HBM4EU science and policy for a healthy future

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

HBM4EU

# POLICY BRIEF

JULY 2022

European Human Biomonitoring Initiative

# Aprotic Solvents

**This policy brief summarizes the adverse human health effects of aprotic solvents, their main exposure pathways for humans, and how human biomonitoring (HBM) could be of value in the development of EU policies.**

**The aprotic solvents NMP, NEP, DMAC and DMF are all reproductive toxicants. They are used in various consumer products such as paints, detergents, and fragrances, as well as in industrial processes.**

## 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.**

## BACKGROUND: HBM4EU

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

## HBM4EU RESULTS

HBM4EU has produced a variety of publicly available groundwork material for a harmonised approach to study planning and conduct in Europe, available in the HBM4EU online library. It includes the toxicological information, biomarkers of exposure and analytics methods for the four aprotic solvents. A statistical analysis plan (SAP) has been developed which addressed the research questions related to exposure since the available data set concerning the general population was limited to two studies from Germany.

A list of suitable biomarkers, matrices and analytical methods was published. Advanced training courses on method improvement for NMP and NEP were held in November 2018 in Germany, with 14 candidate laboratories in seven countries identified for aprotic solvent analysis.

HBM4EU also laid the foundations for a European HBM Network to monitor human exposure to priority chemicals, including aprotic solvents.

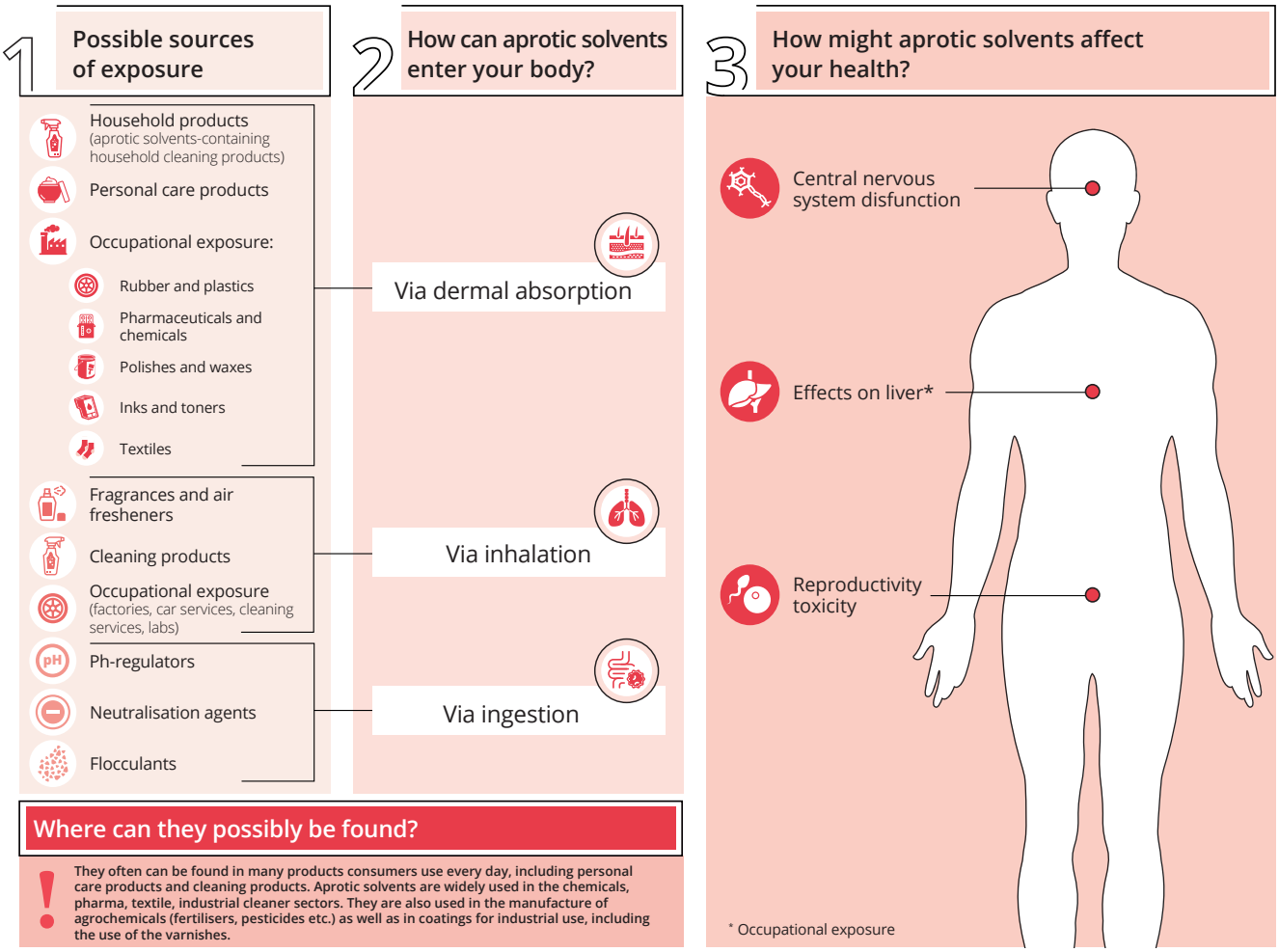
## EXPOSURE & HEALTH EFFECTS

The use of these 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].

The key health concern in a regulatory sense for the aprotic solvents is their reproductive toxicity.

An overview of the main sources of exposure (environmental, occupational, consumer), exposure pathways (oral, inhalation, dermal) and health effects is provided in Figure 1.

**Figure 1.** Overview of potential exposure sources, pathways and health effects associated with aprotic solvents




1 Scoping document (version from September 2020- see link

## INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

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

EU policies have increasingly targeted individual chemicals, but given their similar properties, aprotic solvents are now being treated more consistently, with restrictions introduced to keep workplace exposure below Europe-wide occupational exposure limits, and to strongly limit sales to consumers.

Aprotic solvents are an example of the EU's move towards considering groups of substances 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 three most used aprotic solvents (NMP, DMAC and DMF). 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.

NMP, DMF and DMAC are also identified as substances of very high concern under the REACH regulation. NMP, NEP, DMF and DMAC are included in Annex II of the cosmetic products regulation (i.e., substances prohibited from being used in cosmetic products EU's Regulation 1223/2009 on cosmetic products).

Under REACH, marketing and use of NMP is restricted for most uses with concentrations above 0.3 % unless industry introduces measures to ensure that exposure is limited to 14.4 mg/m3 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.

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 submitted an intention for restriction on DMAC and NEP to ECHA in December 2019. Further documents were submitted in May 2022.

Furthermore, 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).

The International Agency for Research on Cancer categorise DMAC as a probable human carcinogen (category 2A).

Under the EU's Industrial Emissions Directive (2010/75/EU), the CLP Regulation classification means that all four aprotic solvents must be replaced as much 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.

## POLICY QUESTIONS

The answers to the policy questions below are summarised. For more details, please see the Substance Reports available on the substance specific page of the HBM4EU website.

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

For aprotic solvents, data from the questionnaires are available for adults.

HBM-GVs have been derived for workers regarding DMF and DMAC, available in D5.9 3rd substance specific derivation of EU-wide health-based guidance values.

Existing data gaps:

For NEP, information on occupational environments, especially in relation to vulnerable population groups, such as females of reproductive age, mothers, and their young children is missing.

$HBM\text{-}GV_{Workers}$ for NMP and NEP are lacking.

## 2 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-GVGenPop of 15 mg/L has been derived both for NMP and NEP. For DMF, a provisional HBM-GVWorkers 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-GVGenPop 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-GVGenPop. 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-GVGenPop 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-GVGenPop 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-GVGenPop 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).

## 3 Are there geographical differences in the exposure of general population in EU to reprotoxic aprotic solvents?

Since HBM data for the general population for these aprotic solvents are only available from Germany, this question can currently not be answered.

## 4 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.

## KNOWLEDGE GAPS

Despite all the research outputs produced within HBM4EU, information about releases to the environment for NMP, DMF, DMAC, and NEP is missing. There is also no information on contamination of different environmental media, as well as on indoor pollution for NMP, DMF, DMAC, and NEP. Further research is needed, as well as environmental monitoring in different geographical locations within the EU.

There is no information on NMP, DMF, DMAC and NEP in widely used consumer products. Measurements in more countries are needed as, apart from Germany, there is a lack of exposure data on NMP, DMF, DMAC, and NEP in the general population. For NEP, information on occupational environments, especially in relation to vulnerable population groups, such as females of reproductive age, mothers, and their young children is missing. Spatial (geographical) and temporal distribution should be followed-up in the future.

Any association between general population exposure (to NMP, DMF, DMAC or NEP) and lifestyle and consumption patterns in different countries is unclear.

Differences in profiles of NMP, DMF, DMAC, and NEP in relation to exposure and mixture effect is missing as well. The possibility of establishing one common indicator substance (biomarker) should be assessed.

**HBM4EU coordinator:**
German Environment Agency hbm4eu@uba.de

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

www.hbm4eu.eu

HBM4EU science and policy for a healthy future

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