Substance report

June 2022

Bisphenols

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.

Table of contents

List of tables:

List of figures:

Authors and Acknowledgements

Lead authors

First version (March 2021) compiled by project team at Wood: Dr. Ian Keyte, Neil Patton and Dr. Robert Whiting based on scoping documents produced by the chemical group leader (CGL) and colleagues.

The EEA has since updated this document to reflect the work developed before the conclusion of HBM4EU, with the support of the CGL and other colleagues.

Robert Barouki, Elena Tarroja (INSERM)

Contributors

Cathrine Thomsen (NIPH)

Els Heyvaert, Hans Reyders, Karen Van Campenhout (DOMG)

Greet Schoeters, Liese Giles, Kirsten Baken (VITO)

Jean-Philippe Antignac, Laurent Debrauwer (INRA)

Nataša Janey Holcer (Croatia NH)

Coen Graven, Shalenie den Braver-Sewradj (RIVM)

Loic Rambaud (ANSP)

Kim Pack (UBA)

Matthieu Meslin, Christophe Rousselle (ANSES)

Marieta Fernandez, Vicente Mustieles (UGR)

Denis Sarigiannis, Spyros, Karakitsios (AUTH)

Joana Lobo Vicente, Petra Pontier (EEA)

Glossary

Abbreviated name	Full name	CAS No
Bisphenol Compounds		
BPA	4,4'-isopropylidenediphenol	80-05-7
BPS	4,4'-sulphonyldiphenol	80-09-1
BPF	4,4'-methylenediphenol	620-92-8
BPB	4,4'-(1methylpropylidene)bisphenol	77-40-7
BPAF	4,4'-[2,2,2-trifluoro-1(trifluoromethyl)ethylidene]diphenol	1478-61-1
BPM	4,4'-(1,3-phenylene-bis(1methylethylidene))bisphenol	13595-25-0
BPAP	4,4'-(1-Phenylethylidene)bisphenol	1571-75-1
BPFL	9,9-Bis(4- hydroxyphenyl)fluorene	3236-71-3
BP4,4’	Biphenyl-4,4'-diol	92-88-6
BPC	4,4'-isopropylidenedi-o-cresol	79-97-0
BPC12	4,4'-(dichlorovinylidene)diphenol	14868-03-2
BPP	4,4'-(1,4Phenylenediisopropylidene)bisphenol	2167-51-3
BPZ	4,4'-cyclohexylidenebisphenol	843-55-0
BPBP	2,2-bis(2-hydroxy-5-biphenylyl)propane	24038-68-4
BPE	4,4′-Ethylidenebisphenol	2081-08-5
BPPH	4,4'-ihydroxytetraphenylmethane	1844-01-5
BPM	4,4'-(1,3-phenylene-bis(1-methylethylidene))bis-phenol	13595-25-0
BIS2	Bis(2-hydroxyphenyl)methane	2467-09-9
DHDPE	p,p'-oxybisphenol	1965-09-9
Abbreviations		
AOP	Adverse Outcome Pathway	
BP	Bisphenol	
CAS	Chemical Abstracts Service	
C&L	Classification & Labelling	
CGL	Chemical Group Leader	
CLP	The ‘Classification, Labelling, Packaging’ Regulation Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.	
EDC	Endocrine Disrupting Chemical	
EFSA	European Food Safety Authority	

Abbreviated name	Full name	CAS No
EU	European Union	
HBM	Human Biomonitoring	
HBM-GV	Human Biomonitoring Guidance Values	
REACH	The ‘Registration, Evaluation, Authorisation and Restriction of Chemicals’ Regulation Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals	
SVHC	Substance of Very High Concern	
TDI	Tolerable Daily Intake	
C&L Classification Names		
Carc	Carcinogenicity	
Acute Tox	Acute Toxicity	
Repr	Reproductive Toxicity	
Muta	Mutagenicity	
STOT RE	Specific target organ toxicity - repeated exposure	
STOT SE	Specific target organ toxicity- single exposure	
Eye Dam/ Irrit.	Eye Damage / Eye Irritation	
Resp Sens.	Respiratory Sensitivity	
Skin Corr / Irrit.	Skin Corrosion/Irritation	
Skin Sens.	Skin Sensitivity	
WPL	Work Package Leader	
Properties of concern		
R	Toxic to Reproduction	
ED	Endocrine Disrupting	
SS	Skin sensitising	
PBT	Persistent, Bioaccumulative and Toxic	

1 Key Messages

HBM4EU has generated EU-wide human biomonitoring (HBM) data on bisphenols, both by collecting data from different studies and by generating new data in 11 countries representing the 4 European Regions (North, East, South and West). This is by far the largest collection of HBM data on bisphenol A (BPA) and its substituents bisphenol S (BPS) and bisphenol F (BPF) in Europe.

BPA is ubiquitous in the environment, with all adult humans across Europe exposed to at least low levels. BPS and BPF, used as replacements, are detected in 50% of adults analysed under HBM4EU.

BPA levels of exposure are higher than exposure levels for the substituents BPF and BPS in all Europe. Northern area is globally less exposed to these bisphenols than other areas.

Risk from occupational exposure should not be disregarded (a potential risk for workers was identified, especially in industrial scenarios with BPA exposure levels 10-20-fold higher than background exposures.

Based on previous studies and on exposure pathway modelling, the main route of human exposure appears to be through diet, where bisphenols may have migrated into food or drinks from food containers, packaging, or feeding bottles.

HBM4EU modelling studies on toxicokinetics and tissue distribution (including the fetus), Adverse Outcome Pathways and effect biomarkers strengthen the concern that the internal exposure to BPA, BPS and BPF and other bisphenols could be linked to a variety of health outcomes in humans and in the environment. In eight sampling locations out of ten, at least 5% of the European adults (20-39 years) from the HBM4EU Aligned Studies exceeded the HBM-GV of 1 µg/L for BPS, particularly in Southern Europe.

Societal concern towards endocrine-disrupting chemicals is highly connected to bisphenols and to the campaigns to regulate BPA in particular.

2 Introduction

HBM4EU is a project funded under Horizon 2020, running from 2017 to 2022. It generates knowledge to inform the safe management of chemicals and protection of human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts and to improve chemical risk assessment. HBM4EU compares data from across Europe, which allows an understanding of regional differences and helps to identify vulnerable groups, in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This document provides a summary of the known and suspected adverse human health effects of bisphenols and describes the main exposure pathways for humans. It also indicates where HBM could be of value in the development of EU policy, along with the remaining challenges in determining human bisphenol exposure. This substance report is intended to inform scientists, relevant stakeholders and policy makers on the value of HBM to establish the EU population's exposure to bisphenol compounds.

This substance report is based largely on the scoping document for bisphenols and its compounds, as well as the accompanying reports on legislative mapping, and the summary of HBM4EU results in relation to the key policy questions. Where necessary, additional information from ECHA documents including the Classification & Labelling (C&L) Inventory, and legislative text for relevant EU policy areas, have also been used for this report.

2.2 Overview of bisphenols

The list of substances included in the HBM4EU priority substance group "bisphenols" includes 18 individual compounds. The full list and description of all compounds is provided in the Glossary.

Within the group, Bisphenol A (BPA) has historically been produced and used in the highest volumes in Europe. Consumption of BPA in Western Europe in 2005/6 was estimated to be 1.15 million tonnes[1] (Fischer et al., 2014). An overview of key uses for BPA in Europe is shown in Figure 1.

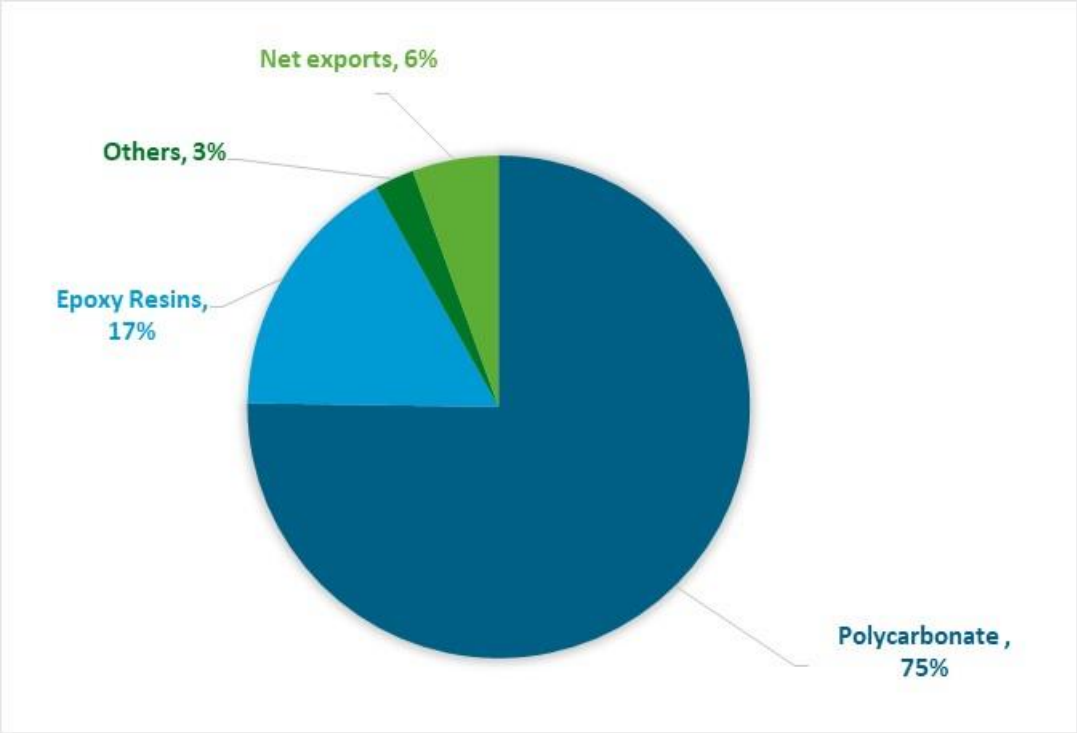


Figure 1 Distribution of uses for BPA in Europe (2005/6 data from Fischer et al., 2014)

The primary use of BPA (75% of all use) has historically been in the manufacture of polycarbonate, a clear plastic-like material which is tougher to abrasion than glass (Fischer et al., 2014). Polycarbonate is used in the manufacture of a wide range of products, such as building and construction materials, coatings for automotive parts and domestic appliances, sports equipment, medical and dental devices, electronic equipment such as DVDs and CDs, as well as in food and beverage storage containers and food packaging materials.

The second biggest use (17% of all use) has been in epoxy resins. It was estimated that 90% of world epoxy production was produced from BPA in 2005/6 (Fischer et al., 2014)[2]. Epoxy resins, have

[1] It should be noted that since 2005/6 BPA has become increasingly more regulated in Europe and the number of uses is more restricted (see Section 5).

[2] It has been indicated that since 2005/6 that the use of BPA in epoxy resin production has been decreasing. For example, one study has noted that the prevalence of epoxy based BPA can linings is approaching zero, see: https://www.cancentral.com/sites/cancentral.com/files/public-documents/CMI%20Washington%20State%20Canned%20Food%20Market%20Basket%20Report%20+%20Raw%20Data.pdf

uses across many sectors, including protective coatings for cars, marine vessels and equipment, laminates, adhesives as well as water infrastructure (pipes, tubes, and associated fittings) and food and beverage cans.

There are concerns that humans can be exposed to bisphenols through migration of the chemicals from food contact materials into food or drinks. BPA (and other bisphenols) have also been used in the manufacture of thermal papers, leading to concerns regarding the exposure of cashiers in frequent contact with thermal paper in receipts (see Section 3), resulting in this use being banned in the EU (see Section 0).

These concerns, and stricter regulations, have prompted industry to develop BPA substitutes, some of which are also compounds in the bisphenol group, for example BPF, BPS, and BPAF are among the main substitutes of BPA (Chen et al., 2016). BPF is used in epoxy resins and BPS is used in production of epoxy resins and polycarbonate, as well as thermal paper. For example, it has been noted by ECHA (2020), that from 2019, it is expected that BPS has taken over the status BPA as the main developer used in thermal paper, with its annual use is projected to increase approximately fivefold between 2014 and 2022.

Because these 'BPA substitute' bisphenols will potentially become more widely used as BPA is becoming increasingly restricted, there is a greater need to fully understand the potential human exposure and health impacts of these substances.

3 Human exposure to bisphenols

Based on available data from biomonitoring studies detecting BPA in blood and urine samples, it has been concluded that the general population is continuously exposed to BPA and is at risk from internal exposure (Vandenberg et al., 2007, 2010).

As discussed above (see Section 2.2), a number of other bisphenols are now being used in increasing amounts, resulting in increasing levels of exposure to these substances. For example, elevated concentrations of BPAF, BPF, and BPS (i.e., similar to or greater than that of BPA) have been reported in environmental and human samples in some regions (Chen et al., 2016).

It is noted that most of the available information on human exposure to bisphenols is derived from studies investigating BPA, with relatively few studies to date investigating other bisphenols. As discussed in Section 2.2, BPA is becoming increasingly restricted and substituted with other bisphenols (e.g., in thermal paper, see ECHA, 2020). In most cases, the level to which this substitution has taken place is not fully understood.

An overview of the main sources of exposure (environmental, occupational, consumer) and exposure pathways (oral, inhalation, dermal) is provided in **Error! Reference source not found.**. Additional information on these sources and pathways is provided below in the following Sections.

Importantly, not all European countries had biomonitoring data on BPA and other bisphenols, so a definitive picture of bisphenol exposure for the whole of Europe was not currently available. Furthermore, while biomonitoring studies are available for BPA, the majority of the studies have a single measurement of exposure so while these are useful to estimate exposure in a particular population and follow time trends, this is not as useful for risk assessment. This illustrates the need to better establish the exposure of the general population to BPA and other bisphenols. The work

programmes of the HBM4EU project have been directed at addressing these needs (see Sections 6,7,8).

3.1 Environmental exposure

There is solid evidence that a majority of the human population has been or is exposed to bisphenols. Human exposure mostly occurs via environmental media, such as air, land, water, food, and drinking water. The extent of exposure differs for different environmental sources. However, relatively small number of studies investigating the exposure route for bisphenols (e.g. RIVM (2014, 2017); Van Goetz et al. (2010); and Vandenberg et al. (2007)), indicate that primary exposure for the general public is expected to be through the diet, largely due to BPs migrating from food and drink containers and packaging. Some studies revealed that exposure to bisphenols, to BPA in particular may occur via breast feeding. One study of preschool children estimated that 99% of exposure came through the diet.

Exposure via the environment (e.g. through releases to atmosphere) is low, although many studies have detected BPA in household air and dust.

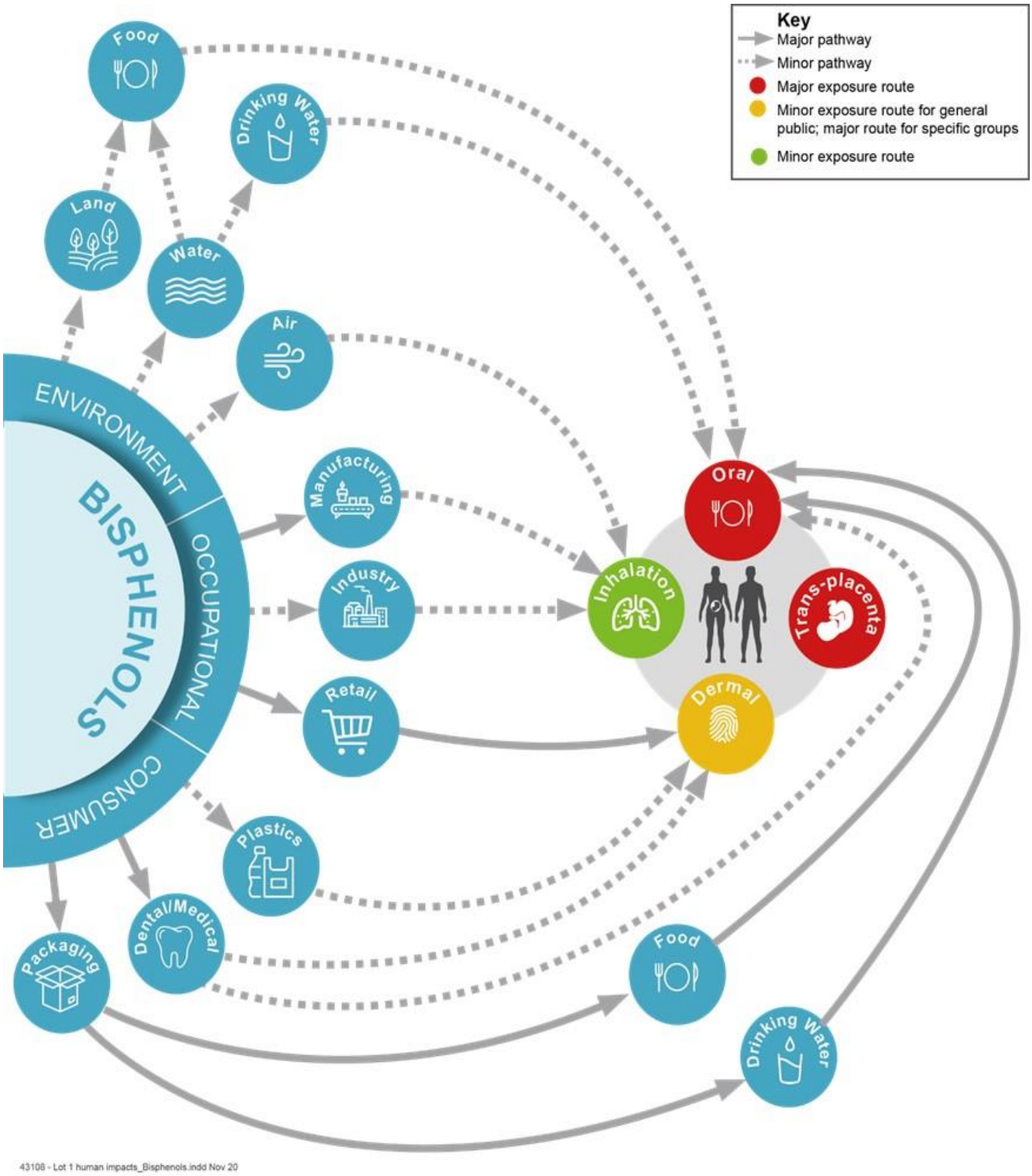


Figure 2 Overview of exposure route and pathways for bisphenols

3.2 Occupational exposure

The analyses of occupational exposure among workers have shown that relatively high levels of dermal exposure can occur through use of thermal paper (e.g. in shop receipts), which will be more significant for workers in retail establishments. However, the use of BPA for this purpose is now restricted in Europe (see Section 5) and, as discussed in Section 2.2, has largely been replaced with BPS (ECHA, 2020). Occupational exposure (e.g. dermal or inhalation) can be significant in certain settings (e.g. in epoxy resin manufacture), but these workers represent a relatively small proportion of the whole population.

3.3 Consumer exposure

The studies identified children and women as the most vulnerable groups with regards to consumer exposure. The estimated BPA dietary intake was highest in infants and toddlers (up to 0.875 µg/kg bw per day). Women of childbearing age had dietary exposures comparable to men of the same age (up to 0.388 µg/kg bw per day) (EFSA (2015a,b)).

A wide range of food-contact packaging serve as potential sources of BPA contamination in foods. For adults, the main route is shown to be through canned food, although not all food and drinks types have been covered in the assessment and there is no certainty which types of food packaging contributed the most to exposure. It has been shown from many studies that BPA can leach from the linings of food cans into food materials including fish, vegetables, and infant formula. For infants and children, the use of polycarbonate baby bottles was shown also to be a significant source of exposure. However, the use of BPA for this purpose is now restricted in Europe (see Section 5).

Some studies concluded that the highest exposure to bisphenols occurred via consumption of non-canned ‘meat and meat products’ (EFSA (2015a,b)), and that ‘vegetables and vegetable products’ was the only canned food category that contributed up to 25-50% in some population groups (RIVM, 2017). However, another study conducted by ANSES (ANSES, 2017) concluded that vegetables contribute to about 40% of food exposure, followed by mixed dishes (about 15%) and meat and meat products (about 10%).

Some polycarbonate containers (e.g., plastic tableware) intended to be used as reusable food containers, have the potential to leach BPA, and since many of these containers are used in the microwave, the heating may increase BPA leaching levels.

Other consumer goods (e.g. dental implants, cosmetics, toys) can result in exposure for certain individuals. The use of BPA in medical devices can result in high levels of exposure for the affected individuals.

4 Health impacts of bisphenols

4.1 Overview of key health impacts from bisphenols

A large number of human health (epidemiological) and animal studies have established that exposure to bisphenols can be linked with increased risk for significant health outcomes in humans. These studies have focussed predominantly on BPA (e.g., WHO and UNEP, 2013; Gore et al., 2015, Vandenberg, 2014, EFSA, 2015a,b, ECHA, 2015).

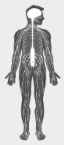
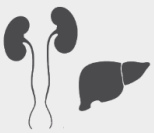
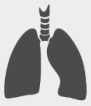
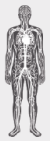
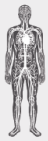
In June 2017, BPA was identified as having endocrine disrupting properties for human health[3]. It has been indicated that BPA elicits a variety of endocrine disrupting effects targeting steroid hormones as well as thyroid hormones. Other bisphenols, including BPF, BPS, BPAF, BPZ, BPE and BPB are also suspected to be endocrine disrupting chemicals (Mesnage et al., 2017).

Several other health outcomes in humans have been linked with exposure to bisphenols. An overview of these effects is provided in Figure 4.1.[4] This is based on a number of reviews conducted on the health effects associated with exposure to BPs (e.g. Gore et al., 2015., Mesnage et al., 2017, Seachrist et al., 2016, UNEP and WHO, 2013, Vandenberg, 2014).

Controversies exist regarding these toxic effects, largely because of discrepancies between different types of experimental studies (regulatory vs academic studies) possibly due to differences in experimental study design, with different levels of evidence being obtained depending on the outcome and the exposure period. Epidemiological studies are, in some cases, difficult to interpret: some studies have established association but cannot reveal a causal link between BPA and a toxic outcome (see ECHA, 2016; EFSA, 2015a,b). The **Figure 3** below presents the breakdown of toxic effects and substances that are grouped by target organs.

[3] https://echa.europa.eu/-/msc-unanimously-agrees-that-bisphenol-a-is-an-endocrine-disruptor

[4] An explanation of the categorisation of the strength of evidence for the health effects presented in Figure 4.1 is provided in Appendix 2.

Target organ of the body	Effects	Relevant Substances	Adults (men)	Adults (women)	Infants / Foetuses
Endocrine system 	Endocrine disrupting effects	BPA	●	●	●
		BPF, BPS, BPAF, BPZ, BPE, BPB	●	●	●
DNA 	Birth defects and reproductive harm	BPA, BPS, BPAF	○	●	●
		BPM	○	●	●
		Other BPs	○	●	●
Central nervous system 	Brain cell damage; neurological, neurodevelopmental and neuroendocrine effects	BPA	●	●	●
		Other BPs	●	●	●
Immune system 	Immunotoxicity	BPA	●	●	●
		Other BPs	●	●	●
Kidney and Liver 	Increased kidney and liver weight' organ damage	BPA	●	●	●
		Other BPs	●	●	●
Lung 	Bronchitis and pneumonitis	All BPs	●	●	●
Blood system 	Carcinogenic potential associated with acute leukaemia	All BPs	●	●	●
Cardiovascular System 	Increased risk of high blood pressure and cardiovascular disease	All BPs	●	●	●

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

43108 - Lot 1 Health impacts_Bisphenols_v5.indd pattn

Figure 3 Overview of health effects associated with bisphenols

4.2 Vulnerable target groups

By comparing a derived Tolerable Daily Intake (t-TDI) (4 µg/kg bw per day) with exposure estimates, The EFSA (2015a,b) opinion on the risks to public health related to the presence of BPA in foodstuffs concluded, “there is no health concern for any age group from dietary exposure and low health concern from aggregated exposure”. However, considerable differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) were noted in establishing the t-TDI values. The EFSA CEP Panel has performed the re-evaluation of EFSA t-TDI for BPA established in 2015, recently open to public consultation[5]. The recent EFSA opinion defines a tolerable daily intake of 0.04 ng BPA/kg bw per day for BPA. Comparison of this TDI with the dietary exposure estimates from the EFSA 2015 opinion showed that both the mean and the 95th percentile **dietary exposures in all age groups exceed the TDI by two to four orders of magnitude**. The EFSA CEP Panel concludes that there is a health concern from dietary BPA exposure for all age groups. The immune system has been identified as the most sensitive health outcome category to BPA exposure in the scientific opinion of EFSA. Specifically, an increase of Th17 cells was identified as the critical effect; these cells are pivotal in cellular immune mechanisms and involved in the development of allergic lung inflammation. The immunotoxic effects of BPA, observed both in experimental animals as well as in human epidemiological studies (Casas & Gascon, 2020; Li et al. 2018a, b), are selected as most sensitive end-point of concern. Other endpoints have also been considered including endocrine and metabolic outcomes for which a wealth of studies are available in the literature.

Other bisphenols, including many BPA substitutes (e.g., BPS, BPF) have been less studied although data suggest they could display similar toxicity and exert similar health effects (see Rochester and Bolden, 2015 and recent studies from HBM4EU e.g., Carvaillo et al., 2019; Rugard et al., 2019).

Human biomonitoring studies are important for establishing links between exposure levels of humans to bisphenols and the observed health responses, e.g. (neuro)developmental, reproductive outcomes and metabolic responses (see Section 6,7,8).

An overview of current EU (ECHA C&L Inventory) and/or IARC classification of bisphenols is provided in Table 4.1 below (see Glossary for full list of terms/classifications).

[5] EFSA draft re-evaluation of the health risks of BPA derived from its presence in food (February 2022).

Table 4.2 Overview of CLP classifications for bisphenols

Substance	Properties of concern				Category according to CLP criteria										ECHA info card
	Toxic to Reproduction (R)	Endocrine Disrupting (ED)	Skin sensitising (SS)	Persistent, Bio accumulative and Toxic (PBT)	Carcinogenicity	Acute Toxicity	Reproductive Toxicity	Mutagenicity	Specific target organ tox (repeated exposure)	Specific target organ tox (single exposure)	Eye Damage/ Eye Irritation	Respiratory Sensitisation	Skin Corrosion/ Irritation	Skin Sensitisation	
BPA							1B*			3*	1*			1*	Link
BPS							2↑								Link
BPF										3			2	1	Link
BPB						4									Link
BPAF							1B#		2		1				Link
BPM							2*							1*	Link
BPAP											2				Link
BPFL											2		2		Link
BP4,4'						4				3	2		2	1	Link
BPC								2	2	3	2		2	1	Link
BPC12										3	2		2		Link
BPP											2		2		Link
DHDPE						4				3	1		2	1	Link
BPZ							2			3	2		2		Link
BPBP							2				2		2	1	Link
BPE										3	2		2		Link
BPPH										3	2		2		Link
BIS2										3	2		2	1	Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.).
↑ The ECHA Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) for BPS of Repr.1B (H360FD) in December 2020, see https://chemicalsinourlife.echa.europa.eu/documents/10162/03fac9dc-94e7-a81c-fed5-1c5008a1c1bc.
BPFA has been proposed for Harmonised Classification and Labelling, see https://echa.europa.eu/documents/10162/eab0126c-4d82-a50e-bcd6-494280e27be6.
Blank cells denote a lack of classification.

Key:

Most of the EU regulation and recommendations for BPA tend to focus on pregnant women and infants. Many of the studies investigating health impacts of BPA have focussed on exposure and health impacts of infants (see Section 3 and 4).

As noted in the overview of results of the activities carried out within HBM4EU, for the studies reported as having a national representativeness level, the majority involved children and new-born infants. In studies with children, bisphenols were among one of the most analysed substances.

HBM studies have also focussed on pregnant women as an important group, to better characterise exposure, owing to ED effects and reproductive toxicity being of particular concern for bisphenols like BPA (see Section 6, 7 and 8).

Occupational exposure and health impacts on workers is also a priority area under the HMB4EU project (see Section 6, 7 and 8).

4.3 Societal concerns

In several countries and probably world-wide, bisphenols have been considered as the typical endocrine disruptor. In many cases, the societal concern towards endocrine disrupting chemicals (EDCs) is highly connected to bisphenols and to the campaigns to regulate BPA in particular. Therefore, there is a lot of expectations in this field. It is important to fill the gaps and to attempt to address the uncertainties, because the bisphenol case appears to be emblematic of the endocrine disrupting chemicals. Whatever we achieve with bisphenols will actually be useful for all EDCs and for the role of public authorities in protecting pregnant women and the next generations.

5 EU Policies on Bisphenols

Several policy measures have been introduced in the EU to address human exposure to bisphenols. These cover i) implementation of international conventions, actions and agreements, and wider chemicals legislation; ii) consumer products; iii) occupational exposure, and iv) the environment (e.g. emissions to air and water). An overview of these regulatory measures at EU level are provided in Table 1.1 below.

Table 1.1 Overview of EU policy measures relating to bisphenols

Chemicals

- Bisphenols are not regulated under any international conventions, actions, or agreements.
- **Strategy on endocrine disrupting chemicals –** In 2018, the European Commission published a communication: "Towards a comprehensive EU framework on endocrine disruptors". BPA and other bisphenols are suspected of being EDCs.
- In June 2017, ECHA identified BPA as a substance of very high concern (SVHC) under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) due potential endocrine disrupting (ED) effects for human health and the environment.
- BPA has been restricted under REACH for use in thermal paper since 2016 (taking effect from 2020) – migration limit of ≤ 0.02%
- A proposal for the restriction on the use of BPA as (i) an additive and the content in, (ii) presence as a residue (also for imported goods), and (iii) for presence in mixtures for non-automated processes (0.02% by weight) is currently being considered.
- In 2020, ECHA Committee for Risk Assessment adopted BPS harmonized classification as H360FD. There is a proposal for a harmonized classification of BPAF as H360F.
- In 2022, ECHA and the Member States have assessed a group of 148 bisphenols and recommended that more than 30 bisphenols need to be restricted due to their potential hormonal or reprotoxic effects.
- Two specific bisphenols (BPA, BPS) covered under HMB4EU are subject to EU **harmonised classification and labelling** under Regulation (EC) No 1272/2008 on classification, labelling and packaging (the CLP Regulation) and others are currently being proposed – see list of classifications above.

Consumer

- **Food Safety** – Regulation (EU) 2018/213 prohibits the use of BPA in varnishes or coatings applied to materials and articles for use in packaging for children's food items (e.g., infant formula, baby food).

  This also sets a migration limit of ≤ 0.05 mg/kg for all food contact plastics and food contact varnished or coated products.

  In its 2015 re-evaluation of BPA exposure and toxicity, EFSA used a more refined methodology and new data, revising the t-TDI for BPA from 50 to 4 µg/kg bw/day.

- **Infant feeding bottles** – since 2011 BPA has been banned from use in the manufacture of polycarbonate infant feeding bottles across Europe [Commission Directive 2011/8/EU].

- **Toys** – Additional rules have been introduced under Directive 2009/48/EC on the safety of toys for toys made for children under the age of 36 months or those which are intended for use in the mouth, setting a specific migration limit of 0.04 mg/l for bisphenol A.

- **Medical devices** – Regulation (EU) 2017/745 on medical devices requires that substances having endocrine-disrupting properties shall only contain the following substances in a concentration that is above 0.1% (w/w) where justified pursuant.

	• **Human biomonitoring (HBM) values** – set by the HBM German Commission. This includes the HBM-I-value* for BPA of 0.2 mg/L in urine for adults and 0.1 mg/L for children.		
Environmental	**Environmental** *Water* • BPA is on the list of substances subject to review for possible identification as priority substances or priority hazardous substances under the Water Framework Directive 2000/60/EC. • In 2018 the European Commission adopted a proposal to revise The Drinking Water Directive (98/83/EC) to include a concentration limit for BPA of 0.01 µg/l in water for public consumption. *Air and Industrial emissions* • Bisphenols are not covered by EU legislation governing air quality or industrial emissions.	**Occupational** • An occupational **exposure limit value (IOELV)** for bisphenol A (inhalable dust) of 2 mg/m^3 (8 hours exposure time) is defined under Directive 2017/164 (EU), implementing Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work • Commission Directive (EU) 2017/164 of 31 January 2017 establishing a fourth list of indicative occupational exposure limit values has set an Occupational Exposure Limit OEL-8h (inhalable fraction) for BPA of 2 mg/m3. Member States have transposed this provision.	Occupational

* The HBM-I-value represents the concentration of a substance in human biological material below which – according to the knowledge and judgement of the HBM Commission – there is no risk for adverse health effects and, consequently, no need for action.

6 Policy questions for bisphenols

6.1 Introduction

Section 5 above presents an overview of current EU policies related to bisphenols. A number of policy-related questions that relate to the commitments under this frame have been developed. To inform this, an ad hoc group of colleagues within the HBM4EU consortium with expertise on bisphenols, were invited to provide input and feedback in formulating the policy questions and HBM4EU actions.

For each of the HBM priority substances stakeholders were asked to identify policy related questions that HBM4EU should address in order to contribute to the strengthening of policy ambitions on bisphenols. Further background detail on bisphenols and how the policy questions were selected is available in the scoping document and the report on stakeholder consultation and mapping of needs.

6.2 What is the current exposure of the EU population to BPA, BPS and BPF?

The European HBM dashboard reports urinary BPA levels comparable between the three age categories (children, teenagers and adults), indicating that BPA exposure is similar for children, teenagers and adults. The individual data collections prepared and made available within HBM4EU also contained aggregated data stratified by sex and educational level. From these stratifications it can be seen that the BPA concentrations are in general higher in men compared to women for all three age categories. Second, there seems a trend that teenagers and adults with higher educational level have lower exposure levels to BPA compared to teenagers and adults with medium educational level.

New HBM data collected in the HBM4EU Aligned Studies show that median levels of urinary BPA are still pronounced in all European regions. The P50 of BPA varied between 0.55 and 2.35 µg/g creatinine and P95 between 2.41 and 12.19 µg/ g creatinine. The substitutes BPF and BPS are also detected in most participants and concern is raised as their toxicity is not well known. P50 and P95 of urinary BPS concentrations are in the range of 0.06 – 0.34 µg/g creatinine (4 studies have a P50 value < detection limit: 0.01, 0.09 and 0.05 µg/L) and 0.39- 8.77 µg/g creatinine, respectively. The share of individuals with exposure levels of BPS exceeding HBM-GV of 1 µg/L range from 0.56%-19.26%.

P50 and P95 of urinary BPF concentrations are in the range of 0.10 -0.72 µg/g creatinine (3 studies have a P50 value < detection limit: 0.03, and 0.15 µg/L) and 0.56-17.03 µg/g creatinine respectively. The P95 values of the substitute BPF are higher compared to those of BPA in 5 of 11 sampling sites.

6.3 Do different regulatory controls across the EU concerning particular BPA lead to different exposures?

Comparing the results of different HBM4EU Aligned Studies between the 4 European geographical areas (North, East, South and West) revealed that median BPA levels of exposure are higher than exposure levels for substituents (BPF and BPS) in all of Europe. The P95 values of the substitute BPF are however higher compared to those of BPA in 5 of 11 sampling sites. The Northern area is globally less exposed to bisphenols than other areas.

When HBM4EU Aligned Studies data were compared to data from the DEMOCOPHES project that preceded HBM4EU, some changes can be observed (e.g. a decrease of BPA in Denmark and an increase in Poland and Luxembourg; an increase in BPS in Czech Republic), but whether this is related to differences in regulation is unclear at this stage. The HBM4EU Aligned Studies data will form baseline European human exposure levels for BPA and its substituents BPS and BPF, allowing follow up studies to monitor increased or decreased usage.

A mapping of BPA substitution which includes human biomonitoring data on less regulated bisphenols is needed as well as the investigation of human exposure and effects and the assessment of need for further regulation.

6.4 Are bisphenols exposure levels of concern for health?

BPA exposure levels measured in the adult population from the HBM4EU Aligned Studies are below the established HBM-GVs based on the temporary tolerable daily intake (t-TDI) of 4 µg/kg bw/day. If the HBM-GVs would be based on the new draft EFSA proposal for a TDI, all measured values would largely exceed the HBM-GV. For populations in which exposure exceeds the HBM-GV, health risks cannot be excluded. In eight sampling locations out of ten, at least 5% of the European adults (20-39 years) from the HBM4EU Aligned Studies exceed the HBM-GV for BPS. The most concerned studies were conducted in Southern Europe.

Human biomonitoring, toxicity and toxicokinetics data are needed to assess the health risk of exposure to other BPA analogues.

Since HBM4EU Aligned Studies indicate co-exposure to BPA and its substituents BPS and BPF, mixture studies should be considered, particularly since BPA substituents appear to display similar effects to BPA and to be linked to similar AOPs.

A cohort HBM4EU case study (INMA-Granada cohort) linked BPA childhood exposure to a potential biomarker of effect, the brain-derived neurotrophic factor (BDNF), and an adverse

outcome pathway leading to behavioural and cognitive alterations. Childhood BPA exposure was linked to higher BDNF DNA methylation at adolescence. An adverse outcome pathway (AOP) network was also constructed, supporting that BPA may interfere with BDNF signalling through different but converging biological mechanisms (thyroid, estrogenic and glutamatergic-related pathways), potentially leading to behavioral and cognitive impairments (Mustieles et al., 2022).

6.5 Is occupational exposure of cashiers a health concern?

Because of the background environmental exposure to bisphenols, it has not been possible to derive an HBM-GV for workers.

Available data in the literature and gathered under the project framework indicate that the risk from occupational exposure should not be disregarded, especially in industrial scenarios with BPA exposure levels 10-20-fold higher than background exposures, and that protective measures need to be taken regarding BPS exposure.

Regarding the data coming from the HBM4EU Aligned Studies of bisphenols, the estimated median daily intake of BPA for adults across different European countries was 0.19 µg/kg_bw/day. The estimated median daily intake level of BPF for adults of France and Luxembourg was 0.004 µg/kg_bw/day. For BPS, it was 0.0001 µg/kg_bw/day for adults of Czech Republic, France and Luxembourg. As regards the data coming from other studies, the countries with the lower exposure to BPA were Belgium, Czech Republic and Denmark with the median daily intake for adults of 0.13 µg/kg_bw/day compared to Israel where the median concentration was 0.27 µg/kg_bw/day. These data indicate that exposure of adults does not exceed the reference levels for any of the adults, independent of their occupational activity. However, should the newly proposed TDI of 0.04 ng/kg_bw/day be established, occupational exposure of cashiers (similarly to other non-occupational groups) to BPA will be of health concern.

Taking into account the current policies leading to the substitution of BPA by analogue substances, there is a need for research on the occupational exposure to these compounds, including BPS and BPF. This would include studying cashier work in which BPS may have replaced BPA (Bousoumah et al. 2021).

6.6 What is the toxicity of BPA substitutes and are current exposure level of concern?

Using computational tools developed under the project framework, obesity appeared as one of the major potential health endpoints of BPS exposure (Carvaillo et al.2019). BPF has been linked to an adverse outcome pathway (AOP) network for thyroid cancer (Rugard et al. 2020).

Both a lifecourse PBTK model and a pregnancy PBTK model were used to allow for more accurate reconstruction of external exposure taking note of the physiological and metabolic differences characteristic of different age windows during the lifecourse and in utero. Estimated internal exposure levels of the developing foetus were only 10 to 20% higher than in the mother.

The recommended HBM-GV for BPS is based on endocrine disrupting health effects occurring in animals at very low doses and was set in HBM4EU at 1 µg/L based on animal toxicity studies for mammary gland and neurodevelopmental toxicity (since these were the outcomes with highest sensitivity to BPS). Between 2014-2021, in all sampling locations except Poland and Germany, the P95 value, representing the 5% most exposed participants, exceeds the guidance value of 1 µg/L.

Because of the current EFSA re-evaluation and draft proposal for a (much lower) TDI value for BPA, it is critical to revise those for BPA substituents as well.

There is a need to explore the health impacts of bisphenols further (particularly substituents), to support hazard and risk assessment as well as evaluate the impact of regulatory actions - those already in place and future wider restrictions on bisphenol exposure in European population.

6.7 Are health risks age and gender dependent?

From the collected HBM data (sampling between 2005 and 2015) that are available via the European HBM dashboard, it seems that urinary BPA levels are similar for children, teenagers and adults. However, the HBM-GV of BPA for children is lower than for adults, illustrating their higher sensitivity to adverse health effects of BPA exposure.

The individual data collections prepared and made available within HBM4EU also contained aggregated data stratified by sex and educational level. From these stratifications it can be seen that the BPA concentrations are in general higher in men compared to women for all three age categories.

For BPA we were able to estimate intake levels based on the available HBM data and to differentiate internal dose in relation to age, accounting for the significant differences in bioavailability related to the age-dependent maturity of the detoxification process (slower in early developmental stages and maximal capacity at one year of age). Internal exposure levels of the developing foetus are 10 to 20% higher than in the mother. Also, internal dose modification under co-exposure to BPA, BPS and BPF has been investigated; co-exposure to BPS and BPF only marginally changes the foetal exposure to BPA.

Estimated median adult daily intake levels of BPA, BPF and BPS derived from the HBM4EU Aligned Studies showed no significant difference between male and female gender.

6.8 Can we find evidence for low-dose effects within mixtures?

Two different HBM4EU case studies refer to low-dose effects within mixtures. A biomonitoring survey of co-exposure to bisphenols (BPA and analogues) by consumers of canned foodstuffs indicates that participants with a diet rich in canned food were more exposed to BPA when compared to the control group. Trace levels of other BP analogues were found only promptly, but at much lower quantities than those of BPA.

A mixture risk assessment with focus on male reproductive health shows that combined exposures to bisphenols and other chemicals is associated with declines in semen quality in Western countries (Kortencamp et al. 2022). The exposure levels to these chemicals were relatively low since they were determined based on human biomonitoring studies.

6.9 How can HBM feed into assessment of the Tolerable Daily Intake (TDI) for BPA, as set by the European Food Safety Authority (EFSA)?

An HBM-GV of 230 µg /L was derived for BPA exposure in adults and 135 µg/L for BPA exposure in children (>3 years). Below these values no adverse effects are expected according to current knowledge. The HBM-GV was set at a urinary concentration of total BPA consistent with a steady-state exposure to the temporary TDI of 4 µg/kg bw/day derived by EFSA in 2015 based on kidney weight increase in mice. The EFSA Panel on Food Contact and Materials, Enzymes and Processing Aids (CEP) recently released a consultation for a re-evaluation of the t-TDI set in 2015 that would result in a TDI of 0.04 ng/kg bw/d of total BPA. The provisional HBM-GVs recalculated based on the proposed TDI using PBPK modelling are 2.3 ng total BPA/l urine for adults and 1.4

ng total BPA/l urine for children assuming 100% oral intake in each case. If these new values would be confirmed this would mean that essentially all the European population is above the TDI and health risks cannot be excluded. HBM4EU recommends that the guidance values for the BPA substituents should in this case also be revisited.

6.10 Is it important to eliminate legacy BPA from material cycles (i.e. waste till receipt rolls) when implementing a circular economy in order to protect human health?

HBM4EU prepares a report on certain chemicals in the circular economy. The report will focus on how human biomonitoring can support understanding of exposure to chemicals via secondary material flows and recycling. This will be addressed through five case studies, three of which will focus on bisphenols - in consumer goods made from recycled plastics, in recycled paper, and in dietary exposure from reusing sewage sludge and wastewater on agricultural lands.

7 HBM4EU outputs to date

7.1 Categorisation

The bisphenol compounds within the scope of the HBM4EU project (see Section 1 and Glossary) have been categorised depending on availability of toxicology and human biomarker data (see Table).

Table 2.1 HBM4EU categorisation for bisphenols

Category		Priority substance(s)	Details
A	Sufficient HBM data exists with risk management measures implemented; focus is on policy-related research questions	BPA	BPA has been widely monitored in humans. The routes of exposure (see Section 2), health effects (see Section 3) are relatively well understood. Risk management measures have been implemented (see Section 5)
B	HBM data exist but not for across Europe	-	-
C	HBM data are scarce or non-existent	BPS, BPF, BPB, BPAF, BPM, BPAP, BPFL, BP4,4', BPC, BPC12, BPP, DHDPE, BPZ BPBP, BPE, BPPH, BIS2	Monitoring data on BPA substitutes and other bisphenols is lacking; understanding of exposure, health impacts is poor.

7.2 Key outputs

The HBM4EU project has produced an initial scoping document to answer the main policy questions for bisphenols with the available data at the time.

An updated version of this reporting was produced for HMB4EU Additional Deliverable (AD)5.7, available for download here.

Exposure and methodology

- In order to further support current and future HBM studies, HBM4EU developed a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe. (WP7, HBM4EU online library).
- A prioritised list with most suitable biomarkers, matrices and analytical methods has been produced (WP9, D9.2, D9.7).
- Interlaboratory assays (ICI/EQUAS) have been organised. Chemical analyses of BPS and BPF have been improved. A total of 32 laboratories participated in the ICI/EQUAS. The number of qualified laboratories per biomarker are: 24 for BPA, 18 for BPS and 13 for BPF (WP9, D9.8).
- A sampling frame has been established to align the planning of ongoing/planned studies to collect HBM data of the prioritised chemicals (including bisphenols) with EU wide coverage (WP8, D8.8).
- The HBM4EU Aligned Studies (2014-2021) have measured bisphenols (3 markers: BPA, BPS and BPF) in urine samples from adult men and women between 20 and 39 years of age from 11 different sampling sites in Europe (DK, IS, FI, PL, CZ. HR, PT, FR, CH, DE, LU) representing 2756 individuals. Not all biomarkers were analysed in all contributing studies, therefore the number of sampling sites and data points can vary per biomarker.
- A specific statistic data analysis plan for bisphenols has been elaborated (WP10, D10.5).
- In addition, the European HBM dashboard provides summary statistics for HBM data from different European countries, with 33 aggregated datasets including bisphenols exposure data. In IPCHEM, metadata are available for 44 datasets on Bisphenols. Aggregated data for BPA concentration in urine samples were reported in 13 studies involving children, in 8 studies involving teenagers and in 12 studies involving adults. All studies included at least 54 participants and samples were collected between 2005 and 2015. Aggregated data for bisphenol F, S and BPA free/unconjugated could not be obtained as for each of the three chemicals, only 1 study involving children and only 1 study involving adults were reported.
- HBM based indicators for bisphenols with indicator graphs on time patterns, geographical differences and health impact have been developed under WP5 (statistical analysis in progress).

Regulatory differences and TDI

- The Policy Brief and Substance Report for Bisphenols presents an overview of current EU policies related to bisphenols (WP2). Since 2011 different measures have been taken to limit population exposure to BPA at the European level. It has been banned from infant feeding bottles across Europe (Commission Directive 2011/8/EU) and its use in certain food-contact materials has been further restricted since 2018. Additional measures have been taken in several countries. For example, France banned BPA in all food contact materials (French Law No 2012-1442), and other countries (Denmark, Belgium and Sweden) banned it in those materials intended for children under the age of 3.

- HBM4EU has generated EU-wide HBM data on bisphenols both by collecting data from different existing studies and by generating new data in 11 countries representing the 4 European Regions (North, East, South and West) in the HBM4EU Aligned Studies.
- HBM based indicators for bisphenols with indicator graphs on time patterns, geographical differences and health impact are being developed under WP5 (statistical analysis in progress).
- Human Biomonitoring Guidance Values (HBM-GVs) for the general population have been derived for BPA and BPS, and a substance dossier on BPF has been prepared. Data for derivation of HBMB-GVs for BF were not sufficiently robust. An HBM-GV for BPA has also been derived based on the recent draft opinion of EFSA on TDI (WP5, D5.14)

Health concerns

- Human Biomonitoring Guidance Values (HBM-GVs) for the general population have been derived for BPA and BPS, and a substance dossier on BPF has been prepared. Data for derivation of HBMB-GVs for BF were not sufficiently robust. HBM-GVs for BPA have also been derived based on the recent draft opinion of EFSA on TDI (WP5, D5.14 - see answer to Policy Question 8)
- Risk assessment based on HBM data for bisphenols has been performed for BPA and BPS (WP5, D5.8).
- A strategy for the selection of effect biomarkers for potential implementation in HBM4EU aligned studies has been outlined in relation to bisphenols (WP14, AD14.3).
- First inventory of effect biomarkers for bisphenols has been produced through extensive literature review: BDNF, kisspeptin and gene expression of nuclear receptors were prioritized (WP14, D14.3; Mustieles et al. 2020, Steffensen et al. 2020). New effect biomarkers were developed linking BPA to health effects (e.g. behaviour, Mustieles et al. 2022) and were shown to have added value in human studies, increasing the weight of evidence for causal relationship between exposure and adverse health outcome.
- A report on adverse outcome pathways (AOPs) for the first set of HBM4EU prioritised substances (including bisphenols) within HBM4EU has been produced (D13.4)

Occupational exposure

- The presence of BPA in thermal paper represents a threat most especially to cashiers, who are in constant contact with the material. BPA was restricted from use in thermal paper in 2016, with entering into force in 2020.
- Risk assessment based HBM data for bisphenols has been performed for BPA and BPS (WP5, D5.8).
- A HBM4EU systematic review on retrieved 30 studies on occupational human biomonitoring of BPA and only 4 and 2 publications on BPS and BPF, respectively (Bousoumah et al. 2022).
- Bisphenol intake estimates have been derived based on the aggregate data available within the European HBM dashboard, that include both the HBM4EU repository data, as well as the data from the HBM4EU Aligned Studies (WP12, AD12.13).
- A report on “HBM4EU Priority Substances in the Circular Economy” focuses on how human biomonitoring can support understanding of exposure to chemicals via secondary material flows and recycling. (WP2, in progress).

Health risks

- New computational tools, based on text mining (using artificial intelligence) and on systems biology tools, have been developed to assess the most likely toxic outcomes of exposure to BPS and BPF.

- Adverse Outcome Pathways studies on BPS and BPF suggested that these compounds are linked to health effects such as metabolic diseases and cancer.
- European HBM dashboard: the BPA exposure of the Elfe study in pregnant women was estimated individually from the HBM data (here, the urinary concentration of total BPA) using a reverse dosimetry approach based on PBPK modelling. The aim was to estimate the internal exposure in the mothers and their foetuses (WP12, AD12.5).
- Human Biomonitoring Guidance Values (HBM-GVs) for the general population have been derived for BPA and BPS, and a substance dossier on BPF has been prepared. Data for derivation of HBMB-GVs for BF were not sufficiently robust. HBM-GVs for BPA have also been derived based on the recent draft opinion of EFSA on TDI (WP5, D5.14 - see answer to Policy Question 8)
- HBM based indicators for bisphenols with indicator graphs on time patterns, geographical differences and health impact are being developed under WP5 (statistical analysis in progress).
- An online consultation on existing HBM surveys (124 surveys analysed) was performed. Results showed that bisphenols were mostly studied in the Northern and Western Region. In studies in children, bisphenols were among the most analysed substances (WP 7, D7.1)
- The HBM4EU Aligned Studies (2014-2021) have measured bisphenols (3 markers: BPA, BPS and BPF) in urine samples from adult men and women between 20 and 39 years of age from 11 different sampling sites in Europe (DK, IS, FI, PL, CZ. HR, PT, FR, CH, DE, LU) representing 2756 individuals.
- Specific questionnaires for different age and sex groups were developed to identify exposure levels and sources of exposure to bisphenols.
- A specific statistic data analysis plan for bisphenols has been elaborated (WP10, D10.5).
- In addition, the European HBM dashboard provides summary statistics for HBM data from different European countries, with 33 datasets including Bisphenols exposure data. In IPCHEM, metadata are available for 44 datasets on Bisphenols.
- Biological half-lives (t1/2) in human have been compiled to inform exposure modelling (WP12, D12.3).
- A dedicated physiology-based toxicokinetic (PBTK) model to link HBM data, environmental monitoring and external exposure modelling was developed and implemented to obtain BPA, BPS and BPF intake estimates derived from the HBM4EU HBM data (WP12, D12.8). The BPA exposure of the Elfe study in pregnant women was estimated individually from the HBM data (urinary concentration of total BPA) using a reverse dosimetry approach based on PBPK modelling. Also, the placental levels were estimated based on urinary levels.
- Bisphenol intake estimates have been derived based on the aggregate data available within the European HBM dashboard, that include both the HBM4EU repository data, as well as the one from the HBM4EU aligned studies (WP12, AD12.13).

Mixtures

- A biomonitoring case study was performed assessing co-exposure to BPA and five bisphenol analogues in blood and urine samples of an adult cohort with a diet rich in canned foodstuffs (Gonzalez et al.2020).
- A mixture risk assessment case study was performed assessing combined exposures to bisphenols and other chemicals with focus on male reproductive health outcomes (WP15).

7.3 Key data gaps

A full description of all the relevant policy questions and associated actions and data gaps is in the HBM4EU scoping document here.

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

Based on the policy questions, outlined above in Section 6 and 7, the key knowledge gaps to be addressed and ongoing activities to address these aspects, are summarised in Table 3.1 and Table 4. below, according to the four broad themes.

Table 3.1 Summary of knowledge gaps

#	Theme	Knowledge gaps and activities needed	Relevant HBM4EU WPs[6]
1	**Exposure and health effects**	• To carry out targeted assessment of toxic effects of BPS/BPF as compared to BPA, e.g. for cancer, reproductive, hormonal, metabolic, immune, and neurological effects.	WP13, WP14, WP15
		• To further identify effect biomarkers associated to bisphenol exposure and to determine whether those effect markers are common to all bisphenol compounds. This was partially achieved under WP14.	WP14
		• To carry on the investigation the effect of combined exposures to substance mixtures within the bisphenol family and with other families and whether this could impact health guidance (e.g. in food contamination, cosmetics, other plasticizers, etc.)	WP15
		• To perform risk assessments for different age groups and sex (and possibly for mixtures).	WP5
		• To establish if there are HBM data or suitable samples available before and after the ban in FR, SE, DK.	WP7, WP8
		• To determine whether different regulatory controls across EU MS lead to different exposures.	WP8, WP9, WP10
		• To develop indicators for combined exposures and impacts.	WP5
2	**Vulnerable groups**	• To gather data on environmental persistence and the fate of bisphenols to determine exposure risks to humans and ecosystems (e.g./ photo-degradation and microbial degradation) to provide understanding of environmental transformation products and fate of bisphenols. (This will be done in the follow-up Partnership for the Assessment of Risks in Chemicals - PARC.) • To correlate environmental monitoring data with HBM4EU data.	WP12

[6] HBM4EU WP description:

#	Theme	Knowledge gaps and activities needed	Relevant HBM4EU WPs[6]
		• These studies are unlikely to be completed with HBM4EU but are better suited for PARC which includes a large environmental section.	

WP1: Programme management and coordination ; WP2: Knowledge hub; WP4: Prioritisation and input to the annual work plan; WP5: Translation of results into policy; WP6: Sustainability and capacity building; WP7: Survey design and fieldwork preparation; WP8: Targeted field work surveys and alignment at EU level; WP9: Laboratory analysis and quality assurance; WP10: Data management and analysis; WP11: Linking HBM, health surveys and registers ; WP12: From HBM to exposure; WP13: Establishing exposure health relationships; WP14: Effect biomarkers; WP15: Mixtures, HBM and human health risks; WP16: Emerging chemicals.

Table 4.1 Summary of knowledge gaps and ongoing activities for bisphenols relating to analytical methods and procedures

#	Theme	Knowledge gaps and activities needed	Relevant HBM4EU WPs
1	**Exposure and health effects**	• To further identify effect biomarkers associated to bisphenol exposure (including biochemical and epigenetic) and to determine whether those effect markers are common to all bisphenol compounds.	WP14

8 Future recommendations

HBM4EU has developed quality research in support of the policy questions and identified key knowledge gaps that still remain as well as future recommendations to advance on the sound risk management of bisphenols.

A mapping of BPA substitution which includes human biomonitoring data on less regulated bisphenols is needed as well as, the investigation of human exposure and the assessment of need for further regulation.

Since bisphenols are short half-life contaminants, it is important to reassess the sampling protocols: are spot samplings sufficient to reflect exposure or should we combine several samples per individual to decrease errors from exposure variation?

There is also a need to further explore health impacts of bisphenols (particularly substituents) to support hazard and risk assessment. This is also linked with the need to continue assessing results of regulatory actions already in place and future broader bisphenols restrictions on exposure in the European population. Regulation at group level is highly recommended.

It is also necessary to further identify effect biomarkers associated to bisphenol exposure (including biochemical and epigenetic) and to determine whether those effect markers are common to all bisphenol compounds.

It is urgent to carry on with the investigation of exposure to mixtures of bisphenols and their health effects.

HBM4EU outcomes show a trend of higher BPA exposure levels in lower educational level population. It is crucial to guarantee the protection of socially more disadvantaged population. Communication to the citizens on how potential risks are evaluated and managed is critical at this stage.

9 References

HBM4EU, 2019, Scoping document for bisphenols, v4.1 part of the scoping document set.

HBM4EU, 2019, Prioritised substance group, bisphenols – policy-related questions.

HBM4EU, 2020, Legislative mapping for bisphenols, summary document prepared by RPA on behalf of the European Environment Agency.

ANSES (2017). Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the results of bisphenol A contamination of non-canned foodstuffs of animal origin. French Agency for Food, Environmental and Occupational Health & Safety (ANSES), Maisons-Alfort Cedex.

Bousoumah R, Leso V, Iavicoli I, Huuskonen P, Viegas S, Porras SP., Santonen T, Frery N, Robert A, Ndaw S. (2021). Biomonitoring of occupational exposure to bisphenol A, bisphenol S and bisphenol F: A systematic review. *Sci Total Environ*. 783, 146905. https://doi.org/10.1016/j.scitotenv.2021.146905

Casas M, Gascon M. (2020) Prenatal Exposure to Endocrine-Disrupting Chemicals and Asthma and Allergic Diseases. *J Investig Allergol Clin Immunol.* 30(4):215-228. https://doi.org/10.18176/jiaci.0580Carvaillo, J-C., Barouki, R., Coumoul, X., Audouze, K. (2019). Linking bisphenol S as an environmental chemical stressor to key events and adverse outcomes using a text mining-based computational approach*. Environ Health Perspect*;127(4), 47005.

Chen, D. Kannan, K., Tan, H., Zheng, Z., Feng, Y., Wu, Y., Widelka, M. (2016). Bisphenol Analogues Other than BPA: Environmental Occurrence, Human Exposure, and Toxicity – A Review, Environmental Science & Technology, 50 (11), p.p. 5438-5453.

González N, Marquès M, Cunha SC, Fernandes JO, Domingo JL, Nadal M. Biomonitoring of co-exposure to bisphenols by consumers of canned foodstuffs, Environment International, Volume 140, 2020, 105760, https://doi.org/10.1016/j.envint.2020.105760

ECHA (2015). Committee for Risk Assessment (RAC) Opinion on an Annex XV dossier proposing restrictions on bisphenol A, ECHA/RAC/RES-O-0000001412-86-56/F

ECHA (2020). The use of bisphenol A and its alternatives in thermal paper in the EU during 2014 – 2022. Available at: https://echa.europa.eu/documents/10162/23294236/bpa_thermal_paper_report_2020_en.pdf/59eca269-c788-7942-5c17-3bd822d9cba0

EFSA (2015a). Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment. Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA Journal,* 13(1):3978. [396 pp.].

EFSA (2015b). Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II –Toxicological assessment and risk characterisation. Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA Journal* 13(1):3978. [621 pp.].

Fischer, B. Milunov, M., Floredo, Y., Hofbauer, P., Joas, A. (2014). Identification of relevant emission pathways to the environment and quantification of environmental exposure for Bisphenol A. Available at: https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte_41_2014_identfifcation_of_relevant_emission_pathways_of_bisphenol_a_0.pdf.

Gao P., Wang L., Yang N., Wen J., Zhao M., Su G., Zhang J., Weng D. (2020) Peroxisome proliferator-activated receptor gamma (PPARγ) activation and metabolism disturbance induced by bisphenol A and its replacement analog bisphenol S using in vitro macrophages and in vivo mouse models. Environment International,134, 105328. https://doi.org/10.1016/j.envint.2019.105328.

Gore, A. C., Chappell, V. A., Fenton, S. E., Flaws, J. A., Nadal, A., Prins, G. S., Topari,J., Zoeller, R. T. (2015). EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews*, 36(6), p.p. E1–E150.

Kortenkamp A, Scholze M, Ermler S, Priskorn L, Jørgensen N, Andersson A.M., Frederiksen H. (2022) Combined exposures to bisphenols, polychlorinated dioxins, paracetamol, and phthalates as drivers of deteriorating semen quality, Environment International, 107322. https://doi.org/10.1016/j.envint.2022.107322.

Li J, Bach A, Crawford RB, Phadnis-Moghe AS, Chen W, D'Ingillo S, Kovalova N, Suarez-Martinez JE, Zhou J, Kaplan BLF, Kaminski NE. (2018a) CLARITY-BPA: Effects of chronic Bisphenol A exposure on the immune system: Part 1 - Quantification of the relative number and proportion of leukocyte populations in the spleen and thymus. *Toxicol* 396-397:46-53. https://doi.org/10.1016/j.tox.2018.01.004

Li J, Bach A, Crawford RB, Phadnis-Moghe AS, Chen W, D'Ingillo S, Kovalova N, Suarez-Martinez JE, Zhou J, Kaplan BLF, Kaminski NE. (2018b) CLARITY-BPA: Effects of chronic Bisphenol A exposure on the immune system: Part 2 - Characterization of lymphoproliferative and immune effector responses by splenic leukocytes. *Toxicol* 396-397:54-67. https://doi.org/10.1016/j.tox.2018.02.004

Mesnage, R. Phedonos, A., Arno, M., Balu, S., Corton, J.C., Antoniou, M.N. (2017). Transcriptome profiling reveals bisphenol A alternatives activate estrogen receptor alpha in human breast cancer cells. *Toxicological Sciences,* 158(2), p.p. 431-443.

Ndaw, S., Remy, A., Jargot, D., Robert, A. (2016). Occupational exposure of cashiers to Bisphenol A via thermal paper: urinary biomonitoring study. *Int Arch Occup Environ Health*. 89(6) p.p. 935-946.

Ndaw S., Remy A., Denis F, Marsan, P., Jargot, D., Robert,(2018) A. Occupational exposure of cashiers to bisphenol S via thermal paper, *Toxicol Lett*, 298, p.p. 106-111.

Ougier E, Zeman F, Antignac JP, Rousselle C, Lange R, Kolossa-Gehring M, Appel P. (2021) Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for bisphenol A. *Environment International*, 154, 106563, https://doi.org/10.1016/j.envint.2021.106563

RIVM (2014). Bisphenol A, Part 1: Fact and Figures on human and environmental health issues and regulatory perspectives. Available at: https://www.rivm.nl/bibliotheek/rapporten/601351001.html.

RIVM (2017). Dietary sources of exposure to bisphenol A in the Netherlands. RIVM Letter report 2017-0187. Available at: https://www.rivm.nl/bibliotheek/rapporten/2017-0187.pdf

Rochester, J. R., Bolden, A. L. (2015). Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environmental Health Perspectives*, 123(7), p.p. 643–650.

Rugard, M., Coumoul, X., Carvaillo,J-C., Barouki R., Audouze,K. (2020). Deciphering Adverse Outcome Pathway Network Linked to Bisphenol F Using Text Mining and Systems Toxicology Approaches, *Toxicol Sci*. 173(1), p.p. 32 – 40.

Seachrist, D. D., Bonk, K. W., Ho, S.-M., Prins, G. S., Soto, A. M., and Keri, R. A. (2016). A Review of the Carcinogenic Potential of Bisphenol A. *Reproductive Toxicology* (Elmsford, N.Y.), 59, p.p.167–182.

United Nations Environment Programme and the World Health Organization (2013) State of the Science of Endocrine Disrupting Chemicals – 2012: An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme and World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/78102/WHO_HSE_PHE_IHE_2013.1_eng.pdf

Vandenberg, L. N., Hauser, R., Marcus, M., Olea, N., Welshons, W. V. (2007). Human exposure to Bisphenol A (BPA). *Reproductive Toxicology* 24(2), p.p. 139-177.

Vandenberg, L. N.,Chahoud,I.,Heindel, J.J., Padmanabhan, V., Paumgartten F.J.R., and Schoenfelder, G. (2010). Urinary, Circulating, and Tissue Biomonitoring Studies Indicate Widespread Exposure to Bisphenol A. *Environmental Health Perspectives*, 118(8): 1055-1070. doi: 10.1289/ehp.0901716.

Vandenberg, L. N. (2014). Low-dose effects of hormones and endocrine disruptors. Vitam Horm, 94, p.p. 129-65.

Van Goetz, N., Wormuth, M., Scheringer, M. and Hungerbühler, K. (2010). Bisphenol A: How the Most Relevant Exposure Sources Contribute to Total Consumer Exposure. *Risk Anal*., 30(3):p.p. 473-487.

Wilson, N.K., Chuang, J.C., Morgan, M.K., Lordo, R.A. and Sheldon, L.S. (2007). An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and day care. *Environmental Research*,103, p.p. 9-20.

Yang Y, Yang Y, Zhang J, Shao B, Yin J. (2019) Assessment of bisphenol A alternatives in paper products from the Chinese market and their dermal exposure in the general population. Environmental Pollution, 244, 238-246. https://doi.org/10.1016/j.envpol.2018.10.049

Appendix 1: Additional information on exposure routes

Source of exposure	Reference
Environmental	
Exposure via the environment (e.g. through releases to atmosphere) is low, although many studies have detected BPA in household air and dust.	Vandenberg et al. (2007).
Occupational	
Occupational exposure (e.g. dermal or inhalation) can be significant in certain settings (e.g. in epoxy resin manufacture), but these workers represent a relatively small proportion of the whole population.	Scoping Document Vandenberg et al. (2007).
Relatively high levels of dermal exposure can occur through use of thermal paper (e.g. in shop receipts), which will be more significant for workers in retail establishments. However, the use of BPS for this purpose is now restricted in Europe (see Section 5).	Scoping Document Wilson et al. (2007)
Consumer	
Primary exposure for the general public is expected to be through the diet, largely due to BPs migrating from food and drink containers and packaging.	Vandenberg et al. (2007).
A wide range of food-contact papers and cardboards serve as potential sources of BPA contamination in foods.	Vandenberg et al. (2007).
For infants and children, the use of polycarbonate baby bottles was shown to be a significant source of exposure.	RIVM (2014). Van Goetz et al. (2010)
For adults, the main route is shown to be through canned food, although not all food and drinks types have been covered in the assessment.	RIVM (2014) Van Goetz et al. (2010)
Metallic food cans are protected from rusting and corrosion by the application of epoxy resins as inner coatings, which are commonly made using BPA (See Section 2). It has been shown from many studies that BPA can leach from the linings of food cans into food materials including fish, vegetables, and infant formula.	Vandenberg et al. (2007)
Some polycarbonate containers (e.g., Tupperware) intended to be used as reusable food containers, have the potential to leach BPA, and since	Vandenberg et al. (2007)

Source of exposure	Reference
many of these containers are used in the microwave, the heating may increase BPA leaching levels.	
Other types of consumer use (e.g. dental implants, cosmetics, toys) can result in exposure for certain individuals.	Vandenberg et al. (2007)
The use of BPA in medical devices can result in high levels of exposure for the affected individuals.	RIVM (2014)

Route of exposure	
Oral Primary exposure for the general public is expected to be through the diet, largely due to BPs migrating from food and drink containers and packaging. One study of preschool children estimated that 99% of exposure came through the diet.	Scoping Document Wilson et al. (2007)
Dermal Occupational exposure (e.g. dermal) can be significant in certain settings (e.g. in epoxy resin manufacture), but these workers represent a relatively small proportion of the whole population Relatively high levels of dermal exposure can occur through use of thermal paper (e.g. in shop receipts), which will be more significant for workers in retail establishments. However, the use of BPS for this purpose is now restricted in Europe (see Section 5)	Scoping Document Vandenberg et al. (2007).
Inhalation Occupational exposure (e.g. inhalation) can be significant in certain settings (e.g. in epoxy resin manufacture), but these workers represent a relatively small proportion of the whole population.	Scoping Document Vandenberg et al. (2007)
Trans-placenta BPA may partition into fat and breast milk so can result in exposure to breastfeeding infants. Experiments indicate that the human foetus is likely to be exposed to BPA throughout foetal development and may be exposed to levels that are even higher than those measured in adult blood.	Scoping Document

Appendix 2: Additional information on health effects

Human health effect	Category	Justification for category	References
Endocrine system (endocrine disrupting effects)	BPA (strong) BPF, BPS, BPAF, BPZ, BPE, BPB (suspected)	Based on a systematic review of studies in the literature – as discussed in scoping document ECHA SVHC designation for BPA and designation of other bisphenols (see Table 4.1).	WHO and UNEP, 2012; Gore et al., 2015, Vandenberg, 2014, EFSA, 2015a,b. https://echa.europa.eu/-/msc-unanimously-agrees-that-bisphenol-a-is-an-endocrine-disruptor
DNA (birth defects and reproductive harm)	BPA, BPS, BPAF (strong) BPM (suspected) Other BPs (evidence lacking)	Based on harmonised listing of Repr.1B (BPA, BPS, BPAF) and harmonised listing of Repr.2 (BPM) and lack of classification for other BPs.	See Table 4.1 EFSA, 2015a,b.; ECHA (2015)
Central nervous system - Brain cell damage ; neurological, neurodevelopmental and neuroendocrine effects	BPA (suspected) Other BPs (evidence lacking)	Indications from prospective studies in humans that prenatal BPA exposure during pregnancy may be associated with altered child behaviour. However, the associations were not consistent across the studies and it cannot be ruled out that the results are confounded by diet or concurrent exposure factors. A number of new studies report changes that may indicate effects of BPA on brain development	EFSA, 2015a,b. ECHA (2015)
Immune system / immunotoxicity	BPA (suspected) Other BPs (evidence lacking)	Based on recent human studies, there are indications that BPA may be linked to immunological outcomes in humans, although these studies had limitations and confounding factors may have been present.	EFSA, 2015a,b.; ECHA (2015)
Kidney and liver	BPA (suspected)	BPA was found to affect kidney and liver weight in parental animals and in all the generations of rats and	WHO and UNEP, 2012; Gore et al., 2015, Vandenberg, 2014, EFSA, 2015a,b.

	Other BPs (evidence lacking)	mice examined in multi-generation studies.	
Blood system - Carcinogenic potential associated with acute leukaemia	All BPs (evidence lacking)	Based on a systematic review of studies in the literature – as discussed in scoping document.	WHO and UNEP, 2012; Gore et al., 2015, Vandenberg, 2014, EFSA, 2015a,b.
Lungs - Bronchitis and pneumonitis	All BPs (evidence lacking)	Based on a systematic review of studies in the literature – as discussed in scoping document.	WHO and UNEP, 2012; Gore et al., 2015, Vandenberg, 2014, EFSA, 2015a,b.
Cardiovascular system - Increased risk of high blood pressure and cardiovascular disease	All BPs (evidence lacking)	Of the reviewed human studies on metabolic effects only two were prospective while 22 were cross-sectional and thus not suitable on their own to study exposure-disease associations	EFSA (2015a,b)
Cancers	All BPs (evidence lacking)	Some studies provide evidence that BPA may be reasonably anticipated to be a human carcinogen in the breast and prostate. Very few epidemiological studies published to date have investigated a possible association between exposure to BPA and incidence of certain cancers	Seachrist et al. (2016) EFSA (2015a,b)

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

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