6.5 How is the exposure of the general population to reprotoxic aprotic solvents correlated with lifestyle and consumption patterns, what is the main exposure route?

Based on German HBM data the exposure to NEP was highest in adolescents and participants with low socio-economic status or migration background. Associations to usage of personal care products suggested that the choice of products had a distinct impact on NEP exposure.

7 HBM4EU outputs to date

7.1 Categorisation

Substances under HBM4EU have been categorised depending on availability of HBM data. The categorisation indicates the information gaps and hence allows 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 7.1: Categorisation of aprotic solvents

Category		Priority substance(s)
A	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.	
B	HBM data exists, but not sufficiently to have a clear picture across Europe.	NMP, DMF
C	HBM data scarcely or does not exists. Efforts to develop an analytical method to obtain relevant HBM results need to be done	DMAC
D	A toxicological concern exists but HBM data are not available.	NEP
E	Not yet identified as of toxicological concern and for which no HBM data are available	

7.2 Key outputs

A full description of all the relevant policy questions and associated actions and data gaps is in the HBM4EU short overview report here.

Details of the specific deliverables (Work Packages, WPs) under the HBM4EU project are also detailed on the HBM4EU web page.

Methods and biomarkers

To answer questions on exposure levels and sources and further support current and future HBM studies, WP7 has produced a variety of materials to provide the groundwork for a harmonised approach to study planning and conduct in Europe. For Aprotic solvents, questionnaires for adults are made available.

No new data were obtained for aprotic solvents in the HBM4EU aligned studies. A literature search was carried out.

Statistical analysis plan (SAP) for aprotic solvents is developed within WP10. The aim of the SAP is to set a procedure for answering the exposure related research questions defined in the scoping document. The general part of the SAP includes statistical plans for the evaluation of time trends, geographic comparisons, evaluation of exposure determinants, a strategy for the calculation of EU reference values and a plan for conducting uncertainty analysis. It is assumed that urine (urine-spot, urine-24h, urine-morning) will be the obligatory matrix to be used for determination of chosen NMP, NEP, DMF and DMAC metabolites. Optionally a number of parameters characterising urine will be determined - total volume of urine collected, urine density of the sample, concentration of creatinine in urine of the sample, osmotic concentration of urine of the sample, specific gravity of urine (ratio of urine density compared with water density). Certain obligatory or optional variables characterising participants of the study will be applied – age, sex, education, current labour status,

industrial sector of occupation, lifestyle (frequent use of chemical household products (for cleaning, etc.) or focus on natural „ecological“ products) and consumption patterns (frequency of usage of cosmetics).

Comprehensive information on toxicokinetics of NMP, NEP, DMF and DMAC including the biological half-life and internal dosimetry of substances in question is gathered, available in D 12.7. Based on this information, available human physiologically based pharmacokinetic (PBPK) models for NMP, NEP, DMF and DMAC linking an external exposure to an internal dosimetry (e.g., concentration in blood, urine or in tissues) are reviewed, available in AD 12.8 and AD 12.10.

14 candidate laboratories in 7 countries have been identified for analysis of NMP, NEP, DMF and DMAC metabolite, available in D 9.6.

HBM-GVs have been derived for the general population regarding NMP and NEP and for workers regarding DMF and DMAC, available in D 5.9. Publication on NMP and NEP is available (David et al., 2021).

The European HBM dashboard has 2 datasets with aprotic solvents exposure data integrated.

Risk assessment of NMP, NEP and DMF with respect to the general population regarding reproductive toxicity has been performed in WP 5.3. (D5.11). It is based on German exposure data including the newly obtained German DMF exposure data as well as the newly derived HBM-GV_{GenPop}.

7.3 Key data gaps

Table 7.2 summarises key knowledge gaps identified through work under the HBM4EU programme so far, for the four aprotic solvents.

Table 7.1 Key knowledge gaps for aprotic solvents

Knowledge area	NMP	NEP	DMAC	DMF
Very general knowledge about releases to environment - the related information should be gathered.	✓	✓	✓	✓
No information on contamination of different environmental media - published information must be searched and environmental monitoring should be arranged in different geographical locations within EU.	✓	✓	✓	✓
No information on content in widely used consumers` products - investigations should be arranged.	✓	✓	✓	✓
Information on indoor pollution is lacking - special investigations should be arranged.	✓	✓	✓	✓
Lacking information on exposure in the general population - published information must be searched and biomonitoring shall be arranged, especially in relation to vulnerable population groups, namely, females at reproductive age, mothers, and their young children. Spatial	✓	✓ (lacking information for occupational environment)	✓	✓

Knowledge area	NMP	NEP	DMAC	DMF
(geographical) and temporal distribution shall be followed-up.				
No systematic investigations on exposure levels caused by different industrial sectors and geographical locations within EU - such information should be gathered by additional literature search.	✓	✓	✓	✓
Information on success of legislation is lacking - investigations needed.	✓ (REACH restriction, ban in cosmetics)	✓ (REACH restriction, ban in cosmetics)	✓ (REACH restriction, ban in cosmetics)	✓ (REACH restriction, ban in cosmetics)
Association between exposure of general population and lifestyle and consumption patterns is unclear - special investigations shall be arranged.	✓	✓	✓	✓

8 Future recommendations

The literature search revealed the scarcity of exposure data for the European general population for the four aprotic solvents (i.e., NMP, NEP, DMAC and DMF) in question. Monitoring for these substances in the European population is therefore recommended in the future. In addition, new biomonitoring data will allow to assess the eligibility of restriction measures approved for aprotic solvents in question as some of them were entered into force just in 2020.

Further study populations should be investigated to broaden the database on exposure to the four aprotic solvents, including susceptible subpopulations such as pregnant women.

The sources of the aprotic solvents need to be further investigated and linked to environmental monitoring in different compartments as well as to indoor air monitoring in dwellings.

Only filling of the knowledge gaps indicated above can provide answers to policy questions formulated in the Scoping document for aprotic solvents in question.

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Appendix 1: Additional information on sources of information on exposure.

Source of exposure	References
Environmental Release to the environment can occur from: • Indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners); • Outdoor use (e.g. hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids); and • Industrial use, manufacturing of the substance, formulation of mixtures, in processing aids at industrial sites and as an intermediate step in further manufacturing of another substance (use of intermediates). Detailed information on possible uses and releases to environment can be found on ECHA web pages	Scoping document • ECHA database of REACH registered substances: ○ For NMP - https://echa.europa.eu/brief-profile/-/briefprofile/100.011.662 ○ For NEP - https://echa.europa.eu/brief-profile/-/briefprofile/100.018.409 ○ For DMAC - https://echa.europa.eu/brief-profile/-/briefprofile/100.004.389 For DMF - https://echa.europa.eu/brief-profile/-/briefprofile/100.000.617
Occupational • Both occupational exposure and exposure to the general public is relevant for reprotoxic aprotic solvents. • Prevalence of high exposure is expected due to wide use and high production volume of substances	• Scientific Committee on Occupational Exposure Limits (SCOEL), 2015, SCOEL/REC/119, NMP) • US EPA, 2017, Scope of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-). https://www.epa.gov/sites/production/files/2017-06/documents/nmp_scope_6-22-17_0.pdf Ulrich et al. (2018)
Consumer • Exposure sources are ingredients in paints, graffiti remover, cleaning formulations, children's toys, textiles, carpets, inks, toner, pH-regulators, floccants, precipitants, neutrallisation agents, laboratory chemicals.	• Scoping document • Ulrich et al. (2018) • ECHA database of REACH registered substances: ○ For NMP - https://echa.europa.eu/brief-profile/-/briefprofile/100.011.662 ○ For NEP - https://echa.europa.eu/brief-profile/-/briefprofile/100.018.409 ○ For DMAC - https://echa.europa.eu/brief-profile/-/briefprofile/100.004.389 ○ For DMF - https://echa.europa.eu/brief-profile/-/briefprofile/100.000.617

Route of exposure	
Oral • Oral exposure through mists that deposit in the upper respiratory tract and are swallowed should be considered	Original references can be found in the Scoping document on Arsenic.

Dermal Dermal exposure is considered to be especially significant. Dermal exposure (possibly including cosmetic products containing aprotic solvents NMP is readily absorbed by all routes of exposure, but, due to its low vapour pressure, absorption through the skin represents the most likely and potentially the most important route of exposure to NMP under most known consumer use conditions. At the workplace, however, inhalation and dermal uptake can be assumed to be the important routes of exposure.	Scoping document
Inhalation Inhalation exposure to indoor emissions from consumer products and articles. At the workplace, however, inhalation and dermal uptake can be assumed to be the important routes of exposure.	Scoping document
Trans-placenta Transplacental exposure shall be taken into account (in risk assessments).	Scoping document

Appendix 2: Additional information on health effects

Human health effect	Category	Justification for category	References
Reproductive organs and unborn child (Reproductive toxicity)	NMP, NEP, DMAC, DMF (strong)	These substances are classified under harmonised CLP category 1B reproductive toxicants. Other supporting references are also provided.	CLP classification[4,5,6,7] Saillenfait et al., 2002; Saillenfait et al., 2003; Saillenfait et al., 2007; Flick et al. 2009.
Pregnant women (Reproductive toxicity)	NMP, NEP, DMAC, DMF (suspected)	Exposure to pregnant women causes effects on the unborn child (as above) but it is also suspected that the mother may be subject to effects (e.g. reduced food consumption and weight gain was observed in rats).	Becci et al., 1982; Saillenfait et al., 2007; U.S. EPA. 1986; U.S. EPA. 1999;
Liver - Hepatitis, other liver injuries	DMAC, DMF (strong – adults and women) DMAC, DMF (suspected – infants/foetuses)	"toxic hepatitis from DMAC occurred … on a new acrylic-fiber production line" – scoping document "Chronic occupational exposure to DMF by inhalation has resulted in effects on the liver … in workers" – scoping document Effects are suspected for children because the strong evidence is based on occupational exposure of workers.	Baum and Suruda. 1997; U.S. EPA. 1999; Lee et al., 2006.
Skin - Skin irritation	NMP (strong) NEP (suspected)	Harmonised CLP confirms NMP causes skin irritation. Notified CLP suggests NEP causes skin irritation.	CLP classification
Eyes - Eye irritation	NMP, DMF (strong) NEP, DMAC (suspected)	Harmonised CLP confirms NMP and DMF cause eye irritation. Notified CLP suggests NEP and DMAC cause eye irritation.	Notified CLP Classification
Lungs - Respiratory irritation	NMP (strong)	Harmonised CLP confirms NMP causes respiratory irritation (STOT SE 3).	CLP classification

[4] NMP harmonised CLP https://echa.europa.eu/en/information-on-chemicals/cl-inventory-database/-/discli/details/49861

[5] NEP harmonised CLP https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/112556

[6] DMAC harmonised CLP https://echa.europa.eu/en/information-on-chemicals/cl-inventory-database/-/discli/details/116425

[7] DMF harmonised CLP https://echa.europa.eu/en/information-on-chemicals/cl-inventory-database/-/discli/details/2384

	NEP (suspected)	Notified CLP suggests NEP causes respiratory irritation.	

For the categorisation of the strength of evidence for human health effects, the following criteria has been used:

- **Strong –** where the health effect is confirmed by either a harmonised classification indicating that there is a known effect (e.g. 1A or 1B for CMRs) (see Table 4.1), or where there is no applicable C&L classification, a statement in the Scoping Document that concludes there is strong evidence (or where a significant body of evidence is presented in the scoping document).
- **Suspected –** where there is either (a) a harmonised classification indicating that there is a suspected effect (e.g. category 2 CMRs or similar); (b) notified classification for that effect, or (c) where there is no applicable C&L classification, a statement in the Scoping Document (or other references presented in the Table above) that there is a suspected health impact.
- **Evidence lacking –** where a health effect is noted in the Scoping Document (or other evidence sources referenced in the Table above), but it is stated that evidence is currently lacking or there are uncertainties or inconsistencies in the available evidence.
- **Not applicable –** where a health effect does not apply to a specific group/gender