HBM4EU science and policy for a healthy future

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HBM4EU

POLICY BRIEF

JUNE 2022

European Human Biomonitoring Initiative

Pesticides

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

Pesticides are substances used to kill pests. They include herbicides, insecticides, and fungicides. Under HBM4EU, the following pesticides were investigated in support of policy: pyrethroids (group), chlorpyrifos, dimethoate, glyphosate (including the co-formulant POEtallow amine) and fipronil.

KEY MESSAGES

- EU-wide human biomonitoring (HBM) data on pesticide exposure is scarce. To obtain a better EU coverage, HBM4EU Aligned Studies (2014-2021) have generated new data on pyrethroids, chlorpyrifos, and glyphosate for children (6-11 years) and adults (20-39 years).
- Biomarkers for chlorpyrifos (TCPy), and pyrethroids (3-PBA, 4-F-3-PBA, cis-DBCA, cis-DCCA, trans-DCCA, CIF3CA) were analysed in children from Slovenia, France, Belgium, Cyprus, the Netherlands and Israel (867 urine samples) and in adults from Switzerland, Israel, Iceland, Portugal, France, Germany and the Netherlands (1480 samples). The results showed a widespread exposure to pyrethroids and chlorpyrifos (with detection rates > 90% for TCPy and 3-PBA in most data collections) but marked differences in exposure levels between the countries.
- Glyphosate/AMPA were analysed in urine samples from children from Slovenia, France, Germany, Belgium, and Cyprus (971 samples) and in adults from Switzerland, France, Iceland, and Germany (912 samples). The results showed a widespread low exposure with median values of urinary concentrations below the limit of quantification in most sampling locations.
- Children had higher urinary concentrations of the pesticide biomarkers than adults, reflecting a higher internal exposure to pesticides among children. This may be caused by a higher intake of food per kilogram (kg) body weight and thus higher exposure to pesticide residues in food.
- The HBM4EU data provides a baseline for internal exposure to these pesticides within the European population for future assessment of the effectiveness of reducing pesticide use under the Farm to Fork Strategy.
- Biomonitoring Guidance Values (HBM-GVs) were derived for two pyrethroids: deltamethrin and cyfluthrin, and a first-tier screening HBM-GV for the cumulative exposure to pyrethroids based on the generic pyrethroid biomarker, 3-PBA, was derived based on current ADI values. Comparison with the HBM data on pyrethroids from the HBM4EU Aligned Studies suggests a low concern for the general population, but a risk cannot be dismissed for some highly exposed children. This is particularly worrying as the ADIs set for most pyrethroids are based on neurotoxicity observed in adult experimental animals, which may not sufficiently protect against developmental neurotoxicity.
- A risk assessment for chlorpyrifos, based on a margin of exposure approach, confirmed concerns for adverse health effects in all countries, especially among children. For children, the highest risk levels were observed in Israel and Cyprus. For adults, the highest risk levels were observed in Israel and Portugal. It should be noted that the urine samples from the HBM4EU Aligned Studies used for this risk assessment were collected before the withdrawal of authorization for chlorpyrifos in February 2020.
- Populations living close to areas treated with pesticides are likely to be more exposed, but the knowledge on exposure levels and combination of pesticides profiles are very limited. Therefore, a dedicated survey, the SPECIMen study, was performed to address this issue.

- **The SPECIMEn study revealed a total of 95 pesticide-related markers in urine samples from parent-child pairs in five European countries using suspect screening techniques. A subset of the markers was identified with a high level of confidence; these relate to 30 parent pesticides. Their detection frequency varied substantially between countries. However, consistent strong contributions from agricultural application to detection rates in hotspots or in spraying season were not observed.**
- **HBM data on occupational exposure levels (e.g. agricultural field workers, biocide applicators and veterinary personnel) are very limited for most of the prioritised pesticides.**

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

The main HBM4EU results include an overview of available HBM data on pyrethroids and organophosphates (OP) from European and American studies which is available in the Scoping Document. This document includes suggested biomarkers and their matrix as well as analytical methods in Annex 2.

HBM4EU laid the foundations for a European HBM Platform to monitor human exposure to priority chemicals (including pesticides) and related health effects in a harmonized and quality-controlled way. A Quality Assurance/Quality Control Programme was implemented in order to establish a European database of candidate laboratories that are equally qualified for exposure biomarker analysis.

To further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach, to study planning and conduct in Europe, available in the HBM4EU online library.

Furthermore, the HBM4EU network has helped to answer a request from the Directorate-General for Health and Food Safety (DG SANTE) on copper compounds with regards to the renewable of plant protection products.

In the SPECIMEn (Survey on PestiCIde Mixtures in Europe) study, pesticide-related HBM levels were assessed in Czech Republic, Hungary, Latvia, Spain, and the Netherlands. For each country, this was done in urine samples from parent-child pairs living in hotspot (residences within 250 m of pesticide application sites) or control areas, in the spraying and non-spraying season. In Switzerland pesticides were measured in urine from 300 adults in a different design. Using suspect screening techniques, 95 pesticide-related markers were detected. This number was reduced to 30 markers when focusing on parent pesticides with the highest two confidence levels in identification. We did not observe consistent strong contributions from agricultural application to detection rates in hotspots or in spraying season.

Aligned studies have provided urine samples for new harmonised HBM-data on biomarkers for pyrethroids and OPs in children and adults across Europe. Biomarker concentrations were on average higher in children compared to adults. In some children the biomarker concentrations exceeded the health-based guidance values.

Biomarkers of co-occurring non-persistent pesticides were associated with more behavioural problems in adolescent boys of the Spanish INMA cohort. They were also associated with altered thyroid and reproductive hormones and with changes in BDNF DNA methylation which was identified as a promising effect biomarker (Rodríguez-Carrillo et al. 2022; Freire et al. 2021).

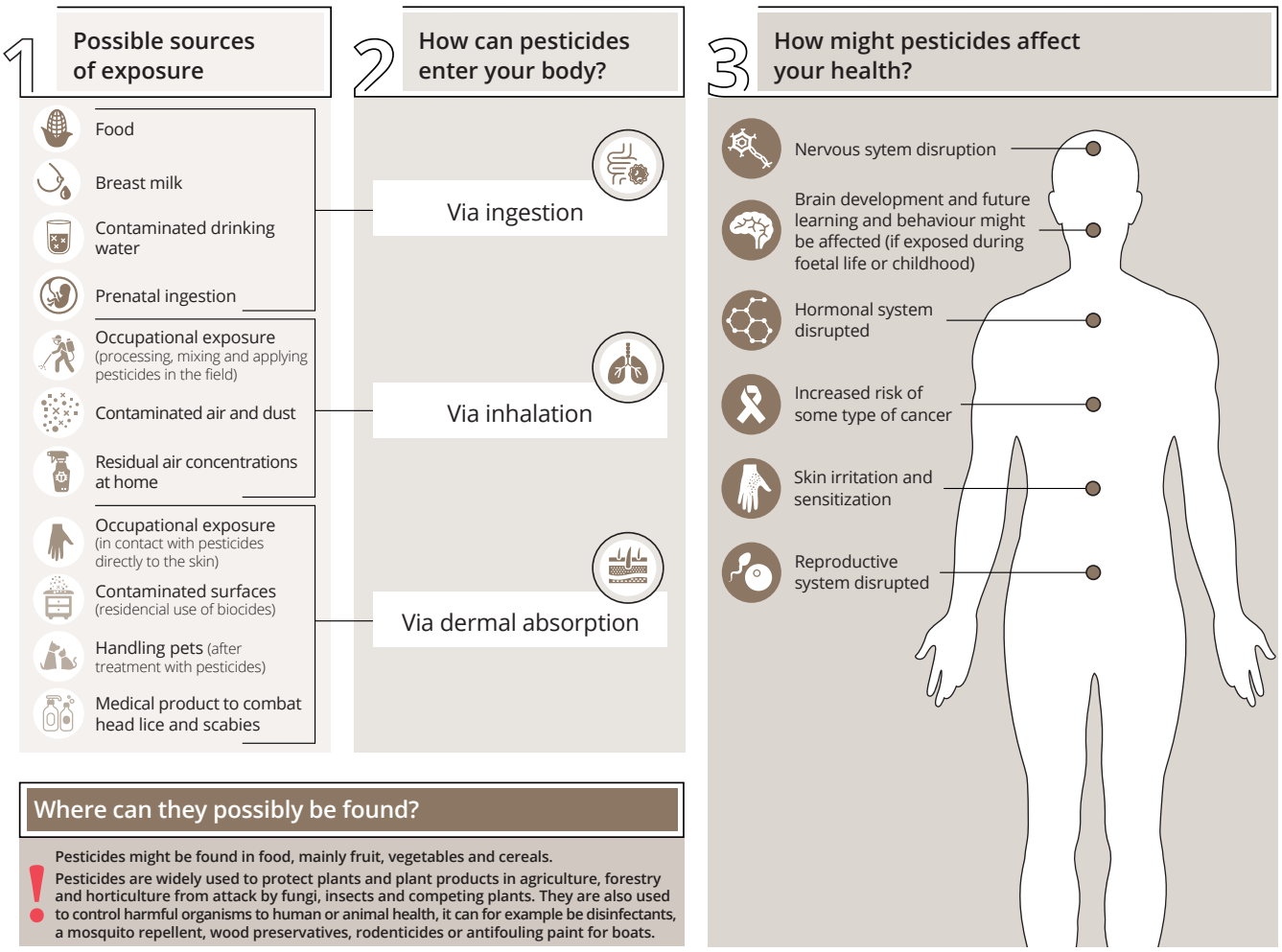
HBM data are taken up and contribute to developing a strategy for refining future risk assessment of mixtures relevant to national food safety authorities, public health institutes, the European Food Safety Authority (EFSA), the European Chemical Agency (ECHA), industry, regulatory bodies and other stakeholders.

EXPOSURE & HEALTH EFFECTS

The main source of pesticide exposure for the general population is residues on food products. Exposure from occupational settings or consumer products for residential use of pesticides may be significant for certain individuals or groups in some areas, as well as for the general public.

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

Figure 1. Overview of exposure sources, pathways and health effects associated with pesticides



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as the directive on Safe and Sustainable Use of Pesticides. These are available in the HBM4EU Science to Policy section.

Several policy measures have already been introduced in the EU to address human exposure to pesticides and manage risks. The latest policy is the Farm to Fork Strategy embedded in the European Green Deal, which includes the target to reduce the use of chemicals and more hazardous pesticides by 50% by 2030. Furthermore, the Commission aims to promote evidence-based policymaking on pesticides by overcoming data gaps. In general, the existing EU policies cover regulations on chemicals, consumer products, the environment and occupational exposure.

Part of the pesticides considered under HBM4EU is subject to Regulation (EC) 1107/2009 on placing plant protection products on the market. They are also subject to Regulation (EU) 528/2012 on making the available on the market and the use of biocidal products.

The pesticides' registration and registered uses are covered under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

In April 2022, 22 additional chemicals were added to PIC (Prior Informed Consent) which restricts import and export of listed substances. Out of these, 15 were pesticides and seven industrial chemicals, including all substances containing benzene as a constituent in concentrations above 0.1% weight by weight. The PIC regulation includes dimethoate, and the pyrethroids allethrin and cypermethrin.

The Drinking Water Directive (98/83/EC) limits the concentration of individual pesticides in water for public consumption to 0.1 µg/L. The sum of all individual pesticides detected is limited to 0.5 µg/L. Regulation (EU) 649/2012 on export and import of hazardous chemicals bans pyrethroids permethrin and fenpropathrin.

On consumer products, maximum residue levels of pesticides in or on food and feed of plant and animal origin (e.g. 10 mg/kg wheat) are regulated under Regulation (EC) 396/2005.

Pesticide residues in infant and follow-on formulae are subject to Directive 2006/141/EC. The standard maximum residue level (MRL) is set to 0.01 mg/kg, whereas specific MRLs for certain pesticides are defined as well (e.g., fipronil 0.004 mg/kg).

The reduction of risks and impacts of pesticide use on human health and the environment is regulated under Directive 2009/128/EC on sustainable use of pesticides. In occupational settings, his comprises of the inspection of equipment and training for professional users.

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 Which are the most suitable HBM methods and biomarkers of exposure?

Urinary biomarkers for glyphosate, chlorpyrifos and pyrethroids were identified and the most suitable analytical methods were evaluated and included in the HBM4EU online library. The biomarkers include glyphosate and AMPA for glyphosate, TCPy for chlorpyrifos, and a group-specific biomarker, 3PBA, representing the combined exposure to many pyrethroids, 5 semi-specific biomarkers representing exposure to two-three pyrethroids, and a specific biomarker for deltamethrin exposure.

No suitable specific urinary biomarkers were available for dimethoate or fipronil, and no information was found for biomarkers for the glyphosate co-formulant Polyethoxylated tallow amine (POEA) or the pyrethroid co-formulant piperonyl butoxide (PBO) and therefor no methods could be selected.

2 What are the current exposure levels of the EU population to the prioritised pesticides: pyrethroids, chlorpyrifos and dimethoate, glyphosate (in combination with polyethoxylated tallow amine (POEA)), and fipronil and do the exposure levels differ between countries?

The results from the aligned studies indicate a marked difference in exposure between EU –countries, but a better EU coverage of harmonized HBM data for these pesticides are needed to get a full picture of the exposure situation across Europe. No information on exposure to dimethoate, polyethoxylated tallow amine (POEA), and fipronil have been collected because no suitable biomarker methods were available.

A data platform was set up with information on existing, ongoing and planned general and occupational HBM studies in the HBM4EU consortium: http://hbmjps.topick.pt/

Results from European HBM studies, including the HBM4EU Aligned Studies and presented in the HBM European Dashboard and show a widespread exposure to pyrethroids and chlorpyrifos in the EU-population with detection rates of TCPy and 3-PBA (formed by several pyrethroids) of above 90 % in most studies/data-collections. High detection rates were also seen for the more specific pyrethroid biomarkers in the HBM4EU Aligned Studies, except for 4-F-3-PBA (specific biomarker for cyfluthrin). Lower detection rates of these biomarkers were seen in most published studies, likely due to higher LODs/LOQs.

In the HBM4EU Aligned Studies, the median urinary TCPy concentrations among children varied between 6.5 ng/ml (Cyprus) to below LOQ of 0.05 ng/ml (France). Among adults the medians varied between 2.75 ng/ml (Israel) and below LOQ (France). For pyrethroids, medians for the group specific biomarker, 3-PBA, among children varied between 1.9 ng/ml (Cyprus) and 0.72 ng/ml (Slovenia), and between 0.82 ng/ml (France) and 0.21 ng/ml (Germany). Detection frequencies and medians for the more specific pyrethroid biomarkers differed between the countries and more detailed analyses of the exposure profiles are still ongoing.

Glyphosate/AMPA measurements in children showed that the exposure is wide across the EU with similar low concentrations for glyphosate and AMPA close to or below the LOQ. At the higher end of the exposure distribution (95 percentiles), the highest urinary concentrations were observed for both glyphosate and AMPA among children in Cyprus (1.03 and 0.66 ng/ml) and lowest in Slovenia (0.18 and 0.29 ng/ml).

3 What are the main dietary sources of exposure across the member states? What are other potential sources and pathways of exposure?

Questionnaire data of HBM studies are not detailed enough to identify,specific dietary sources that contribute most to internal exposure to pesticides. . The SPECIMEn study did not find a significant contribution of agricultural pesticide applications to the biomarker levels in children and mothers living near fields.

4 What are the exposure levels among occupationally exposed workers?

None of the HBM4EU data collections contains occupationally exposed individuals and very few published studies have addressed this issue. Thus, new HBM data are needed to get information on exposure levels among populations occupationally exposed to pesticides.

5 Are the exposure levels of health-relevance/concern for vulnerable groups (infants, children and pregnant women) or high exposure population groups (e.g. occupational exposure)?

Evidence from epidemiological studies (including EU cohorts) combined with biological plausibility captured from toxicology studies and the capability of pyrethroids to interfere with neurodevelopmental key events (KEs) included in established Adverse Outcome Pathways (AOPs) suggest that pyrethroids are developmental neurotoxicants. The developing brain is particularly vulnerable to neurotoxicants, and exposure during major windows of vulnerability in foetal and early life, even at low doses, may have a long-term impact on neurodevelopment. Thus, current exposure levels of pyrethroid mixtures might be of concern for vulnerable population groups, such as pregnant women and children. However, the lack of harmonised analytical methods for the urinary biomarkers combined with the variety in outcome measurements in the published studies hampers the possibility to evaluate exposure-response relationships. Thus, more (longitudinal) studies on neurodevelopmental outcomes using harmonized/comparable methods for assessment of exposure biomarkers, (early) effect biomarkers and health outcomes would be highly relevant for establishing safe exposure levels.

Additional evidence from toxicology data and effect biomarkers analysed in the INMA Granada birth cohort suggests the association of pyrethroids with reproductive and endocrine disturbances. However, studies on health effects associated with low chronic pyrethroid exposure are in general scarce and more studies are needed to confirm these findings and the potential mechanisms.

Based on the HBM data obtained from the HBM4EU Aligned Studies, risk assessments were performed for pyrethroids and chlorpyrifos. Generally, the HBM data on pyrethroids suggests a low concern for the general population. However, for some highly exposed children, risk cannot be excluded. Thus, generation of data on the potential developmental neurotoxicity of pyrethroids is strongly encouraged as part of EU (re)evaluation of pyrethroids. Nevertheless, the developed approach provides a model for the setting of screening level HBM-GV for pyrethroid exposure and for its use in the assessment of the risks of pyrethroid mixtures. This same approach might be taken for other pesticides/pesticide groups to identify those for which a health risk cannot be excluded.

Regarding the risk assessment for chlorpyrifos, the HBM data confirms concerns in all countries for several population groups, especially children, highlighting that the risk for children is clearly higher than for adults. The highest risk levels for children were observed for Israel and Cyprus and the highest risk levels for adults were observed for Israel and Portugal. It should be noted that urine samples from the aligned studies used for this risk assessment were collected before the withdrawal of authorization for chlorpyrifos in February 2020. Thus, the exposure of EU citizens has likely been markedly reduced afterwards, which could be confirmed by collecting new data on TCPy from EU-populations.

6 How can cumulative risks of pesticide mixtures on sensitive health outcomes be assessed and integrated in regulations?

Besides the approach to assess the risk of exposure to a relevant mixture of pyrethroids via the group-specific biomarker 3-PBA, a major activity related to cumulative risk assessment is the investigation of exposure to mixtures of pesticides among residents living close to pesticide treated areas in the SPECIMEn study.

By using suspect screening analyses, HBM4EU generated valuable exposure data across Europe on a broad combination of pesticides. Consistent strong contributions from agricultural application to detection rates in hotspots or in spraying season were not observed.

Mixture risk assessment would strongly benefit from a strategy for the measurement of multiple exposure and effect biomarkers in the same subject in HBM programmes. This requires the development of an inclusive HBM/exposome infrastructure in Europe.

7 Is it possible to establish EU-wide accepted HBM guidance values for pesticides that takes into account potential mixture effects and evidence from epidemiological studies?

HBM guidance values (HBM-GVs) for the single substances deltamethrin and cyfluthrin have been derived. Concepts referring to potential mixture effects need to be further elaborated but a first-tier screening HBM-GV, based on 3-PBA, for the cumulative exposure to mixtures of pyrethroids was derived and could be used for a screening risk assessment.

8 How can HBM data from HBM4EU feed into prioritisation of the pesticides for risk assessments and regulatory decision-making?

It is recommended to take potential analysis of exposure to a particular substance by means of HBM data into account as part of EU (re)evaluation of pesticides. This would mean that suitable metabolites for HBM studies should be proposed and HBM-GVs derived in all cases where this is possible. A respective section might be included in the overall evaluation and would be subject to peer review by member states. The applicants should be requested to provide own proposals for analysis of their active ingredients and metabolites in HBM studies.

Chlorpyrifos and chlorpyrifos-methyl are no longer authorized in the EU and all MRLs are set at the default value. The results based on real human exposure support this decision. Nevertheless, it should be noted that a similar assessment conducted with the “legally binding ADI” at the time of collecting the urine samples would have resulted in very different risk characterization results. This fact confirms the need for rapid regulatory implementation of the scientific updates on pesticide toxicity. The combination of TCP with a second biomarker, based on urinary levels of alkyl phosphate metabolites, should be considered for future activities.

KNOWLEDGE GAPS

HBM4EU has helped to identify a number of specific data gaps that need to be filled in order to give policymakers relevant and strategic data to establish appropriate regulations and improve chemical risk management. However, some gaps and needs for action will remain at the end of HBM4EU, which should be addressed in the future:

- Long-term monitoring of exposure levels to evaluate differences between countries and population groups, time trends, and age-related differences in exposure including policy efficacy implemented to reduce human exposure (e.g. Farm to Fork Strategy).
- Evaluation of exposure through breast milk.
- Evaluation of exposure through residential use of pesticides.
- Development of occupational acceptable operator exposure level (AOEL) (including farm families, bystanders and residents living in the vicinity).
- Evaluation of exposure levels among occupationally exposed workers.
- Urinary marker TCPy covers only two closely related active substances, chlorpyrifos and chlorpyrifos-methyl and thus is not relevant for covering cumulative risk to pesticide mixtures. However, setting human biomonitoring programmes would facilitate the implementation and prioritization of human biomonitoring and the generation of data for policy uptake.

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