HBM4EU science and policy for a healthy future

HORIZON2020 Programme
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Second list of HBM4EU priority substances and Chemical Substance Group Leaders for 2019-2021

Deliverable Report

D 4.5

WP 4 - Prioritisation and input to the Annual Work Plan

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Entity	Name of person responsible	Short name of institution	Approved Date
Coordinator	Marike KOLOSSA-GEHRING	UBA	10/08/2018
Grant Signatory	Marie-Pascale MARTEL	INSERM	10/08/2018
Pillar Leader	Greet SCHOETERS	VITO	12/06/2018
Work Package Leader	Catherine GANZLEBEN	EEA	12/06/2018
Task leader	Jean-Nicolas ORMSBY Christophe ROUSSELLE	ANSES	12/06/2018

Responsible author	Eva OUGIER	E-mail	eva.ougier@anses.fr
Short name of institution	ANSES	Phone	+33 (0)1 77 74 17 28
Co-authors	Pierre LECOQ, Christophe ROUSSELLE, Jean-Nicolas ORMSBY		

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Authors and acknowledgements

Lead authors

Eva OUGIER (ANSES)

Pierre LECOQ (ANSES)

Jean-Nicolas ORMSBY (ANSES)

Christophe ROUSSELLE (ANSES)

Contributors

Greet SCHOETERS (VITO)

Jos BESSEMS (VITO)

Madlen DAVID (UBA)

Rosa LANGE (UBA)

Morgane CABARET-LOUX (ANSES intern)

Marie-Odile RAMBOURG (ANSES)

Paule VASSEUR (ANSES external expert)

Claude VIAU (ANSES external expert)

Tiina SANTONEN (FIOH)

Jelle VLAANDEREN (IRAS)

Loïc RAMBAUD (ANSP)

Catherine GANZLEBEN (EEA)

Joana LOBO (EEA)

Glossary

ADI	Acceptable Daily Intake
AEL	Acceptable Exposure Limit
ANSES	French Agency for Food, Environmental and Occupational Health & Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
BP-3	Benzophenone-3
BDs	Background Documents
BLV	Biological Limit Value
BMDL	Benchmark Dose Level
BGV	Biological Guidance value
CGL	Chemical Group Leader
CLP	Classification, Labelling, Packaging
DEET	N,N-diethyl-m-toluamide
DEMOCOPHES	Demonstration of a study to Coordinate and Perform Human Biomonitoring on a European Scale
DG EMPL	Directorate General for Employment, Social Affairs and Inclusion
DG GROW	Directorate General for Internal Market, Industry, Entrepreneurship and SMEs
DG RTD	Directorate General for Research and Innovation
DG SANTE	Directorate General for Health and Food Safety
DMA	Dimethylarsinic Acid
DMF	N,N-dimethylformamide
DON	Deoxynivalenol
ECHA	European Chemicals Agency
ED	Endocrine disrupting
EEA	European Environment Agency
EEB	European Environmental Bureau
EFSA	European Food Safety Authority
ESTeSL	Lisbon School of Health Technology (Escola Superior de Tecnologia da Saúde de Lisboa)
EU	European Union
FAO	Food and Agriculture Organization
FIOH	Finnish Institute of Occupational Health
FNUSA	St. Anne's University Hospital Brno
HBGV	Health-based Guidance Value

HBM	Human Biomonitoring
HEAL	Health and Environment Alliance
IARC	International Agency for Research on Cancer
iAs	Inorganic Arsenic
INSA	Portuguese National Institute of Health (Instituto Nacional de Saúde)
IPCHEM	Information Platform for Chemical Monitoring
ISS	Italian National Institute for Health (Istituto Superiore di Sanità)
JRC	Joint Research Centre
JSI	Jožef Stefan Institute
KI	Karolinska Institute
MAK Commission	German permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
4-MBC	3-(4-methylbenzylidene)camphor
4,4-MDI	4,4-methylenediphenyldiisocyanate
MOE	Margin of Exposure
MOH	Ministry of Health
MMA	Monomethylarsonic Acid
NEP	1-ethylpyrrolidin-2-one
NH	National Hub
NIOM	Nofer Institute of Occupational Medicine
NIOSH	National Institute for Occupational Safety and Health
NMP	1-methyl-2-pyrrolidone
NPHI	National Public Health Institute
OEL	Occupational Exposure Limit
OSH	Occupational Safety and Health
PBTK	Physiologically Based Toxicokinetic
POEA	Polyoxyethylene tallow amine
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference Dose
RIKILT	Dutch Institute of Food Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
SDU	University of Southern Denmark
SVHC	Substances of Very High Concern
RIVM	Netherlands National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)
2,4-TDI	2,4-diisocyanato-1-methylbenzene

2,6-TDI	1,3-diisocyanato-2-methylbenzene
UBA	German Environment Agency (Umweltbundesamt)
VIAA	Latvian State Education Development Agency (Valsts Izglitibas Attistibas Agentura)
VITO	Flemish Institute for Technological Research (Vlaamse Instelling voor Technologisch Onderzoek)
WHO	World Health Organization
WP	Work Package

1 Abstract/Summary

This deliverable presents the 2nd list of HBM4EU Priority Substances. It also describes the process undertaken to identify Chemical Substance Group Leaders (CGLs) for the substances on the 2nd list.

The first exercise to prioritise substances for action within HBM4EU was performed in 2015 and resulted in the nine substance groupings that have been the focus of HBM4EU activities in 2017 and 2018. HBM4EU partners built on the experience gained with the first prioritisation exercise to make the process of prioritising substances for future analysis under HBM4EU more accountable, transparent and legitimate. The prioritisation strategy was developed in 2017 and was approved by the 1st meeting of the HBM4EU Governing Board in September 2017.

The prioritisation strategy was implemented in two distinct tasks: task 4.1 on the mapping of knowledge needs; and Task 4.2 on the prioritisation of substances, as described in Deliverable D4.3 on the Prioritisation strategy and criteria, produced by ANSES. Implementation of the process is documented in Deliverable 4.4 on the 1st report on the stakeholder consultation and the mapping of needs.

The draft 2nd list of HBM4EU Priority Substances was agreed at a joint meeting of the HBM4EU Management Board and the European Union (EU) Policy Board in March 2018. The resulting draft 2nd list of prioritised substances was sent to the Governing Board for approval in May 2018. The Governing Board approved the list, which is presented below.

Second list of HBM4EU priority substances
Acrylamide
Aprotic solvents
Arsenic
Diisocyanates
Lead
Mercury
Mycotoxins
Pesticides: glyphosate, chlorpyrifos, fipronil and pyrethroids
UV filters – benzophenones

This deliverable provides a summary of the rationale behind selection of the 2nd list, as well as initial proposals for activities to be performed under HBM4EU.

These proposals will feed into the scoping documents to be produced by the CGLs for the 2nd list of HBM4EU priority substances, and ultimately captured in the annual work plans.

The CGLs for the 2nd list of HBM4EU priority substances were identified via a process of consultation with the Governing Board, whereby the Governing Board was asked to nominated experts. These proposals were then reviewed by the Management Board, with the explicit aim of including partners from countries not currently holding the position of CGL for substances on the 1st list of HBM4EU priority substances. The CGLs for the 2nd list substances were approved by the management Board and Governing Board in June and July 2018 respectively.

2 Introduction to the prioritisation of chemicals under HBM4EU

2.1 Prioritising substances for action within HBM4EU

The first exercise to prioritise substances for action within HBM4EU was performed in 2015, taking into account both national and EU level policy needs for knowledge on chemical exposure and health outcomes. This first prioritisation exercise was undertaken by national and European representatives, as members of the Steering Group for the second European Human Biomonitoring Initiative organised by the Directorate General for Research and Innovation (DG RTD). It resulted in the nine substance groupings that are the focus of HBM4EU activities in 2017 and 2018.

The 1st list of HBM4EU priority group of substances includes:

- phthalates and Hexamoll® DINCH;
- bisphenols;
- per-/polyfluorinated compounds;
- flame retardants;
- cadmium and chromium VI;
- polycyclic aromatic hydrocarbons;
- aniline family;
- chemical mixtures; and
- emerging substances.

HBM4EU partners have built on the experience gained with the first prioritisation exercise to make the process of prioritising substances for future analysis under HBM4EU more accountable, transparent and legitimate.

The prioritisation strategy was developed in 2017 and was approved by the 1st meeting of the HBM4EU Governing Board in September 2017. The process is described in Deliverable 4.3 on the Prioritisation strategy and criteria, produced by ANSES. The detailed description of how this prioritisation strategy was implemented in practice, the inputs received and the methodology applied for selecting substances to include in the second list of prioritised substances is the subject of the **Deliverable D4.4 (lead EEA)**.

The prioritisation strategy was implemented in two distinct tasks:

- Task 4.1 on the the mapping of knowledge needs; and
- Task 4.2 on the prioritisation of substances.

Task 4.1 on the mapping of needs generated the input that fed into Task 4.2 on the prioritisation of substances. The objective was to understand the demands of the National Hubs, EU policy makers and members of the HBM4EU Stakeholder Forum for HBM evidence on specific substances and substance groups. This involved running an **online survey** requesting the nomination of substances for research under HBM4EU. All nominations were consolidated to produce a **long list** of new single substances and substance groups nominated. Substances on the long list were ranked according to the nomination received, enabling us to reduce the list down to a manageable **short list** of approximately 25 substances and substance groups that could be assessed in greater detailed in the task on the prioritisation of substances. We then produced **background documents** on the substances on the short list, as an input to Task 4.2 on the prioritisation of substances.

Task 4.2 involved scoring the substances against the prioritisation criteria and ranking them. A brief description of the methodology implemented for scoring the substances and groups of substances is given below. The scoring made it possible to rank these substances in terms of priority for inclusion in the HBM4EU programme. This ranked list of substances and groups of substances was the principle input to decision making on the second list of substances to be included for HBM4EU activities in 2019-2021.

The ranked list was discussed at a joint meeting of the HBM4EU Management Board and the European Union (EU) Policy Board in March 2018, where agreement was reached on the **draft 2nd list of HBM4EU priority substances**. The **Governing Board** was then consulted on the draft 2nd list, which they approved in May 2018. The list was then adopted by the HBM4EU Management Board as the **Final 2nd list of HBM4EU Priority Substances**.

The Governing Board members have also been asked to identify a list of candidate institutions and experts for the positions of **CGLs** for the new substances/groups of substances. This process is discussed in section 3 of this report.

The outputs resulting from the sequential implementation of Task 4.1, Task 4.2 and also Task 4.4 on the production of the scoping documents will ultimately feed into the development of the annual work plan for HBM4EU. Figure 1 below illustrates how these tasks under WP4 feed into one another.

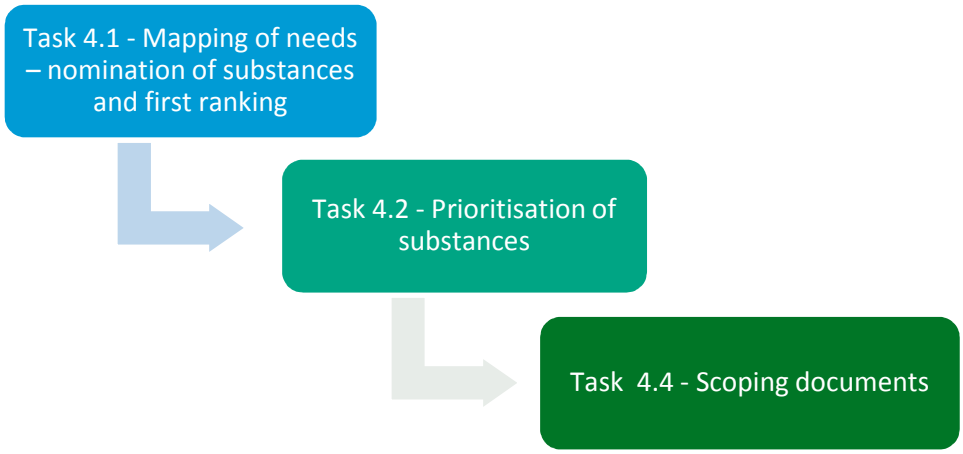

Figure 1: Strategy for the prioritisation of substances

2.2 Timeline of the HBM4EU 2nd round of prioritisation

The starting point of Task 4.2 was the short list of 21 substances/groups of substances provided in November 2017 by EEA, as an output of the mapping of needs under Task 4.1. EEA also provided to the Task 4.2 partners (ANSES, UBA, VITO) draft Background Documents (BDs) that consolidated all the information submitted during the survey of mapping of needs.

The information indicated in these draft BDs were reviewed by the three Task 4.2 partners and when considered necessary, revised to capture additional relevant data against criteria used for the substances scoring and categorisation steps (i.e. hazard properties, exposure characteristics, regulatory status, public concern and technical feasibility for HBM measurement).

The scoring of substances was performed against the following criteria:

- Hazardous properties;
- Exposure characteristics; and
- Public concern.

For substance groups, single substances within the groups were selected and scored, since the methodology did not allow for the scoring of groups. In each case, the partner leading the review of each BD (either ANSES, UBA or VITO), proposed scores for single substances against each criterion according to the prioritisation methodology (see Deliverable 4.4 for more details). Experts from these partners, together with experts with occupational (FIOH) and epidemiological backgrounds (IRAS) then discussed the scores at a workshop held at ANSES on the 8th and 9th February 2018. At the end of the workshop, consensus was reached on the scores for the three criteria for each of the 21 substances and groups of substances. A global score was calculated for each substance/group of substances on the short list. This attributed global score aims to reflect the weight of relevance including the substance (or groups of substances) in the HBM4EU programme.

Along the scores, categories (from A to D) were also attributed to the substances, according to the current level of knowledge available for the substances, especially towards hazardous properties, available exposure data and HBM available analytical methods and data (see Deliverable D4.3 for descriptions of the categories). Indication of the category is meant to help the decision-makers within HBM4EU to choose substances requiring different types of activities and consequently allocate work to the different Work Packages within HBM4EU in a balanced way.

2.3 Resulting list of ranked substances

The ranking of the 21 substances/groups of substances from the short list on the basis of their global scores is presented in Annex – Table 1.

The ranking of substances/groups of substances considering both their global score and category is presented in Annex – Table 2.

These two tables presenting the ranking of the substances and groups of substances on the short list represented the principle input to the discussion and decision regarding the second list of HBM4EU Priority Substances.

3 Second list of prioritised substances

3.1 Process for the drafting of the 2nd list of prioritised substances

During the Management Board meeting on 5 March 2018, members of the Management Board went through the substances/groups of substances, starting from the first substance ranked on the list, according to the global scores. Discussions focused on the relevance and possible interest of including each substances or substance group in the HBM4EU programme. At the end of the meeting, an agreement was reached on the substances to be prioritised from the perspective of the Management Board. Suggestions of activities to be undertaken for each substance/group of substances were also discussed.

A meeting of the EU Policy Board ran in parallel with the Management Board meeting. Its members also discussed the ranking and agreed on the priorities from a policy perspective.

On the 6th of March 2018, a bilateral discussion with both members of the Management Board and the EU Policy Board took place in order to set the second priority list of substances. Overall, the two boards had chosen the same substances for prioritisation, with two exceptions. The Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW) and Directorate General for Employment, Social Affairs and Inclusion (DG EMPL) expressed their interest in including diisocyanates, which was agreed. The Management Board argued for the inclusion of arsenic, which was also agreed.

The resulting 2nd list of prioritised substances is presented in section 3.2 below. Thereafter, we provide a brief summary of the rationale for the selection of each substance or group of substances on the 2nd list of HBM4EU Priority Substances.

We also present the initial proposals for activities to be performed under HBM4EU. These are drawn both from the discussions at the joint meeting of the Management Board and EU Policy Board, as well as from the research proposals put forward in the responses to the online survey. These initial proposals will feed into discussions in the Management Board when drafting the Annual Work Plan for 2019, as well as for future years.

3.2 Overview of the 2nd list of prioritised substances

Table 1 below provides an overview of the substances and substance groups prioritised for inclusion on the 2nd list of HBM4EU priority Substances. The table also identifies which specific substances within substance groups were scored by experts in the prioritisation strategy, together with the global score awarded to each specific substance and the category to which each substance was assigned.

Table 1: 2nd list of HBM4EU Priority Substances

Single substance/group of substances	Substance(s) considered for the scoring	Global score	Category
Lead & its compound	Lead	70.3	A
Mercury & its organic compounds	Mercury	56	A
	Methylmercury	54.2	B
Arsenic inorganic compounds	Inorganic arsenic compounds, including diarsenic trioxide	74.2	B
Acrylamide	Acrylamide	69.4	B
Mycotoxins: initial focus on DON with fumonisins as a second priority (not aflatoxins)	Aflatoxin B1	63.4	B
	Deoxynivalenol (DON)	51.4	C
	Fumonisin B1	47.4	C
Pesticides, including Pyrethroids	Chlorpyrifos	62.5	B
	Dimethoate	61.6	C
	Pyrethroids	61.2	B
	Permethrin (Group of Pyrethroids)	60	B
	Glyphosate	52	B
	Fipronil	45.6	C
UV filters - Benzophenones	Benzophenone-3 (BP-3)	51	B
Aprotic solvents	N,N-dimethylformamide (DMF)	49.6	B
	1-methyl-2-pyrrolidone (NMP)	42.8	B
Diisocyanates	4,4-MDI, 2,4-TDI & 2,6-TDI	53.2	C

3.3 Governing Board approval of the second list of prioritised substances

In May 2018, the Management Board consulted the **Governing Board,** as the highest-level decision making body of the HBM4EU initiative, on the draft 2nd list of HBM4EU Priority Substances. To this end, a Decision Memo on the draft 2nd List of HBM4EU Priority Substances was send to the Governing Board on 16 April 2018, with feedback expected by **1 May 2018**.

The Governing Board approved the list and the list was then adopted by the HBM4EU Management Board as the **Final 2nd list of HBM4EU Priority Substances**.

3.3.1 Lead & its compound

3.3.1.1 Rank

Scoring was performed on **lead metal** (CAS 7439-92-1). It arrives on the **2nd position** of the list of prioritisation, ranked according to the substances global scores. Scores of lead towards its 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria are indicated in table 2 below.

Table 2: Scores against criteria, global score and category for lead

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
2	Lead metal	25.3	36	9	70.3	A

The category proposed for Lead is **Category A**, as HBM data on lead are sufficient to provide an overall picture of exposure in Europe, even if recent data are lacking for some Member States. The health risk is globally well known. Risk management measures are effective in the EU, and the effectiveness to decrease the exposure in the environment has been evaluated in some EU countries. However, data to assess the ongoing exposure in Europe are needed. Some specific scenarios of exposure also still need to be addressed (e.g. REACH restriction considered for the use of lead in ammunitions).

3.3.1.2 Nominating entities

'Lead and its compounds' was nominated by:

- the EU Commission, through DG EMPL
- the Hungarian and British NHs.

In discussions in the EU Policy Board, DG EMPL prioritised lead.

3.3.1.3 Rationale for inclusion on the 2nd list of prioritised substances

- DG EMPL is particularly interested in assessing whether the European legislation (i.e. the Chemical Agents directive 98/24/EC containing a binding Occupational Exposure Limit (OEL) as well as a Biological Limit Value (BLV) for inorganic lead and its compound) has been effectively implemented at Member State level in order to ensure the protection of workers' health.
- The Annex II of the Chemicals Agents Directive 98/24/EC mentions that a more up to date BLV be recommended by the Scientific Committee on Occupational Exposure Limits (SCOEL). The binding BLV for lead indicated by the Directive 98/24/EC is 70 µg /100 ml blood[1], whereas the recommended BLV from the SCOEL is 30 µg /100 ml blood. Moreover, SCOEL specify that the recommended BLV should not be seen as being entirely protective of the offspring of working women. The exposure of fertile women to lead should therefore be minimised. Recently, the International Lead Association (ILA) and the Association of European Automotive and Industrial Battery Manufacturers (EUROBAT) have called the EU to make a health-based review of OEL for lead a priority, as a first step towards lowering the existing EU-wide binding limit. The existing EU BLV would indeed not be reflective of

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:01998L0024-20140325

the current scientific evidence for health effects in the workplace, which is illustrated by the fact that some EU countries have implemented lower binding BLV in their national regulation. An up-to-date and harmonised health-based EU BLV is therefore greatly needed.

- Regarding the general population, having the current exposure profile across Europe and different subgroups of population as children and individuals of lower socio-economic status would be informative for the decision makers. Assessing the trend of the general population internal exposure would also inform on the effectiveness of regulatory efforts in selected EU countries to restrict lead in products in contact with drinking water. The EU commission mentions also the fact that nowadays a great interest in storing renewable energy in lead batteries exists. Human exposure is most likely happening at the manufacture stage, but establishing a background level in the general population would allow monitoring the emission potential of lead from these batteries into the environment in the future.

3.3.1.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the Information Platform for Chemical Monitoring (IPCHEM) platform, in order to draw up the exposure profile of the general population.
- Possible inclusion of lead in occupational human biomonitoring surveys in different EU countries, in order to assess whether current regulatory controls are resulting in effective workers' health protection in practice.
- Where technically possible and relevant for specific exposure pathways, combine any new analysis with the analysis of newer metals.

Proposals suggested by survey participants in the mapping of needs:

- Deriving health-based HBM guidance values for lead in the general population and harmonising the value at the EU-level for workers.
- Determine whether the decreasing trend in blood lead concentrations in the general population continued over the last decade.

3.3.2 Mercury & its organic compounds

3.3.2.1 Rank

The scoring was performed on both elemental mercury (CAS 7439-97-6) and methylmercury (CAS 22967-92-6), one of its organic compound.

Mercury and methylmercury arrive respectively on the **9th position** and the **11th position** of the prioritisation list, ranked according to the substances global scores. Scores of mercury and methylmercury towards their ‘Hazardous properties’, ‘Exposure characteristics’ and ‘Public concern’ criteria are indicated in table 3.

Table 3: Scores against criteria, global score and category for mercury and methylmercury

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
9	Mercury	17.2	28	10.8	56	A
11	Methylmercury	22	23.2	9	54.2	B

The category proposed for mercury is **Category A**, as HBM data from numerous countries across Europe are available. Still, some countries are missing recent data or data on specific population (e.g. children). Mercury's adverse health effects are globally well known. Risk management measures have already been taken by the EU Commission (e.g. restriction of specific uses under Annex XVII of REACH, regulatory maximum levels in foodstuffs). The EU Commission also recently ratified the Minamata Convention, which objective's is to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds.

The category proposed for methylmercury is **Category B,** as HBM data on methylmercury across Europe are much scarcer than for mercury. Methylmercury analysis in hair is time-consuming and expensive, explaining its limitation of being incorporated in large HBM surveys.

3.3.2.2 Nominating entities

'Mercury and its compound' was nominated by:

- the European Environment Agency (EEA);
- the Austrian, Croatian, Cypriot, Czech, Hungarian, Icelandic, Portuguese, Slovenian and Spanish NHs.

In discussions in the EU Policy Board, the European Commission's Joint Research Centre (JRC) and DG RTD both prioritised mercury.

3.3.2.3 Rationale for inclusion on the 2nd list of prioritised substances

Mercury and most of its compounds are highly toxic to humans and the environment. Large amounts can be fatal and even relatively low doses can have serious health effects, affecting the nervous system in particular. Mercury can change into methylmercury in the environment, a more complex and harmful compound. Methylmercury passes both the placental barrier and the blood-brain barrier, and can inhibit children's mental development even before birth. Methylmercury accumulates in fish and seafood, above all in large predatory fish, which may form part of people's diet.

The intentional use of mercury in the EU has been steadily decreasing over the past 15 years, thanks to the adoption and implementation of a comprehensive set of EU rules restricting use in products, such as batteries, lamps and non-electronic measuring devices and in manufacturing processes, such as chlor-alkali production for which use of mercury is being phased out.

Apart from these intentional uses, there are unintentional emissions of mercury into the air from a number of activities using mercury containing fuels or raw materials. The most important are coal burning (for heating, cooking, power and steam generation and in industrial process plants), cement clinker production, non-ferrous metals production and waste incineration.

The Minamata Convention, which the EU ratified in August 2017, provides an international regulatory framework with the aim of protecting human health and the global environment from the harmful effects of mercury. The obligations under the Convention are transposed in the EU by Regulation (EU) 2017/852 on mercury.

Therefore, HBM studies could support the recently entry into force of the Minamata Convention.

Obtaining HBM data on mercury/methylmercury in population groups vulnerable to the toxicological effects of this heavy metal (i.e. women and children) with greater representativeness than in the previous project (nationwide and EU-wide sampling) could allow comparison with EFSA's risk assessment estimations. Refinement of the safe intake level for methylmercury that is without any appreciable health risk in the general European population thus might be made possible.

Communication materials targeted at these vulnerable groups could then be appropriately developed.

3.3.2.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the IPCHEM platform, in order to draw up the exposure profile of the general population. Ensuring in this way the access to the HBM data on mercury measured in the Demonstration of a study to Coordinate and Perform Human Biomonitoring on a European Scale (DEMOCOPHES) pilot biomonitoring study, which ran from 2010 to 2012. Biomonitoring was performed in this study for four key environmental pollutants (mercury, cadmium, cotinine and phthalates) in 17 countries throughout Europe. Participants in this study were children aged 6-11 years and their mothers aged 45 years and under. This Democophes data should be provided to the Secretariat on the Minamata Convention as a baseline to support monitoring under the Convention. Assess whether these existing HBM data on internal exposure to mercury in partner countries provides an adequate baseline to further support monitoring under the Minamata Convention and assess the effectiveness of implementation of new regulations e.g. Regulation (EU) 2017/852 on mercury.
- The Mediterranean countries proposed the inclusion of mercury in regional surveys, with a focus on vulnerable populations. To be further discussed. Assessment of existing data should inform the decision as to whether additional surveys are required at European level or for specific populations. HBM surveys on vulnerable populations (e.g. children and pregnant women) could be required, particularly in countries with diet involving high fish consumption or living next to waste disposals and incinerators.
- Building capacity to ensure:
    - 1) an EU-wide network of QA/QC'd HBM reference laboratories subject to quality assurance and quality control; and
    - 2) application of harmonised procedures for the mercury's sampling, analytical measurements and processing of the data statistical analysis.

Proposals suggested by survey participants in the mapping of needs:

- Identifying the contribution of current sources of mercury emissions in Europe to environmental exposure and ultimately to human exposure, with a particular focus on emissions from small-scale coal combustion plants. Linking internal human exposure to mercury/methylmercury to dietary exposures, environmental concentrations in water bodies and upstream sources of mercury.
- Mercury speciation in biological matrices, particularly blood, would provide characterisation of species-specific exposure, at levels relevant for the EU population. Individual's inherited factors seem to play a role in determining toxic effects of environmental contaminants as mercury. Identification and validation of novel biomarkers of susceptibility would be therefore an important part in exposure-health relationship's investigation.

3.3.3 Arsenic inorganic compounds

3.3.3.1 Rank

'Arsenic inorganic compounds' arrive in the **1st position** of the prioritisation list, ranked according to the substances global scores. Scores towards the 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria, considering various arsenic inorganic compounds altogether, are indicated in table 4.

Table 4: Scores against criteria, global score and category for arsenic inorganic compounds

Rank	Name	Hazard	Exposure	Public concern	Global score	Category
1	Arsenic inorganic compounds	27.2	38	9	74.2	B

The category proposed for arsenic and its inorganic compounds is **Category B**, as HBM data for arsenic as a food and drinking water contaminant are available, but at insufficient level to provide an overall picture of exposure in Europe. Identified data gaps may vary from spatial gaps in HBM measurement data, to gaps in exposure sources and pathways. Inorganic arsenic is regulated as to drinking water and OELs. There is a toxicological concern because of carcinogenicity and suggested reproductive and neurodevelopmental toxicity of arsenic, as well as the low dose effects that relate to cardiovascular diseases, insulin resistance, type-2 diabetes and hypertension.

3.3.3.2 Nominating entities

'Arsenic and its compound' was nominated by:

- the EU Commission through DG EMPL;
- the Belgian, Hungarian and Spanish NHs.

In discussions in the EU Policy Board, DG EMPL prioritised arsenic.

3.3.3.3 Rationale for inclusion on the 2nd list of prioritised substances

Arsenic is widely distributed in the earth's crust as elemental arsenic and as the inorganic ions arsenite (As III) and arsenate (As V). Inorganic arsenic (iAs), a collective name for different naturally occurring chemical species of the two oxyanions, is thus ubiquitous in the environment. Dissolved forms of arsenic in water are essentially inorganic, As III being the dominant species under reducing conditions, and As V the most stable species in oxygenated environments (WHO, 2001). Common iAs metabolites produced by mammals (including humans) are the pentavalent methylated species MMA (monomethylarsonic acid) and DMA (dimethylarsinic acid).

Inorganic arsenic is extremely toxic and current risk assessments of dietary exposure to arsenic are entirely based on the inorganic forms. The general population is exposed to iAs mainly via diet. Food is the major contributor to intake when arsenic concentrations in water are <10 µg/L (WHO guideline value for drinking water), while drinking water becomes the major source of exposure to iAs when water with arsenic concentrations well above 10 µg/L is used for drinking and cooking (EFSA, 2009; FAO/WHO, 2011). Inhalation of As contaminated air and soil may occur in hot spot areas in the vicinity of metal processing installations.

The need for regulatory limits of iAs in food was recognised only recently, much later than for other toxic dietary elements such as cadmium, lead and (methyl)mercury in the U.S. and Europe, despite classification as a human carcinogen following chronic dietary exposure. The delay was due to the difficulty in risk assessment of dietary iAs, which critically relies on chemical speciation analysis providing occurrence data for iAs in food – and not simply for the sum of inorganic and organic arsenic species (i.e. 'total arsenic') (Cubadda et al.,2017).

Susceptibility to the toxic effects of iAs varies considerably between individuals and populations, depending on variations in iAs metabolism related to factors as age, gender, life stage (e.g. pregnancy, lactation), nutritional status, and genetic polymorphisms in the regulation of enzymes responsible for iAs biotransformation (EFSA, 2009). Evidence that the gut microbiota could also play a role is emerging (Carlin et al., 2016).

From these facts, the nominating NHs expressed their concern regarding the EU general population exposure to arsenic and raised related research questions:

- Arsenic being naturally present at high levels in the groundwater in a number of EU countries, high arsenic level in tap water in affected areas has been recognised in the past decades. Intense work has been carried out to develop and apply new techniques to decrease the concentration of arsenic below the limit value. However, adverse health effects associated with the exposure to arsenic through drinking water in the contaminated sites, especially water from private wells, is still a matter of concern. Also, what is the intake of arsenic from vegetables (sprinkled with water with high arsenic concentration) or food (containing ingredients with high arsenic concentration)?
- Studies in vulnerable populations and studies for a better understanding of the health effects of inorganic arsenic in the population at exposure levels in EU are greatly needed. According to the scientific literature, humans can have different capacities to convert toxic arsenic species into non-toxic species, depending on various factors: folic acid, vitamin B12, Vitamin E, Se, gender. But for now, it is not known how much the exposure or human capacity to convert is explaining the measured high or low levels of iAs in humans.
- A more detailed analysis of possible determinants of exposure to toxic forms of arsenic is needed. Therefore, exploring possible links with environmental data and food consumption data or proximity of sources would be necessary. Moreover, determinants of exposure to toxic arsenic species and the influence on the arsenic methylation process are also insufficiently known.

In order to refine current dietary risk assessment of inorganic arsenic there is a need to produce speciation data for different food commodities, to support exposure assessment and dose-response data for the possible health effects. Only a better understanding of (potential) sources and determinants of exposure could allow for relevant targeted reduction measures and sensitisation.

3.3.3.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the IPCHEM platform, in order to draw up the exposure profile of the general population.
- Launching a general population HBM survey to explore the exposure via drinking water and food. Recently developed HBM analytical methods should allow for differentiating species in urine, resulting from inorganic arsenic exposure, including As III, As V and two methylated metabolic products, DMA and MMA.
- Possible assessment of current levels of occupational exposure to arsenic and its inorganic compounds, to determine whether the EU Occupational Safety and Health (OSH) regulatory controls, as transposed into national legislation, are effective in ensuring the protection of workers health. Publications on occupational exposure are available, but the data is rather old and some exposures are not relevant anymore (e.g. exposure when treating wood with chromated copper arsenate, nowadays restricted in residential or domestic constructions).The use of HBM methods which can specifically detect exposure to iAs without confounding effect of DMA and MMA from other sources are recommended.

3.3.4 Acrylamide

3.3.4.1 Rank

Acrylamide (CAS 79-06-1) arrives on the **3rd position** of the prioritisation list, ranked according to the substances global scores. Scores of acrylamide towards its 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria are indicated in table 5.

Table 5: Scores against criteria, global score and category for acrylamide

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
3	Acrylamide	27.2	36.8	5.4	69.4	B

The category proposed for acrylamide is **Category B**, as the HBM data available are not sufficient to have a clear picture of the exposure pattern across Europe. Analytical methods and biomarkers of exposure are available and the toxicological effects have been extensively studied. Acrylamide is registered under REACH and included in the candidate list of authorisation. Its use in cosmetics is prohibited. A draft Commission Regulation establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food is under development.

3.3.4.2 Nominating entities

Acrylamide was nominated by:

- the European Food Safety Authority (EFSA),
- the Netherlands.

In discussions in the EU Policy Board, EFSA and the Directorate General for Health and Food Safety (DG SANTE) prioritised acrylamide.

3.3.4.3 Rationale for inclusion on the 2nd list of prioritised substances

Acrylamide is toxic if swallowed, may cause genetic defects, may cause cancer, causes damage to organs through prolonged or repeated exposure, is harmful in contact with skin, causes serious eye irritation, is harmful if inhaled, is suspected of damaging fertility, causes skin irritation and may cause an allergic skin reaction (ECHA, 2018).

A number of epidemiological studies have studied the possible association between acrylamide and cancer. One of the main limitations of these studies are the methodologies used to estimate the acrylamide intake from food. Urinary biomarkers and the hemoglobin adducts used as blood biomarkers would reflect the internal dose of acrylamide (and its bioactive metabolite, glycidamide) present in the human subjects. It is likely that they may be a more reliable indicator of dose than that derived from dietary estimates, in view of the number of potential variables that might affect the accuracy of the intake determination for acrylamide.

HBM data on the EU level are not sufficient to have a clear pattern of exposure and to determine whether some subgroups of population are more at risks (dietary habits, dermal contact with polyacrylamide products that may contain acrylamide residues).

A RIVM report from 2016-2017 indicates that the margin of exposure (MOE) to acrylamide in the Netherlands is smaller than the targeted MOE of minimum 10 000 indicated by EFSA[2] (EFSA, 2015). Dietary exposure to acrylamide in the Netherlands being about 1 µg/kg bw[3], the resulting value of the MOE is indeed approximately of 170 (Mengelers et al., 2017). This substantially lower value of the MOE thus indicates a clear concern of acrylamide exposure with respect to its neoplastic effects.

3.3.4.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the IPCHEM platform.
- Including acrylamide in general population surveys at national level to assess the EU population‘s exposure to acrylamide. Drawing up the dietary consumption pattern of the survey participants, in order to be able of highlighting the relationship between consumption of certain foodstuff and elevated internal concentration of acrylamide.

Proposals suggested by survey participants in the mapping of needs:

- Deriving EU HBM-HBGVs for workers and if possible for the general population, based on the Biomonitoring Equivalents for non-cancer Reference Dose (RfD) and cancer risk-specific doses, as indicated by Hays and Aylward, 2008.
- Occupational exposure to acrylamide may occur through inhalation but according to the National Institute for Occupational Safety and Health (NIOSH) or SCOEL, it seems that the dominant exposure route for workers is through the skin. Therefore, occupational HBM survey could be informative to assess whether workers are properly protected. The Annex to the SCOEL document “Recommendation on OELs for acrylamide” (SCOEL/SUM/139), published in 2012, gives a recommendation for a biological guidance value (BGV) for acrylamide: acrylamide hemoglobin adducts of 80 pmol/g globin (for non-smokers). The BGV as the SCOEL defines it, represents the upper concentration of the substance or a metabolite of the substance in any appropriate biological medium corresponding to a certain percentile (generally 90th or 95th percentile) in a defined (non-occupationally exposed) reference population. A BGV is established when toxicological data cannot support a health-based BLV.

3.3.5 Mycotoxins

3.3.5.1 Rank

Aflatoxin B1 (CAS 1162-65-8), deoxynivalenol (DON) (CAS 51481-10-8) and fumonisin B1 (CAS 116355-83-0) arrive respectively on the **4th, 15th and 21st position** of the prioritisation list, ranked according to the substances global scores.

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[2] In its scientific opinion on acrylamide in food released in 2015, EFSA performed the risk characterisation for non-neoplastic effects of acrylamide using the MOE approach and the $BMDL_{10}$ value of 0.43 mg/kg b.w. per day for the most relevant and sensitive endpoint for neurotoxicity, i.e. the incidence of peripheral nerve (sciatic) axonal degeneration observed in F344 rats exposed to acrylamide in drinking water for two years in a NTP study (NTP, 2012).

[3] P95 of exposure to acrylamide for the 2-6 years of age in the Netherlands: 1.0 µg (2.5% lower confidence limit of exposure estimate) or 1.4 µg (97.5% upper confidence limit of exposure estimate). P95 of exposure to acrylamide for the 7-69 years of age in the Netherlands: 0.94 µg (2.5% lower confidence limit of exposure estimate) or 1.27 µg (97.5% upper confidence limit of exposure estimate).

Scores of aflatoxin B1, DON and fumonisin B1 towards their 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria are indicated in table 6.

Table 6: Scores against criteria, global score and category for mycotoxins

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
4	Aflatoxin B1	30.8	27.2	5.4	63.4	B
15	DON	18	28	5.4	51.4	C
21	Fumonisin B1	18	24	5.4	47.4	C

The category proposed for aflatoxin B1 is **Category B**, as HBM data are available, but not sufficiently to give a clear picture of the exposure pattern across Europe. 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.

The category proposed for DON is **Category C**, as HBM data scarcely exists. In 2017, recommendations from EFSA for further efforts to standardise the methods for the analysis of urinary DON biomarkers were given. Also, well-designed quantitative studies on DON urinary excretion in different human sub-population groups should be encouraged to enable the use of DON biomarkers for human exposure assessments. Greater knowledge on the carcinogenicity, reproductive and developmental potential, as well as sensitisation potential is needed.

The category proposed for fumonisin B1 is **Category C, as** HBM data scarcely exists in Europe. Hazardous properties of the substances are suspected, but yet greater knowledge on the toxicological characteristics on the human health is needed. Efforts to develop further analytical method to obtain relevant HBM results are also needed.

3.3.5.2 Nominating entities

- Luxembourg and Portugal nominated mycotoxins as a whole,
- The Netherlands nominated the aflatoxins subgroup.
- EFSA nominated two subgroups of mycotoxins, the fumonisins and DON together with its metabolites.

In discussions in the EU Policy Board, EFSA and DG SANTE prioritised work on DON, with work on fumonisins as a second priority. The aflatoxins were not a priority.

3.3.5.3 Rationale for inclusion on the 2nd list of prioritised substances

- The effects of long term, intermittent exposure to low quantities of carcinogens as some mycotoxins are of concern for the general population. Moreover, some of this compounds are also known liver-toxicants.
- The cumulative exposure to various mycotoxins should be further evaluated. Also, predictions in climate changes indicates increased temperature and precipitation during the cereal flowering period in Northern Europe, which may increase the Fusarium infection rate and the occurrence of mycotoxins in cereals in the years to come.
- There is a need to assess human exposure and also the effectiveness of any measures taken to reduce exposure.
- Biomarkers of exposure for some mycotoxins as fumonisin B1 exist but need to be further validated. A validated biomarker could also be useful to further investigate any relationship between fumonisin exposure and certain human diseases (oesophageal cancer, liver cancer, neural tube defects).

3.3.5.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the IPCHEM platform, in order to draw up the exposure profile of the general population.
- Including DON and possibly fumonisins in a general population HBM survey to assess the dietary exposure to these mycotoxins.

Proposals suggested by survey participants in the mapping of needs:

- Assessing the health effects observed in combined exposure of carcinogenic mycotoxins.
- Assessing the trend in mycotoxins human exposure levels, considering climate changes and possibly new agricultural and animal production processes.

3.3.6 Pesticides, including pyrethroids & biocides

3.3.6.1 Rank

Chlorpyrifos, dimethoate, the group of pyrethroids and permethrin, glyphosate and fipronil arrive respectively on the **5th, 6th 7th and 8th, 14th and 22nd position** of the prioritisation list, ranked according to the substances global scores. POE-tallowamine is a surfactant that enhances the activity of herbicides such as glyphosate. It ranked **28th** on the list according to the global score. N,N-diethyl-m-toluamide (DEET) ranked **29th**.

Scores of these substances or group of substances towards their 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria are indicated in table 7 below.

Table 7: Scores against criteria, global score and category for pesticides and biocides

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
5	Chlorpyrifos	13.3	29.2	20	62.5	B
6	Dimethoate	12.4	31.2	18	61.6	C
7	Pyrethroids	16	27.2	18	61.2	B
8	Permethrin (Group of Pyrethroids)	14	28	18	60	B
14	Glyphosate	7.2	32	12.8	52	B
22	Fipronil	16.8	25.2	3.6	45.6	C
28	POE-tallowamine	12	20	3.6	35.6	C
29	N,N-diethyl-m-toluamide (DEET)	7.2	25.2	0	32.4	C

The proposed category for **chlorpyrifos** is **Category B,** as extensive HBM data are available but recent data and data from Eastern European countries is lacking. Furthermore, mainly group-specific organophosphorus metabolites are measured and overall data on the substance-specific metabolite is missing to have a clear picture across Europe. Suspected developmental neurotoxicity and ED properties need to be confirmed. An HBM-HBGV based on physiologically based toxicokinetic (PBTK) modelling is available (Arnold et al, 2015) and HBM levels are well above that limit. Chlorpyrifos is approved as active substance for use as plant protection product as insecticide only until 31.01.2018 and is applied in several EU member states.

The proposed category for **dimethoate** is **Category C**, because only European HBM data on group-specific metabolites are available. Analytical methods and non-specific biomarkers are available. Due to lacking of substance-specific biomarkers, it is not possible to assess the risk

related to the dimethoate exposure only. Its suspected developmental neurotoxicity still needs to be confirmed. Dimethoate is authorised as active substance in insecticides in several EU countries. The expiration of approval was initially set to the 30 September 2017, but this deadline was shifted to the 31 July 2018 (Reg. EU No 2015/404), in order to provide sufficient time to complete the renewal procedure in accordance with the Commission Implementing Regulation (EU) No 844/2012.

Proposed category for **permethrin** (the lead compound named for pyrethroids) is **Category B**, as HBM data of permethrin and other pyrethroids are available but at insufficient level to provide an overall picture of exposure in Europe. The health risk is covered only by national risk assessment schemes in which exposure predictions are compared to the human reference values Acceptable Daily Intake (ADI), Acute Reference Dose (ARfD) and Acceptable Operator Exposure Level (AOEL)/ Acceptable Exposure Limit (AEL). There is concern because of the widespread use of the many different pyrethroids (not permethrin any more) as plant protection product and biocide. Possible vulnerable groups are an issue as well.

Proposed category for **glyphosate** is **Category B**, as some internal exposure data are available but not EU-wide and there is some epidemiological concern. 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. The health risk is covered only by national risk assessment schemes and per regulatory domain (exposure is taken into account in model calculations per domain) in which exposure predictions are compared to the human limit value ADI.

There is concern because of the widespread use of the many different glyphosate-containing products as pesticide and the still ongoing, possible exposure from albeit diminishing use of polyoxyethylene tallow amine (POEA) as co-formulant. Possible vulnerable groups are an issue as well. **POE-tallowamine** is **Category C.**

Proposed category for **fipronil** is **Category C**, as HBM data of fipronil are completely insufficient to provide an overall picture of exposure in Europe. No HBM data were identified, except two peer-reviewed publications on ad hoc monitoring of a few individuals. The health risk is covered only by national risk assessment schemes in which exposure predictions are compared to the human limit values like ARfD, AEL, ADI etc. A validation of fipronil sulfone as suitable exposure biomarker needs to be conducted.

Proposed category for **DEET** is **Category C.**

3.3.6.2 Nominating entities

There is a broad support from EU institutions, NHs and stakeholders to include pesticides in the next list of HBM4EU prioritised substances. The entities that nominated specific pesticides and biocides are identified in table 8 below.

Table 8: Entities nominating different pesticides and biocides

Susbtance / Group of substance	Nominating entities		
	EU Commission	NH	Stakeholder
Pesticides authorised in the EU	EFSA	Austria	-
Chlorpyrifos	-	Spain Israel	Health and Environment Alliance (HEAL)
Dimethoate	DG SANTE	-	-
Pyrethroids (permethrin named as lead substance)	EEA	France Slovenia	-
Glyphosate	DG RTD	Belgium Netherlands Latvia Spain Switzerland	European Environmental Bureau (EEB) HEAL
Fipronil	European Chemicals Agency (ECHA)	-	-
POE-tallowamine, in combination with glyphosate	DG SANTE	-	-
N,N-diethyl-m-toluamide (DEET)	ECHA	-	-

In discussions in the EU Policy Board, the proposal to address a group of pesticides received broad support from the EU institutions, including DG SANTE, EFSA, EEA and ECHA. The group is expected to include:

- Chlorpyrifos;
- Dimethoate;
- Pyrethroids;
- Glyphosate in combination with POE-tallowamine; and
- Fipronil.

DEET was considered, but was ultimately deemed to be of lower priority by the EU Policy Board.

3.3.6.3 Rationale for inclusion on the 2nd list of prioritised substances

Comprehensive and comparable data based on biomonitoring is essential to get a better picture of the exposure of the European population to pesticide and their metabolites.

Development of a better understanding of the potential adverse health effects of such exposure (likely to be continuous and at low doses through food ingestion, water contamination, inhalation or dermal contact) on the population is also needed. Such new knowledge should serve to inform

political decisions about the placing on the market of these pesticides and risk mitigation measures for their use.

Exposure to pesticides which have suspected ED properties, as e.g. chlorpyrifos, dimethoate, glyphosate, various pyrethroids or fipronil are of great concern in particular for the vulnerable population as infants/children and should be investigated further.

3.3.6.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- HBM4EU partners will work together with DG SANTE, EFSA and ECHA to identify active substances to monitor in a general population HBM survey. It is very likely to include glyphosate, chlorpyrifos, fipronil and some pyrethroids. The aim would be to complement the monitoring of these substances in food and feed under the multiannual Community control program for 2018, 2019 and 2020 (Commission Implementing Regulation (EU) 2017/660). This coordinated multiannual control program aims to ensure compliance with maximum residue levels of pesticides and assessment of the consumer exposure to pesticide residues in and on food of plant and animal origin. However, assessment of the consumer exposure in this programme is performed through pesticides measurements in food and feed. Conducting biomonitoring analysis to determine general population exposure for the same time periods would thus allow assessing the actual human exposure.
- The occupational exposure to pesticides is also of interest, thus occupational HBM survey could be considered.
- Activities under work package 15 on mixtures also focus on mixtures of pesticides around orchards, as exposure hot spots.

3.3.7 UV filters – benzophenones

3.3.7.1 Rank

BP-3 arrives on the **16th position** of the prioritisation list, ranked according to the substances global scores. Scores of BP-3 towards its ‘Hazardous properties’, ‘Exposure characteristics’ and ‘Public concern’ criteria are indicated in table 9.

Table 9: Scores against criteria, global score and category for UV filters

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
16	BP-3	12.8	29.2	9	51	B

The category proposed for BP-3 is **Category B**, as European HBM data are available only in some EU countries. The understanding of sources responsible for the human exposure is limited. The only available HBM HBGV, regarding the substances used as UV filters, has been proposed for 3-(4-methylbenzylidene)camphor (4-MBC).

3.3.7.2 Nominating entities

‘Chemical UV filters & absorbers’ were nominated by:

- Norway (nomination of the organic esters octocrylene (CAS 6197-30-4) and homosalate (CAS 118-56-9))
- Denmark (nomination of subgroups: camphorated compounds and benzophenones)
- ChemTrust as stakeholder (nomination of the benzophenones subgroup)

Both Denmark and ChemTrust identified oxybenzone (also called benzophenone-3 (BP-3)) as the lead substance of the nominated group.

ECHA also express its interest during the joint EU Policy Board and Management Board meeting to have benzophenones included in the HBM4EU initiative.

3.3.7.3 Rationale for inclusion on the 2nd list of prioritised substances

Benzophenones are a group of chemicals used in a wide range of everyday life products due to their UV absorbing properties. They prevent plastic products from becoming friable and fragile in the sun, protect colour agents and textiles from bleaching, and act as photo initiators in printing ink and lacquer (see IARC Report 2013; Danish Environmental Protection Agency 2015; Xue et al. 2017). They may also be used in packaging applications to protect the content from harmful UV radiation.

BP-3 is allowed for use as UV filter in sunscreens and other personal care products and is one of the most widely used chemical UV filters. Until 2017, it could constitute up to 10% (w/w) of the product. Since September 2017, the use of BP-3 in the EU has been restricted to 6 % in cosmetic sunscreen products and up to 0.5 % in other cosmetic products (EU Commission Regulation 2017). Moreover, BP-3 is currently evaluated by Denmark in the context of REACH, the reason being its endocrine disrupting (ED) properties and wide dispersive use. A Danish study (Kinnberg et al., 2015) already indicated the ED effects of BP-3 in zebrafish.

Humans may also be exposed to other benzophenones through use of personal care products as they are used as perfume fixative or as flavour (HSDB 2010). Some biomonitoring studies already confirmed human widespread exposure to benzophenones, including pregnant women, children and adolescents (Frederiksen et al. 2014 and 2017; Krause et al. 2018 and 2017; Philippat et al. 2012).

3.3.7.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across the HBM4EU member state countries via the IPCHEM platform, in order to draw up the exposure profile of the general population.
- Exploratory work to understand exposure via use in UV filters and plastics. Not a full survey at this stage.
- Assessing whether common analytical methods to measure benzophenones and other environmental relevant phenols (e.g. triclosan, triclocarban, parabens) exist. Analytical methods should be further developed.

Proposals suggested by survey participants in the mapping of needs:

- HBM data are only available in some countries and population subgroups at this time, thus integrating benzophenones to a general population survey in the future could be very informative. Moreover, biomonitoring could allow assessing the effectiveness of the recent change in regulation of BP-3, aiming to reduce the human exposure.

3.3.8 Aprotic solvents

3.3.8.1 Rank

N,N-dimethylformamide (DMF) and 1-methyl-2-pyrrolidone (NMP) arrive respectively on the **18th** and **24th position** of the prioritisation list, ranked according to the substances global scores. Scores of these two aprotic solvents towards their ‘Hazardous properties’, ‘Exposure characteristics’ and ‘Public concern’ criteria are indicated in table 10.

Table 10: Scores against criteria, global score and category for aprotic solvents

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
18	N,N-dimethylformamide (DMF)	16	30	3.6	49.6	B
24	1-methyl-2-pyrrolidone (NMP)	12	27.2	3.6	42.8	B

The category proposed for NMP and DMF is **Category B**. The nominated substances are classified for their reprotoxic potential (Reprotoxic 1B H360D - May damage the unborn child).

NMP, DMF and N,N-dimethylacetamide (DMAC) are listed on the Candidate List under REACH as substances of very high concern (SVHCs). DMAC and DMF are listed in Annex II of the Cosmetic Products Regulation (list of substances prohibited in cosmetic products).

Reference guidance values as well as BLV were derived. For the interpretation of exposure levels in the general population, the German HBM Commission has derived HBM- I and HBM-II values for both NEP and NMP indicating the levels above which health effects cannot be excluded and above which health effects might occur.

Biological monitoring has been performed mostly in the occupational field. According to ECHA 2014, risks for workers are not sufficiently controlled for a number of industrial and professional uses, especially when it concerns processes under elevated temperatures, open processes and processes that require manual activities.

3.3.8.2 Nominating entities

Aprotic solvents were nominated by:

- the ECHA;
- the German NH.

Both ECHA and Germany proposed NMP and 1-ethylpyrrolidin-2-one (NEP) as lead substances. Besides, ECHA proposed also DMAC and DMF.

ECHA, EEA and DG GROW prioritised aprotic solvents at the meeting of the EU Policy Board.

3.3.8.3 Rationale for inclusion on the 2nd list of prioritised substances

Aprotic solvents have a wide range of industrial uses, including as non-wire coaters, and in electronics, cleaning products and functional fluids. High levels of human exposure are expected due to their wide-spread use and high production volume. Several aprotic solvents are known reproductive toxicants with harmonised classification as Repr. 1B.

There are no specific data gaps regarding the hazard profiles of the substances proposed in the group. Most members of the group are known reproductive toxicants with harmonised classification (Reprotoxic 1B according to CLP Regulation).

NMP, DMF and DMAC are considered SVHCs. NMP has been considered for a restriction under REACH: EU member states have voted to approve a Dutch proposal to restrict the manufacture, marketing and use of the NMP. Companies would not be able to use the substance unless they meet exposure limits for workers. NEP, DMF (proposed by Italy) and DMAC are likely to be considered for restriction in the future.

The substances are subject to regulatory action in EU and elsewhere and biomonitoring is invaluable in considering the need for measures and to develop the risk assessment supporting the measures. It is also essential for monitoring the measures once adopted.

3.3.8.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across HBM4EU member states via the IPCHEM platform, in order to draw up the exposure profile of the general population and assess exposure levels for workers.
- To include in existing human biomonitoring surveys – either general population or occupation – to be confirmed in discussion with ECHA on relevant exposure pathways. According to ECHA, the proposed research activities would be biomonitoring of workers (new data on a specific population groups or subgroups (not more specified)).
- The choice of substances to be measured within the aprotic solvents needs to be discussed with ECHA. The exact number will mostly depend on the analytical options available.

3.3.9 Diisocyanates

3.3.9.1 Rank

4,4-methylenediphenyldiisocyanate (4,4-MDI) (CAS 101-68-8), 2,4-diisocyanato-1-methylbenzene (2,4-TDI) (CAS 584-84-9) and 1,3-diisocyanato-2-methylbenzene (2,6-TDI) (CAS 91-08-7), considered together, arrive on the **13rd position** of the prioritisation list, ranked according to the substances global scores. Scores of these two diisocyanates towards their 'Hazardous properties', 'Exposure characteristics' and 'Public concern' criteria are indicated in table 11.

Table 11: Scores against criteria, global score and category for diisocyanates

Rank	Substance	Hazard	Exposure	Public concern	Global score	Category
13	4,4-MDI, 2,4-TDI & 2,6-TDI	18	28	7.2	53.2	C

The category proposed for each of the following diisocyanates, 4,4-MDI, 2,4-TDI and 2,6-TDI, is **Category C**, as their exposure profile for European citizens is missing. No HBGVs exist at this time. Even if analytical methods, biomarkers of exposure and of effect are available, a need for more specific biomarkers would be needed. The role of MDI in childhood asthma prevalence needs to be investigated further. Some uses of MDI are already restricted under REACH.

3.3.9.2 Nominating entities

Diisocyanates were nominated by:

- the EU Commission, through DG EMPL;
- the Finnish and British NHs.

DG EMPL prioritised diisocyanates during the meeting of the EU Policy Board.

3.3.9.3 Rationale for inclusion on the 2nd list of prioritised substances

Assessing the current levels of occupational exposure to diisocyanates (e.g. MDI,TDI,HDI) would allow to determine whether existing EU Occupational safety and Health (OSH) regulatory controls on acrylamide, as transposed into national legislation, are effective in ensuring the protection of workers health.

Diisocyanates are common occupational respiratory sensitisers and are used in many applications (polyurethane foams, sealants, coatings) throughout the EU. The annual number of new occupational diseases caused by diisocyanates has been estimated to be more than 5000 cases, which is exceptionally high (German CA, 2013).

Diisocyanates can also cause sensitisation via dermal contact. Therefore, air monitoring alone is not enough to identify hazardous exposures. Quite often sensitisation has occurred even though air levels have been below the detection limits. Therefore, sensitive methods for the identification of total (systemic) exposure are needed.

In addition, aromatic diisocyanates (like MDI and TDI) are degraded by hydrolysis or metabolism to yield primary aromatic amines known to be genotoxic carcinogens (MDA and TDA). Thus, there is a concern on carcinogenicity as well (4,4-MDI and TDI has been classified as suspected carcinogens in Europe (Carcinogenic category 2 according to CLP)). An interesting question is also how much carcinogenic diamines are formed at current exposure scenarios.

A proposal for diisocyanates restriction under REACH is been submitted by Germany in 2016. The opinion is currently under development (ECHA's Socio-economic Analysis Committee draft opinion should be released by now, as the deadline was set on the 20/02/2018). It has been suggested that some uses may be exempted from the restriction, if it can be shown (e.g. using biomonitoring) that the exposure is minimal. If this restriction comes into the force, there will be a need to follow-up its effectiveness.

There is also concerns regarding diisocyanates in plastics playing a role in childhood asthma (Krone and Klingner, 2005).

3.3.9.4 Initial proposals for HBM4EU activities

Proposals agreed by the Management Board and EU Policy Board:

- Collecting and sharing existing HBM data across HBM4EU member states via the IPCHEM platform, in order to draw up the exposure profile of the general population and assess exposure levels for workers.
- Possible future occupational study.
- Analytical methods are currently under development and HBM4EU will follow these developments. Biomarkers and analytical methods to measure diisocyanates in urine are available (Kolossa-Gehring et al., 2017). Albumin adducts of 4,4'-MDI in blood can also be measured. But as the expected levels in the general population should be much lower than in the occupational field, the sensitivity of these methods should be assessed.
- Possible future occupational study.

4 Identification of Chemical Substance Group Leaders

4.1 Process for the identification of Chemical Substance Group Leaders for the 2nd list of HBM4EU Priority Substances

An additional task under Work Package 4, Task 4.2, is to identify potential candidates for CGLs for the substances and substance groups on the 2nd list on HBM4EU Priority Substances.

The process for appointing CGLs is described in the Final Grant Agreement, Part B of the Description of Action (page 41), together with the role foreseen for them to play (see box 1).

Box 1: Process for appointing chemical group leaders and role

Chemical substance group leaders (CGLs)

Composition:

During the proposal preparatory phase, Chemical Substance Group Leaders were appointed by a steering committee of national representatives. For the next list of prioritised substances, new Chemical Group Leaders will be proposed by the Management Board and appointed by the Governing Board by consensus.

Role:

In consultation with other scientists, European Commission services and agencies, establish work programmes for the prioritised substance groups. To ensure their work is fully integrated into the project, Chemical Group Leaders will attend a meeting of the Management Board prior to the development of the Annual Work Plan.

In the interest of transparency and openness, the Management Board has decided to ask the Governing Board members to indicate whether their National Hub might have the expertise and interest to perform this task for one of the substances or substance groups on the 2nd list.

The Management Board therefore invited the Governing Board to nominate HBM4EU partners (Grant Signatories or Linked Third Parties) from their National Hubs to act as **CGLs** for the substances and substance groups on the 2nd list of HBM4EU Priority Substances. This invitation was included in the Decision Memo on the 2nd List of HBM4EU Priority Substances send to the Governing Board on 16 April 2018. The members of the Governing Board were asked to respond to the Project Coordinator (UBA), indicating whether they propose partners or linked third parties from their National Hub as possible CGLs, with a short description of relevant expertise.

Nominations received from Governing Board members for experts to act as **CGLs** for the substances and substance groups on the 2nd list of HBM4EU Priority Substances are presented in table 12 below.

Table 12: Overview of nominations for 2nd round Chemical Group Leaders

Substance	Nominations from the Governing Board	
	Country	**Affiliation and name**
Arsenic	Italy	ISS (Italian National Institute for Health), Alessandro Alimonti
Acrylamide	Czech Republic	FNUSA (St. Ann's University Hospital Brno), Manlio Vinciguerra
Aprotic solvents	Germany	UBA
Diisocyanates	No nominations received	
Lead & its compound	Hungary	NPHI (National Public Health Institute), Peter Rudnai
Mercury & its organic compounds	Slovenia	JSI (Jožef Stefan Institute), Milena Horvat
Mycotoxins	Portugal	INSA (Instituto Nacional de Saúde Doutor Ricardo Jorge), Paula Alvito and Maria João Silva, in collaboration with its linked third party; ESTeSL (Escola Superior de Tecnologia da Saúde), Susana Viegas
	Netherlands	RIKILT (Institute of Food Safety)
Pesticides, including Pyrethroids	Denmark	SDU (University of Southern Denmark), Helle Raun Andersen
UV filters - Benzophenones	No nominations received	

The Management Board then assessed the nominations for CGLs and appointed partners or linked third parties on the basis of their **proven expertise on the specific substance or substance group**, while at the same time seeking to establish **an appropriate distribution of the roles across partner countries.**

This assessment took place at the meeting of the Management Board, on 7-8 May 2018. All the experts nominated were judged to be of high quality. The Management Board reflected on the nominations and, in particular, the objective of distributing roles across partners.

With the aim of responding to concerns expressed by some partners that the distribution of roles and budget has not been broad enough, the Management Board explicitly decided to offer the roles of CGLs to partners with a lower level of representation in the project.

Therefore, where nominated partners or countries, from which those partners originate, already hold the position of CGL for substances on the 1st list of HBM4EU priority substances, the Management Board decided to contact other partners that do not already hold such a role, to explore their interest. This served to broaden up the possibility for further partners and countries to act as CGLs under HBM4EU.

The proposed list of CGLs for the 2nd list of HBM4EU substances was approved by the Management Board at their 12th meeting in June 2018. The Governing Board then approved the list in July 2018.

4.2 Chemical Substance Group Leaders for the 2nd list of HBM4EU Priority Substances

The final list of CGLs for the 2nd list of HBM4EU priority substances is provided in table 13 below.

Table 13: Chemical Group Leaders for the 2nd list of HBM4EU priority substances

Substance	Country	Affiliation and name	Partner #
Arsenic	Poland	**Pr. Wojciech Wasowicz, PhD** Department of Environmental and Biological Monitoring Nofer Institute of Occupational Medicine (NIOM)	NIOM Partner 30
Acrylamide	Sweden	**Federica Laguzzi, PhD** Institute of Environmental Medicine, Karolinska Institute (KI)	KI Partner 33.1
Aprotic solvents	Latvia	**Normunds Kadikis** Valsts Izglitibas Attistibas Agentura (VIAA, State Education Development Agency)	VIAA, Partner 26
Diisocyanates	Finland	**Tiina Santonen** Finnish Institute of Occupational Health (FIOH)	FIOH, Partner 16
Lead & its compound	Hungary	**Peter Rudnai** National Public Health Institute (NPHI)	NPHI, Partner 39
Mercury & its organic compounds	Cyprus	**Andromachi Katsonouri-Sazeides** Cyprus Ministry of Health (MOH-CY)	MOH-CY, Partner 6
Mycotoxins	Portugal	**Paula Alvito, Maria João Silva** Instituto Nacional de Saúde (INSA), and **Susana Viegas** Superior de Tecnologia da Saúde (ESTeSL)	INSA, Partner 32 ESTeSL, Partner 32.1
Pesticides, including Pyrethroids	Denmark	**Dr. Helle Raun Andersen** Associate Professor of Environmental Medicine, University of Southern Denmark (SDU)	SDU, Partner 8.1
UV filters - Benzophenones	Israel	**Dr. Tamar Berman** Chief Toxicologist, Environmental Health Israel Ministry of Health (MOH-IL)	MOH-IL Partner 23

4.3 Role of the Chemical Substance Group Leaders

The role of the CGLs is to work in consultation with other scientists, European Commission services and agencies to establish work programmes for the prioritised substance groups. To ensure their work is fully integrated into the project, CGLs will attend a meeting of the Management Board prior to the development of the Annual Work Plan.

A principle task of the CGLs is to draft the scoping document for the substance or substance group under their responsibility by June 2018, with the aim of informing development of the annual work plans. Examples of the scoping documents produced for substances on the 1st List of HBM4EU Priority Substances are available on the HBM4EU website.

For the scoping documents to be developed for the 2nd List of HBM4EU Priority Substances, the CGLs will benefit from the background documents developed under the prioritisation strategy which include a wealth of information against the prioritisation criteria.

CGLs are also asked to:

- Report on activities on their substance group drawing on HBM4EU deliverables under work package 5:
- Provide input to the questionnaires for compound specific information and provide input to the sampling protocols under work package 7;
- Provide input for the selection of the most appropriate matrix and analytical techniques under work package 9;
- Steer the compound specific data analyses under work package 10 to make sure that policy relevant questions are addressed as required by HBM4EU scoping docs; and
- Provide input to work package 15 on mixtures.

An additional task of the CGLs is to ensure coherence in activities on their substances across the work packages.

4.4 Person months allocated to Chemical Substance Group Leaders

The CGLs are allocated person months for their work, with 133.55 person months held in reserve to support the work of **all** the CGLs to be appointed under the 2nd and 3rd rounds of prioritisation.

Table 14 provides an overview of the person months allocated to the CGLs for the substances prioritised in the 1st round and the substances prioritised in the 2nd and 3rd rounds.

Table 14: Person months allocated to Chemical Substance Group Leaders in the 1st, 2nd and 3rd rounds of prioritisation

CGLs for the 1st, 2nd and 3rd round of HBM4EU Priority Substances	Person months allocated under specific work packages and total						
	WP4	WP5	WP7	WP9	WP10	WP15	Total
1st round	13.5	4.50	2.25	15.00	7.00	2.00	44.25
2nd and 3rd round	54	16.50	11.05	30.00	14.00	8.00	133.55
Total for 5 years	**67.50**	**21.00**	**13.30**	**45.00**	**21.00**	**10.00**	**177.8**

Based on discussion with partners, the proposed distribution of person months for the 2nd round CGLs for 2018-2020 is presented in table 15. The distribution of these person months to the CGLs for the 2nd list of HBM4EU Priority Substances will be discussed and settled by the Management Board in drafting the 2019 Annual Work Plan.

Table 15: Proposed distribution of person months to 2nd round Chemical Group Leaders for 2018 to 2020

CGL 2nd round	WP4	WP5	WP7	WP9	WP10	WP15	Total
2018	1*	0	0.5	0.7	0.7	0.1	3
2019	0.45*	0.5	0.5	0.25	0,5	0.1	2.3
2020	0.5*	0.5	-	0.1	0.5	0.1	1.7

* Please note that 1 additional PM will be allocated to the CGL for pesticides under WP4 for the years 2018, 2019 and 2020, recognising that this substance group is complex and will entail additional work and collaboration with the EU Policy Board.

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Annex I: Ranking of nominated substances

Table 16: Ranking of nominated single substances & groups according to their global score only.

The yellow shading identifies substances/groups of substances selected for inclusion in the 2nd list of prioritisation.

Rank	Name	Hazard score	Exposure score	Public concern score	Global score	Category
1	Arsenic inorganic compounds	27.2	38	9	74.2	B
2	Lead (Lead & its compound group)	25.3	36	9	70.3	A
3	Acrylamide	27.2	36.8	5.4	69.4	B
4	Aflatoxin B1 (Mycotoxins group)	30.8	27.2	5.4	63.4	B
5	Chlorpyrifos	13.3	29.2	20	62.5	B
6	Dimethoate	12.4	31.2	18	61.6	C
7	Pyrethroids	16	27.2	18	61.2	B
8	Permethrin (Pyrethroids group)	14	28	18	60	B
9	Mercury (Mercury & its organic compounds group)	17.2	28	10,8	56	A
10	DDAC (QACs group)	9.2	32.8	12.8	54.8	C
11	Methylmercury (Mercury & its organic compounds group)	22	23.2	9	54.2	B
12	Nano titanium dioxide (Nanomaterials group)	16	26.8	10.8	53.6	D
13	4,4-MDI, 2,4-TDI & 2,6-TDI (Diisocyanates group)	18	28	7.2	53.2	C
14	Glyphosate	7.2	32	12.8	52	C
15	Deoxynivalenol (Mycotoxins group)	18	28	5.4	51.4	C
16	BP-3 (UV filters-Benzophenones group)	12.8	29.2	9	51	B
17	D4 (Cyclic siloxanes group)	5.6	33.2	11	49.8	C
18	N,N-dimethylformamide (DMF) (Reprotoxic aprotic solvents group)	16	30	3.6	49.6	B
19	Nano Silver (Nanomaterials group)	14	26	9	49	D
20	BHT	14	32.8	1.8	48.6	C
21	Fumonisin B1 (Mycotoxins group)	18	24	5.4	47.4	C
22	Fipronil	16.8	25.2	3.6	45.6	C
23	Perchlorate	13.2	30	1.8	45	C
24	1-methyl-2-pyrrolidone (NMP) (Reprotoxic aprotic solvents group)	12	27.2	3.6	42.8	B
25	UV-328 (Phenolic benzotriazoles group)	12	27.2	3.6	41	C
26	Carbon nanotube (CNTs) (Nanomaterials group)	12.8	18.8	9	40.6	D

Rank	Name	Hazard score	Exposure score	Public concern score	Global score	Category
27	BENPAT (Substituted phenylenediamines group)	15.2	24.8	0	40	D
28	POE-tallowamine	12	20	3.6	35.6	C
29	N,N-diethyl-m-toluamide (DEET)	7.2	25.2	0	32.4	C

Table 16: Ranking of substances and groups on the short list according to their category and global score

The yellow shading identifies those substances and groups of substances included in the 2nd list of HBM4EU priority substances.

Name	Hazard score	Exposure score	Public concern score	Global score	Category
Lead (Lead & its compounds group)	25.3	36	9	70.3	A
Mercury (Mercury & its organic compounds group)	17.2	28	10.8	56	A
Arsenic inorganic compounds	27.2	38	9	74.2	B
Acrylamide	27.2	36.8	5.4	69.4	B
Aflatoxin B1 (Mycotoxins group)	30.8	27.2	5.4	63.4	B
Chlorpyrifos	13.3	29.2	20	62.5	B
Pyrethroids	16	27.2	18	61.2	B
Permethrin (Pyrethroids group)	14	28	18	60	B
Methylmercury (Mercury & its organic compounds group)	22	23.2	9	54.2	B
Glyphosate	7.2	32	12.8	52	B
BP-3 (UV filters-Benzophenones group)	12.8	29.2	9	51	B
N,N-dimethylformamide (DMF) (Reprotoxic aprotic solvents group)	16	30	3.6	49.6	B
1-methyl-2-pyrrolidone (NMP) (Reprotoxic aprotic solvents group)	12	27.2	3.6	42.8	B
Dimethoate	12.4	31.2	18	61.6	C
DDAC (QACs group)	9.2	32.8	12.8	54.8	C
Diisocyanates (4,4-MDI, 2,4-TDI & 2,6-TDI)	18	28	7,2	53,2	C
Deoxynivalenol (DON) (Mycotoxins group)	18	28	5.4	51.4	C
D4 (Cyclic siloxanes group)	5.6	33.2	11	49.8	C
BHT	14	32.8	1.8	48.6	C
Fumonisin B1 (Mycotoxins group)	18	24	5.4	47.4	C

Name	Hazard score	Exposure score	Public concern score	Global score	Category
Fipronil	16.8	25.2	3.6	45.6	C
Perchlorate	13.2	30	1.8	45	C
UV 328 (Phenolic benzotriazoles group)	12	27.2	1.8	41	C
POE-tallowamine	12	20	3.6	35.6	C
N,N-diethyl-m-toluamide (DEET)	7.2	25.2	0	32.4	C
Nano titanium dioxide (Nanomaterials group)	16	26.8	10.8	53.6	D
Nano Silver (Nanomaterials group)	14	26	9	49	D
Carbon nanotube (CNTs) (Nanomaterials group)	12.8	18.8	9	40.6	D
BENPAT (Substituted phenylenediamines group)	15.2	24.8	0	40	D