HBM4EU science and policy for a healthy future

RESEARCH BRIEF

Priority Substances and Cancer

KEY MESSAGES

- In Europe, cancer is the most frequent non-communicable disease and the **second most common cause of death**.
- This high cancer frequency can be explained by a **variety of causes and factors,** including lifestyle (e.g., tobacco smoke, alcohol consumption), ageing, early detection and screening, and chronic exposures to low doses of carcinogens present in our environment (e.g., air pollutants), in food, consumers products, medicines or in the workplace (1).
- WHO estimates that around 20 % of the disease burden is due to **environmental (including occupational) factors**, and thus **preventable** (2). A significant part of those exposures concerns chemicals in the environment and in the workplace.
- This research brief summarizes the key information on chemicals carcinogenicity, and use of **HBM for cancer risk assessment,** collected within HBM4EU for its list of priority substances.

BACKGROUND

Cancer impacts the lives of millions of Europeans, with well over 3 million new patients diagnosed each year, almost 2 million deaths, and severe consequences for the economy and health systems of EU countries (3,4). About 23 % of cancer cases globally happen in Europe, although it is home to only 9 % of the world's population (5). In Europe, cancer is the most frequent form of non-communicable disease and the second most common cause of death. This high cancer prevalence can be explained by a variety of causes and factors, including lifestyles, ageing, early detection and screening, and chronic exposures to low doses of carcinogens present in our environment (e.g., air pollutants), in food, consumers products, medicines or in the workplace (1). WHO estimates that around 20 % of the disease burden is due to environmental (including occupational) factors, and thus preventable (2). A significant part of those exposures concerns chemicals in the environment and in the workplace. About 120,000 work-related cancer cases and 80,000 related fatalities occur each year as a result of exposure to carcinogens at work in the EU[1].

Reducing preventable contributing risks to cancer has been at the core of several European policies, including the umbrella regulations and policies concerning pollution prevention and chemical safety. Europe's Beating Cancer Plan is the most recent European Union's (EU) response to the urgent needs of better cancer prevention, treatment and care. Structured around four key areas, the Beating Cancer Plan makes, within the prevention pillar, an explicit commitment to reduce exposure to carcinogenic substances[2]. Reducing exposure, however, requires identifying and measuring it with reasonable accuracy. While we have some estimates, we are not certain about the actual contribution of environmental risks to the burden of cancer, particularly from low level exposures to combinations of chemicals since the conception (in utero) and throughout our lifetime. A substantial part of the chemicals in the market and the environment have not undergone carcinogenicity testing, and significant knowledge gaps remain on possible low dose effects well below those of traditional toxicological studies (6). Those knowledge gaps, combined with our evolving understanding of the biology of cancer, make the assessment of cancer risk from environmental exposures a formidable research and regulatory challenge.

Human biomonitoring (HBM) can play a key role in real-life exposure assessment to carcinogenic chemicals and ultimately on the calculation of increases in cancer risk. This application is at the heart of the prioritization strategy of HBM4EU, based on the substances' hazardous properties (including carcinogenicity), exposures and societal concern, among others.

1 https://osha.europa.eu/es/themes/work-related-diseases/work-related-cancer

2 https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union/cancer-plan-europe_en

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

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CARCINOGENICITY OF THE HBM4EU PRIORITY SUBSTANCES

Several of the substances within the HBM4EU priority substances have carcinogenic properties, with varying levels and quality of evidence in laboratory, animal studies and human epidemiological studies in occupational settings and elsewhere. A succinct summary is presented according to the priority list (see Table 1 for carcinogenicity categorizations and Figure 1 for carcinogenicity target organs).

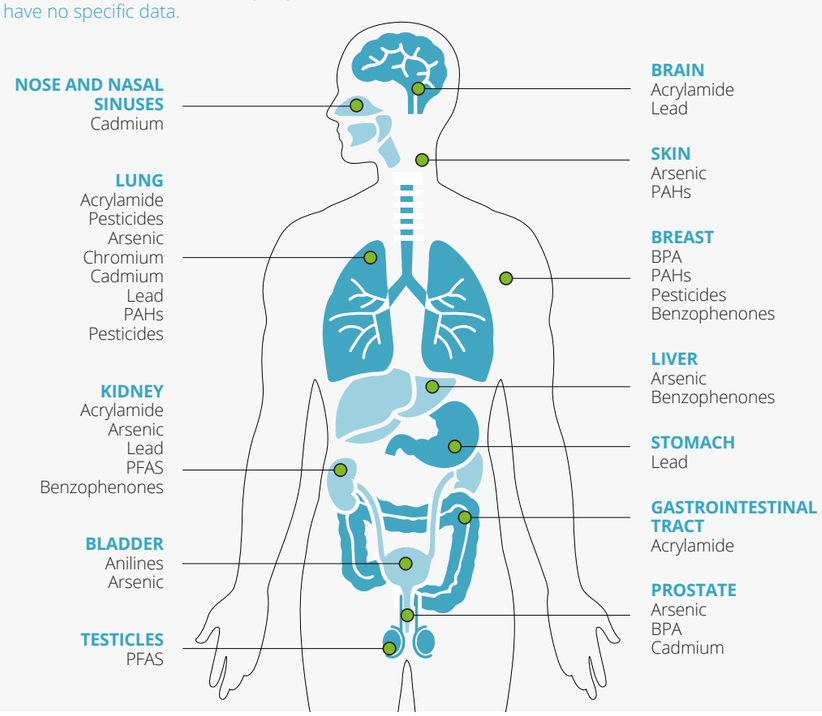
Acrylamide: Evidence from animal and laboratory studies have pointed out that acrylamide and its main metabolite glycidamide may be carcinogenic at any level (7). Although epidemiological studies have not consistently observed an increasing risk of common cancers in relation to dietary acrylamide, there is a concern about its carcinogenic effects in humans, possibly contributing to 19 human tumor types in 14 different organs. There is limited knowledge on a mixture effect of acrylamide and other carcinogens, particularly dietary carcinogens (8).

Aniline family: Various anilines have carcinogenic properties. Classical members of this family are bladder carcinogens 2-naphtylamine and benzidine, which use has been restricted in EU. 4,4′-methylenebis[2-chloroaniline] (MOCA) and 4,4′-methylenedianiline (MDA) are both genotoxic carcinogens to which a threshold for carcinogenic effects cannot be assigned, and for which ECHA has developed dose-response analyses (ECHA 2015a, 2015b). Aniline is a genotoxic carcinogen, as is o-Toluidine. Other chemicals in the family, such as 4,4′-methylenediphenyl diisocyanate (MDI) and p-Toluidine, are suspected carcinogens.

Aprotic solvents: There is a variety of aprotic solvents, including acetone, acetonitrile, dimethylformamide, dimethylsulfoxide, etc. While not all have been comprehensively assessed for carcinogenicity, N,N-dimethylacetamide (DMAC) is currently considered possibly (i.e. limited or inadequate evidence in humans – categorization 2B) carcinogenic by IARC.

Heavy metals (Arsenic, Cadmium, Chromium, Lead and Mercury): Inorganic Arsenic is a known carcinogen (9), contributing to skin, lung and bladder, liver, kidney, and prostate cancer; whereas the evidence is less conclusive for organic forms. The studies in animals showed a carcinogenic potential for Dimethylarsinic acid (DMA) metabolite; however the data regarding human carcinogenicity are inconclusive, hence IARC classified these methylated forms as possibly carcinogenic to humans (10). Cadmium and cadmium compounds are known carcinogens, that can induce lung and prostate cancer in laboratory animals and in the same and some other organs in humans (11). Hexavalent chromium is associated with increased lung cancer risk among workers in certain industries and also cancer of the nose and nasal sinuses (12). Inorganic Lead is linked in epidemiological studies to a higher risk of cancers of the stomach, lung, kidney, and brain in workers exposed to inorganic lead (13). Several studies indicated its genotoxicity and ability to generate reactive oxygen species. Inorganic Mercury is considered as not classifiable regarding its human carcinogenicity, whereas Methylmercury is considered a possible human carcinogen.

Substances with carcinogenic effects: Aprotic solventes, emerging chemicals, flame retardants, mercury, mycotoxins and phthalates have no specific data.



Benzophenones: Within this group, Benzophenone is possibly carcinogenic to humans, based on sufficient evidence in experimental animals, exerting tumorigenic effects in rats and mice in the liver, the kidney and in the haemopoietic system, including rare histiocytic sarcomas (14). According to an assessment by EFSA, 4-methyl benzophenone (4-MBP) is expected to be a non-genotoxic carcinogen (15).

Bisphenols: Studies have indicated that 4,4′-Bisphenol A (BPA) could be associated with increased risk for breast and prostate cancer or at least significant breast tissue remodeling (16,17), in association with gestational and neonatal exposure (18) (19). BPS could be linked to adverse outcome pathway networks leading to thyroid cancer (20).

Flame retardants: Carcinogenicity is one of the wide range of adverse health effects of Polybrominated diphenyl ethers (PBDEs) and Hexabromocyclododecanes (HBCDDs). 2,2′,6,6′-tetrabromo-4,4′-isopropylidenediphenol (TBBPA) has shown carcinogenic properties in laboratory and animals and is categorized as a potential or possible carcinogen by regulatory agencies in Europe and elsewhere. Tris(2-chloro-1-methylethyl) phosphate (TCIPP) is potentially carcinogenic, as is Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCIPP). There are clear knowledge gaps concerning the carcinogenicity of mixtures of flame retardants, especially for hormonal cancers.

Mycotoxins: Currently, the main known human and animal health burdens of mycotoxin exposure are related to chronic toxicity, such as carcinogenic effects. The International Agency for Research on Cancer (IARC) classified some mycotoxins from carcinogenic to humans (e.g. aflatoxin B1 – AF B1) to not classifiable regarding its carcinogenicity to humans (e.g. deoxynivalenol) (21–24). Fumonisin B (FB1) is a suspected carcinogen according to the Classification, Labelling and Packaging (CLP) regulation classification and it is classified by IARC as possibly carcinogenic to humans (22) .

Per-/polyfluorinated compounds (PFAS): This groups of chemicals is the subject of increasing societal concern, with cancer being one of the perceived associated health risks. Substances which are best-known, such as Heptadecafluorooctane-1-sulphonic acid (PFOS), Pentadecafluorooctanoic acid (PFOA) and Perfluorononan-1-oic acid (PFNA) are classified as suspected carcinogens in European regulations (25). PFOA has shown epidemiologic evidence of associations with cancers of the kidney and testis in heavily exposed subjects (26), though overall, the evidence for an association between cancer and PFAS remains sparse and likely to be better informed by long term follow-up of large-sized cohorts (27).

Pesticides: There is a vast diversity of pesticides with varying toxicological -including carcinogenic- properties. Some widely used pyrethroid pesticides were assessed by IARC as not classifiable as to its carcinogenicity to humans. However, Permethrin (a pyrethroid) is listed as a high priority compound for assessment by IARC, classified as "likely to be carcinogenic to humans" after oral exposure by the US EPA (28), and listed on the Annex III inventory as meeting mutagenicity criteria. Furthermore, genotoxic properties for different pyrethroids have been indicated in experimental studies (29–31). Within organophosphates, potential associations with carcinogenicity are not conclusive. Some epidemiological studies have associated chlorpyrifos with lung, rectal, and breast cancer and increased risk of Non-Hodgkin Lymphoma (32–35)(36). Neither chlorpyrifos nor dimethoate are classified as carcinogenic, despite in vitro genotoxicity concerns (37). In 2015 IARC classified glyphosate as probably carcinogenic to humans (38), triggering debate over health risks of this substance. A 2016 EFSA review deemed glyphosate unlikely to pose a carcinogenic hazard to humans and the evidence does not support carcinogenicity classification in EU regulations (39), an assessment consistent with that of the Joint FAO/WHO Meeting on Pesticide Residues in food (40). However, the US state of California and the Danish Working Environment Authority (WEA) have listed glyphosate as causing cancer. Although the regulatory risk assessment of pesticides currently practiced in the EU is comprehensive there are some concerns in the scientific community, that this risk assessment is inadequate at addressing mixed exposures, specifically for carcinogenic effects (6).

Phthalates, hexamoll® dinch: There is no conclusive evidence of the carcinogenicity of Phthalates, as epidemiologic evidence has been inconsistent (41). Bis(2-ethylhexyl) phthalate (DEHP), one of the most widely used phthalates, causes liver carcinogenicity in rodents and is possibly carcinogenic to humans, although it is disputed if the mechanism involved (peroxisome proliferation) is relevant for humans (42). Several Phthalates (DnOP, DiDP, DnPeP, Hexamoll® DINCH, DHNUP, DnHP, and DMEP)[3] are classified as suspected carcinogens in the CHL/Annex III entry classification.

Polycyclic aromatic hydrocarbons (PAHs): PAHs are ubiquitous pollutants frequently found in a variety of environments, including occupational settings and in food products and water. Many PAHs are known or suspected human carcinogenic and mutagenic compounds after being metabolized in the body. For example, benzo[a]pyrene (BaP) is a known carcinogen, whereas dibenzo(a,h) anthracene (DBAhA) is a probable carcinogen, and various others benzo(a) anthracene (BaA), Chrysene (CHR), benzo(b)fluoranthene (BbF), benzo(b)fluoranthene (BjF), benzo(b)fluoranthene (BkF) and Naphthalene are classified as possible carcinogens by IARC and presumed carcinogens or suspected (Naphthalene) carcinogens in CLP. There are indications that the carcinogenic potency of some further PAH congeners, e.g. some of the dibenzopyrenes, may even be considerably higher than that of the lead compound BaP. United States EPA recommends using toxicity equivalency factors (TEFs) to convert concentrations of 19 carcinogenic PAHs (cPAHs) to an equivalent concentration of benzo(a)pyrene (BaP). Humans are commonly exposed to mixtures rather than to a single PAH and their combined effects remain largely unexplored.

[3] For details, see Phthalates and Hexamoll® DINCH – HBM4EU – science and policy for a healthy future

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

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Table 1 summarizes the carcinogenicity categorizations, where applicable, of selected chemicals within the list of HBM4EU priority substances.

Table 1: Carcinogenicity categorization of selected chemicals within HBM4EU Priority Substances

			IARC category						CLP carc. cat.				
PRIORITY GROUP	**SUBSTANCE**	**CAS NR**	**1**	**1B**	**2A**	**2B**	**3**	**N/A**	**1A**	**1B**	**2**	**NOA**	**N/A**
Acrylamide	Acrylamide	79-06-1											
Aniline family	MOCA	101-14-4											
	MDA	101-77-9											
	MDI	101-68-8											
	Aniline	62-53-3											
	o-Toluidine	95-53-4											
	p-Toluidine	106-49-0											
	p-PDA	106-50-3											
Aprotic solvents	DMAC	127-19-5											
Arsenic	Arsenic	7440-38-2											
	DMA	75-60-5											
Benzophenones	BP	119-61-9											
Bisphenols	BPA	80-05-7											
Cadmium	Cd	7440-43-9											
Chromium VI	Cr(VI)	18540-29-9											
Flame retardants	TBBPA	79-94-7											
	TCDIPP	13674-87-8											
	TCIPP	13674-84-5											
Lead	Inorganic Lead	7439-92-1											
Mercury	Inorganic Mercury	7439-97-6											
	Methylmercury	22967-92-6											
Mycotoxins	AFB1	1162-65-8											
	FB1	116355-83-0											
Per-/ polyfluorinated compounds	Deoxynivalenol	51481-10-8											
	PFOA	335-67-1											
	PFOS	1763-23-1											
	PFNA	375-95-1											
Pesticides	Pyrethroids	Various											
	Glyphosate	1071-83-6											
Phthalates	DEHP	117-81-7											
	Other phthalates	Various											
Polycyclic aromatic hydrocarbons	BaP	50-32-8											
	Benzene	71-43-2											
	BeP	192-97-2											
	BaA	56-55-3											
	Chrysene (CHR)	218-01-9											
	BbF	205-99-2											
	BjF	205-82-3											
	BkF	207-08-9											
	(DBAhA)	53-70-3											
	Naphthalene	91-20-3											
	Formaldehyde	50-00-0											

IARC category

- **1** – Carcinogenic
- **1B** - presumed carcinogenic
- **2A** – probably carcinogenic
- **2B** – possibly carcinogenic
- **3** – Not classifiable
- **N/A** – not assessed

CLP carc. cat.

- **1A** – Known
- **1B** – Presumed
- **2** – Suspected
- **NOA** – No overall agreement
- **N/A** – not assessed

USE OF HBM IN CANCER RISK ASSESSMENT PERFORMED AS PART OF HBM4EU

As mentioned, the increasing use of HBM as a direct estimate of human internal exposure and aggregating exposure from various sources and exposure routes is opening up possibilities of increasingly accurate cancer risk assessments from chemical exposures. HBM4EU summarized examples of use of HBM in risk assessments (some including cancer as an outcome) of HBM4EU priority chemicals – see Deliverable 5.1 on "Human biomonitoring in risk assessment: analysis of the current practice and 1st examples on the use of HBM in risk assessments of HBM4EU priority chemicals"[4], and then performed risk assessments for substances within the priority list.

Anilines (o-Toluidine): A one-compartment model-based approach was used to estimate the urinary levels corresponding to the external intake levels or vice versa. This allowed the comparison between available HBM data and existing binding occupational exposure level (OEL) and established cancer risk estimates. An existing cancer risk assessment resulted in a Benchmark Dose causing 10% urinary bladder tumor incidence above background level (BMD10) of 42.2 mg/kg bw/day in rats, corresponding to an inhaled dose scaled to humans of 210 mg/m3 at occupational exposure. This level corresponds to a urinary level of 1000 mg/L by assuming a 70-kg bw, a 1.5 L/day urinary volume and 75% excretion. Similarly, a cancer risk level of 1:10 000 corresponds approximately to a steady state urinary level of 1 mg/l. As estimated through this method, the workers exposed to o-toluidine had a cancer risk of 1:20 000 in the worst-case scenario (0.5 mg/L in urine). The exposure levels calculated based on HBM data were below the binding occupational exposure level (BOELV, 0.44 mg/m3 corresponding 2.2 mg/l as urinary total o-toluidine) set under the EU Carcinogens and Mutagens Directive.

Cr (VI): This assessment focused on studying whether inclusion of HBM data would improve an existing occupational risk assessment by the Health Council of the Netherlands (2016) on historic exposure to Cr (VI) related to maintenance of military equipment between 1984 and 2006, based on external exposure data (42). For the dose response assessment, a published equation for lung cancer risk was used (43). For the exposure assessment, HBM data on Cr (VI) were retrieved from the Finnish Institute of Occupational Health (FIOH) database, based on all the HBM samples sent to the Institute for monitoring chemical exposure by the occupational health care units of the work places since 1980s. HBM data (p95 values) were converted into corresponding air levels using two previously published conversion equations, and estimated lung cancer risks calculated in the same manner as in the original Dutch risk assessment. That original assessment calculated for a worker with 21 years (1984-2006) of exposure a relative risk (RR) of 1.43 compared with the general population. The HBM-supported risk assessment showed a similar estimate and highlighted that the inclusion of HBM data supported the original Dutch one and improved its reliability.

PAH: The work on Polycyclic aromatic hydrocarbons was based on a literature review, and the risk assessment was done considering the general population (inhalation and oral exposure), and also an occupational risk assessment.

- General population – inhalation exposure: the metabolite 1-hydroxypyrene (1-OH-PYR), was used as an indirect urinary biomarker of exposure to PAH mixtures that include benzo[a]pyrene (BaP). The estimation of the excess life-time cancer risk (ELCR) for lung cancer was done following the ECHA-RAC dose-response relationship. However, the low levels of 1-OH-PYR described in urine in the reviewed studies did not allow the back-calculation of exposure levels to external doses using HBM in the RAC 2018 approach, thus no values of HBM-based ELCR concerning general population have been determined. The estimates of ELCR based on the airborne BaP concentrations reported in the literature were below the relevant WHO guidance.
- General population – oral exposure: the ECHA-RAC (2018) dose-response relationships for oral exposure were used to estimate ELCR, of dietary (oral) exposure to four PAHs congeners (PAH4: BaA, BbF, BaP and CHR) and to eight PAHs congeners (PAH8: PAH4 + BkF, BghiP, DBahA and IP) (for detailed calculations see HBM4EU Deliverable 5.5). ELCRs at the determined exposure doses of PAH4 for mean and high-level consumers amounted to 4.02×10^{-5} and to 7.11×10^{-5}, respectively, and for PAH8 were 2.79×10^{-5} and to 4.93×10^{-5}, respectively. These estimates indicate that cancer risk for general population, mean and high consumers, might not be tolerable since the indicative tolerable risk level for the general population proposed by the EC (2016) was 10^{-6}. Alternatively, ELCR was estimated based on pyrene intake following the ECHA-RAC equations. By assuming that pyrene is an indirect marker of exposure to PAH mixtures and that 1-OH-PYR has been linked to dietary exposures (44) (Nethery et al., 2012), the ELCRs were estimated at 9.27×10^{-5} (non-smokers) and at 4.45×10^{-4} (smokers).
- Occupational exposure: Based on the 1-OH-PYR values, the excess lifetime cancer risk (ELCR) for workers, concerning lung cancer, was estimated following the ECHA recent approach. ELCR values were calculated using air and HBM data. The approach described for inhalation exposure, based on the ECHA RAC 2018 dose response function, was followed. In the presented ELCR estimates the calculations yielded risk levels of the same order of magnitude (10^{-5}) with an exception for smokers (10^{-4}). As the risk level around 10 times lower (10^{-6}) was estimated using air monitoring data (external measurements), this indicates that using solely air monitoring data may underestimate the risk.

[4] https://www.hbm4eu.eu/result/deliverables/

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

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Table 2 below summarizes these examples.

Table 2: HBM4EU examples of risk assessments related to carcinogenicity

Substance Group	Specific substances included	Population covered	Exposure assessment: HBM exposure data used	Hazard assessment methods
Acrylamide	Acrylamide	General	Aligned studies[5] data for children and adults	Hazard assessment based on an EFSA acrylamide RA (2015)
Anilines	ortho-toluidine	Occupational	Published data from literature	Dose response for carcinogenicity by SCOEL and BE approach to convert biomonitoring data as external intake
Arsenic	Inorganic arsenic	General population	Published data from literature	Lung, skin and urinary bladder cancer. ECHA dose response (2013) for the carcinogenicity of arsenic
Cr	Chromium VI	Occupational	Finnish Occupational Institute of Health occupational HBM data (Urinary Cr) converted into corresponding air levels for exposure assessment	Dose response equation for lung cancer risk (Seidler et al., 2013). Use of existing occupational data on the correlations between air and U-Cr levels
PAHs	PYR, BaP, PAH4, PAH8	General	Published data (FLEHS, literature) Aligned studies data for adults	Dose response for carcinogenicity (several types of cancer, including lung cancer) by RAC
	PYR, BaP	Occupational	Published data from literature	Dose response for carcinogenicity (lung, bladder, skin) by RAC

SOCIETAL CONCERN ON THE CARCINOGENICITY OF CHEMICALS

The inclusion of citizen perspectives and perceptions in a systematic, transparent, and participatory way was central within the HBM4EU strategy. To achieve this, HBM4EU conducted a survey of European citizens to inform the prioritization process (i.e., identification of relevant substances and their health effects following chemical exposure should be addressed)[6]. Thereafter, HBM4EU delved deeper into citizen's perceptions of risk and benefits or chemicals and human biomonitoring through focus groups hosted in 10 countries. The focus groups were intended to gather further understanding on (i) citizens' perception of chemical exposure in their daily lives and HBM; (ii) their concerns regarding exposure to chemical substances; (iii) beliefs towards chemical exposure and safety, as well as regarding HBM (45).

Concerning the carcinogenicity of chemicals in the environment, workplace and consumer products, the outcome of the focus group discussions confirmed that this idea is firmly set as a concern in the public's mind, as illustrated by their references to chemical substances contributing to a higher incidence of 'well-known' diseases, such as cancer. Cancer was, in fact, identified by the focus groups as an outcome for which combined exposures would matter particularly. Personal or family experiences were stressed as especially important aspects in raising high concern. Participants made links of cancer diagnoses with occupational exposures and hazardous chemicals in food, drinking water, and indoor and outdoor air; and specific mentions to air pollutants, pesticides, heavy metals, organic solvents, and other families of chemicals that include substances with known carcinogenicity (46). Furthermore, focus group's participants expected that human biomonitoring would provide a better understanding of disease etiology and the potential to reduce risk through changing behavior, allowing scientific information to better translate into policies and effective protection of human health (45).

5 The aligned studies are a survey aimed at collecting HBM samples and data from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

6 https://www.hbm4eu.eu/citizens-corner/outreach-to-the-european-public/

CONCLUSIONS

Several of the HBM4EU priority substances have carcinogenic properties, though for many there is a clear need for further evidence. In particular, the assessment of carcinogenicity of low levels of exposure of a combination of chemicals is a clear research challenge. **Human biomonitoring can contribute crucially to more accurate and evidence-based exposure assessments and more realistic assessments or excess cancer risk due to chemicals.** This application, requiring **significant research efforts to bridge existing knowledge gaps,** can **strongly support EU policies aimed at cancer prevention,** such as the prevention pillar of the Beating Cancer Plan. HBM4EU citizen engagement research suggest that this application of human biomonitoring may be supported by the public, insofar as it could help change behaviors and be used for **better health protection policies**.

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

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