NOTE

on the current state of knowledge regarding uses, exposure sources and toxicity for several polybrominated compounds

Presentation of the issue raised and organisation of the expert appraisal

In June 2009, the Agency received a formal request from the Directorate General for Health (DGS) (Request No 2009-SA-0331) for a health risk assessment (HRA) regarding exposure to category 2 reprotoxic and/or endocrine disrupting (ED) substances found in consumer products marketed in France. This request covered the general population, including vulnerable populations and people in the workplace handling so-called “consumer” products in the context of their occupational activity, excluding production, processing, distribution and disposal. Of all of the substances subject to the expert appraisal, there were two belonging to the class of polybrominated compounds:

- BDE 47 (2, 2’, 4, 4’-tetraBDE), (CAS No 5436-43-1)
- BDE 209 (2, 2’, 3, 3’, 4, 4’, 5, 5’, 6, 6’-decaBDE), (CAS No 1163-19-1)

Other polybrominated compounds may however be found in consumer goods and products and in various compartments of the environment.

ANSES therefore considered, in agreement with its expert appraisal bodies (Working Group on Endocrine disruptors (ED WG), Expert Committees (CESs) on “Assessment of the risks related to chemical substances” and “Characterisation of substance hazards and toxicity reference values”), that the available data should be summarised for an expanded list of chemical substances belonging to the class of polybrominated compounds (see below), in order to document the regulations governing the use of these substances, as well as the associated exposure and risks. The Agency also considered that sources of potential exposure to these substances should include food, water, air and dust.

This note concisely describes the main sections of a three-volume report resulting from the compilation of the available data on regulations and uses related to the substances of interest, contamination levels in various marketed products and environmental compartments, and potential risks related to polybrominated compounds. All of these data are presented in the three volumes of the report:

Volume 1: Knowledge of regulations on and the identification, chemical properties, production and uses of substances in the class of polybrominated compounds and particularly 2,2’,4,4’-

tetrabromodiphenyl ether (tetra-BDE) (CAS No 5436-43-1) and decabromodiphenylether (deca-BDE) (CAS No 1163-19-5).

Volume 2: Knowledge of contamination data and exposure for substances in the class of polybrominated compounds.

Volume 3: Knowledge of toxicity data for substances in the class of polybrominated compounds.

The ultimate aim of the expert appraisal was to characterise the main toxic effects of exposure to these compounds and determine the main sources of human exposure. Data on toxicity and exposure did not undergo a scientific assessment for robustness. Nonetheless, this work helped identify substances for which a health risk assessment may be justified in light of their widespread use and/or persistence in the human body or the environment, and in light of their potential toxicity to humans, particularly for reproductive function and development.

1 Procedure for handling the request

1.1 Means implemented and organisation

ANSES submitted this report for comments to the ED WG and the CES on "Characterisation of substance hazards and toxicity reference values" (CES Substances) in charge of examining the DGS's request on endocrine disruptors (Request No 2009-SA-0331). This report was thus discussed in ED WG meetings and at the meeting of the CES Substances. The current version of this three-volume report takes into account the comments and additional information provided by the members of the consulted WG and CESs.

This note was written based on the aforementioned summary report, whose sources of information included:

- various documents, surveys and reports available internally that had been produced by ANSES;
- publications by other expert appraisal organisations in France and abroad;
- a dissertation produced by Marylise Lagalle (pharmaceutical intern at ANSES in 2016).

Substances subject to the expert appraisal:

- BDE 47 and BDE 209 (see above)

Ultimately, the appraisal took into consideration congeners for which data on contamination in environments falling within the Agency's sphere of competence (air, water, food and dust) were available:

- polybromodiphenylethers (PBDEs), particularly BDEs 28, 47, 99, 100, 153, 154, 183 and 209,
- tetrabromobisphenol A (TBBPA),
- hexabromocyclododecane (HBCDD).

The data available for the various environments illustrated below (Figure 1) are described in Volume 2:

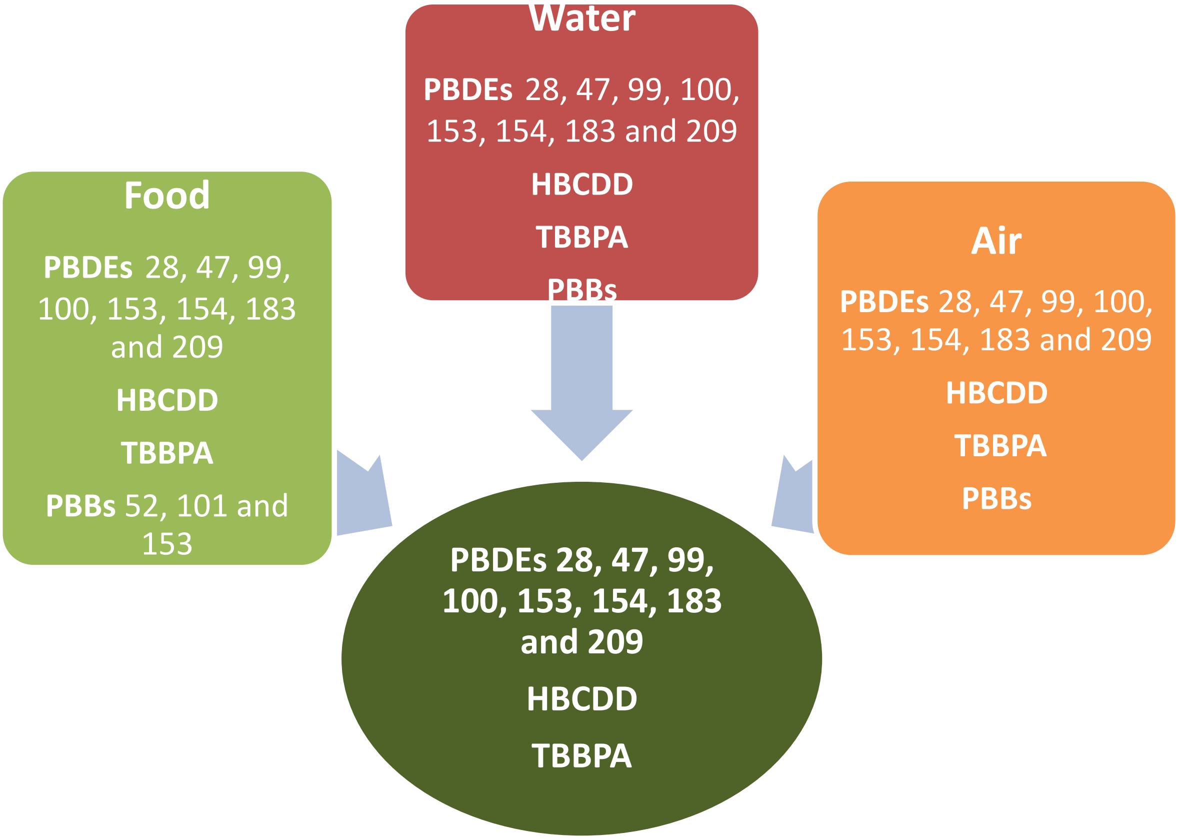

Figure 1: Prioritisation of substances and grouping of data for the various environments considered

2 Findings of the expert appraisal

2.1 Nomenclature and use of polybrominated compounds

The class of PBDEs consists of 209 congeners having the following chemical structure:

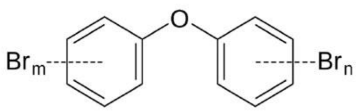

Fig. 2: General structure of PBDEs (m and n represent the degree of bromination)

PBDEs are used as both additive and reactive flame retardants in the manufacture of a wide variety of polymers such as polystyrene foam, compact polystyrene, epoxy resin, etc. They are synthesised in the form of commercial mixtures named after the type of congener most represented: pentabromodiphenylether (penta-mix), octabromodiphenylether (octa-mix) and decabromodiphenylether (deca-mix). Penta-mix and octa-mix have been prohibited since 2003. It should be noted that in some studies, "penta-mix" is referred to as "penta-BDE". Penta-mix is also called DE-71.

HBCDD can contain 70% to 95% gamma-HBCDD and 3% to 30% alpha-HBCDD and beta-HBCDD. This additive flame retardant is mainly found in expanded and extruded polystyrene foams used for the manufacture of insulation boards in the building industry.

TBBPA, synthesised from bisphenol A, is used as a reactive or additive flame retardant in the preparation of epoxy, ABS and phenolic resins.

2.2 Levels of polybrominated compounds in air and dust

The findings of the studies described in Volume 2 show that:

- Of the BDEs, BDEs 47, 99, 100, 153, 154 and 209 are the compounds covered by the most publications.
- A growing number of studies have focused on the presence of “new” flame retardants used as substitutes for BDEs in indoor and outdoor environments. Most of the available studies deal with HBCDD and TBBPA.
- Most studies involve the presence of flame retardants in settled dust. Few data on contamination in outdoor air were identified in the literature.
- The data on contamination in indoor air and dust are primarily related to homes. A few studies presenting contamination data, for schools, day-care centres and offices in particular, were identified.
- In France, quantified data for air and/or settled dust in homes are available for the following compounds: BDEs 28, 47, 99, 100, 153, 154 and 209 (Ecos-Habitat). Quantified data for settled dust measured in homes are also available for BDEs 28, 49, 66, 71, 75, 77, 85, 119, 138, 183 and 190 and for HBCDD (Greenpeace campaign).

2.3 Levels of polybrominated compounds in food

Dietary exposure to brominated compounds was assessed for the following populations:

- The general population in mainland France *via* the French Total Diet Study[1] (TDS2 2006-2010),
- Pregnant women from the EDEN study on pre- and postnatal determinants for child development and health, launched in 2003,
- Non-breastfed children between the ages of 0 and 3 years in mainland France *via* the infant Total Diet Study (iTDS, 2016).

The dietary contamination data for polybrominated compounds in the TDS2 and iTDS studies involved the following substances:

- Polybrominated diphenyl ethers (PBDEs): BDEs 28, 47, 99, 100, 153, 154, 183 and 209;
- Hexabromocyclododecane (HBCDD): the three congeners α, β and γ;
- Polybrominated biphenyls: PBBs 52, 101 and 153;
- Tetrabromobisphenol A (only in the iTDS).

2.4 Concentrations in food

The estimated concentrations of these substances in food for the general population in mainland France were as follows: The share of censored data (non-detected congeners) for brominated flame retardants varied considerably, from 7.1% for BDE 99 to 96.9% for PBB 101. Overall, likely due to their prohibition, PBBs (PBBs 52, 101 and 153) were detected less often than PBDEs (BDEs 28, 47, 99, 100, 153, 154, 183 and 209).

The highest mean levels for the sum of the three HBCDD congeners (alpha, beta and gamma) were found in fish, delicatessen meats, shellfish, molluscs, and meats.

For the sum of the three PBB congeners, the highest levels were found in oils and margarines. Given the high percentages of non-detected congeners, the lower-bound (LB) estimates were zero for a number of food groups.

For the sum of the seven PBDE congeners (excluding BDE 209), the food groups with the highest levels were fish, shellfish, molluscs and butter. For all food groups, the levels were around four to 12 times lower than those reported for Europe in the JECFA[2] report (JECFA 2006b). These differences may have been related to the 2002 prohibition of certain formulations through the publication of directive on electronic equipment (2002/95/EC, 2002/96/EC, 2003/11/EC), with entry into force on 1 July 2006. Furthermore, the data used by JECFA in 2005 were not only

[1] TDS: "Total Diet Studies" (TDSs) are cross-cutting national surveys designed to estimate exposure to chemical compounds by ingestion. They include in particular the analysis of a large number of substances in food samples that reflect the diet of the population under study. To achieve this, they rely on national food consumption surveys. TDSs make it possible to identify the substances for which there is a risk of inadequate intake (for minerals) and/or excessive exposure (for minerals and contaminants) in the population, as well as the foods contributing most to this intake or exposure.

[2] FAO/WHO Expert Committee on Food Additives

European but were also North American; and yet the PBDE profiles used in the United States differed significantly from those used in Europe before they were prohibited.

When the BDE 209 congener was added to the sum of the seven PBDE congeners, i.e. for the sum of the eight PBDEs, the groups with the highest contamination levels included dairy-based desserts and cream desserts, sandwiches and snacks, and margarines.

2.5 Assessment of dietary exposure for the general population in mainland France

Hexabromocyclododecane (HBCDD)

For adults, mean daily exposure to the sum of the three HBCDD congeners was 0.165 ng/kg bw/day for the lower bound (LB)[3] (0.091-0.351) and 0.211 ng/kg bw/day for the upper bound (UB) (0.133-0.401).

For children (aged three to 17), mean exposure was 0.237 ng/kg bw/day for the LB (0.152-0.402) and 0.320 ng/kg bw/day for the UB (0.231-0.488).

At the 95th percentile, exposure for adults was 0.391 ng/kg bw/day for the LB (0.194-1.335) and 0.448 ng/kg bw/day for the UB (0.240-1.379). For children (aged three to 17), exposure at the 95th percentile was 0.616 ng/kg bw/day for the LB (0.326-1.490) and 0.734 ng/kg bw/day for the UB (0.406-1.638).

Polybromodiphenylethers (BDEs 28, 47, 99, 100, 153, 154 and 183)

For adults, mean exposure to the sum of the seven PBDE congeners was 0.202 ng/kg bw/day for the LB (0.144-0.235) and 0.212 ng/kg bw/day for the UB (0.153-0.244).

For children (aged three to 17), exposure was 0.313 ng/kg bw/day for the LB (0.252-0.389) and 0.331 ng/kg bw/day for the UB (0.272-0.409).

For adults, exposure at the 95th percentile was 0.636 ng/kg bw/day for the LB (0.411-0.787) and 0.643 ng/kg bw/day for the UB (0.422-0.798).

For children, exposure at the 95th percentile was 0.868 ng/kg bw/day for the LB (0.548-1.268) and 0.894 ng/kg bw/day for the UB (0.628-1.301).

Polybromodiphenylethers (BDEs 28, 47, 99, 100, 153, 154, 183 and 209)

[3] LB and UB: Censored data refer to results below the limit of detection (LD) or quantification (LQ). A substitution method, adapted from the WHO recommendations (WHO, 2013), was used to process these data. It involved framing the actual level using the lowest (low assumption or lower bound, LB) and highest (high assumption or upper bound, UB) values possible: the LB was calculated by considering that all values below the LD were equal to zero and those between the LD and LQ were equal to the LD; the UB was calculated by considering that all values below the LD were equal to the LD and those between the LD and LQ were equal to the LQ.

When the PBDE 209 congener was added to the previous sum, exposure levels increased by a factor of 2 to 3. For adults, mean exposure was 0.540 ng/kg bw/day for the LB (0.463-0.648) and 0.550 ng/kg bw/day for the UB (0.472-0.659).

For adults, exposure at the 95th percentile was 1.164 ng/kg bw/day for the LB (0.892-1.419) and 1.176 ng/kg bw/day for the UB (0.898-1.436). For children, it was 2.337 ng/kg bw/day for the LB (2.013-3.039) and 2.368 ng/kg bw/day for the UB (2.037-3.086).

For children, mean exposure was 1.008 ng/kg bw/day for the LB (0.888-1.217) and 1.026 ng/kg bw/day for the UB (0.907-1.238).

2.6 Contribution of foods to dietary exposure for the general population in mainland France

HBCDD: The main contributors for adults and for children were delicatessen meats (27-29%), meat (15-21%), fish for adults (14%) and mixed dishes for children (14%).

Polybromodiphenylethers (BDEs 28, 47, 99, 100, 153, 154 and 183): The main contributor was fish, for both adults and children (>33%). These exposure levels were 12 to 15 times lower than the estimates determined for the general French population in 2006 based on consumption data from the national study of individual food consumption (INCA1), and French and international contamination data.

Polybromodiphenylethers (BDEs 28, 47, 99, 100, 153, 154, 183 and 209): Irrespective of the assumption, the highest contributors to exposure for adults as well as for children were dairy-based desserts and cream desserts (15-23%), fish (12-17%), and ultra-fresh dairy products (11-15%).

In conclusion: When a conservative approach was adopted, the 95th percentile for exposure in children to all eight PBDEs (BDEs 28, 47, 99, 100, 153, 154, 183 and 209) for the UB was more than 40,000 times lower than the value selected by JECFA of 100 µg/kg bw/day for the two congeners deemed the most toxic (BDEs 47 and 99), below which no toxic effect occurs. This exposure level was also below the value of 10 ng/kg bw/day proposed by ANSES's Expert Committee on “Physical and chemical contaminants and residues” to characterise the risk related to PBDEs. PBDEs thus pose no health risks to the French population in the current state of knowledge. Nonetheless, research into the toxicity of these compounds should be continued.

2.7 Estimated concentrations in foods, in the population of children under the age of three in mainland France

Sum of the HBCDDs: The concentrations measured in infant foods varied considerably, with values ranging from 2.46 to 42.85 $pg.g^{-1}$ fresh weight for the UB. An atypical value was observed in a sample of first infant formulas with a concentration of 307 $pg.g^{-1}$ fresh weight (whereas the values observed for the other first infant formulas ranged from 0.22 to 8.15 $pg.g^{-1}$ fresh weight). The highest mean levels for the sum of the HBCDDs were observed in infant dairy desserts (43 $pg.g^{-1}$ fresh weight for the LB and UB) and in milk drinks (23 $pg.g^{-1}$ fresh weight for the LB and UB). For normal foods, the highest mean concentrations for the sum of the HBCDDs were found in fish (177 pg.g^{-1} fresh weight for the LB and 185 pg.g^{-1} fresh weight for the UB) and delicatessen meat (140 pg.g^{-1} fresh weight for the LB and 150 pg.g^{-1} fresh weight for the UB).

TBBPA: The highest mean concentrations were observed in croissant-like pastries (914 ng.kg^{-1}), and then in first and second infant formulas (45 to 60 ng.kg^{-1} depending on the assumption for processing censored data), poultry (42 ng.kg^{-1} for the LB and 54 ng.kg^{-1} for the UB), and chocolate (32 ng.kg^{-1} for the LB and 62 ng.kg^{-1} for the UB). The highest concentration was measured in a sample of brioche and brioche-like bread (914 ng.kg^{-1}).

BDE 209: The highest mean levels were observed in dairy desserts and infant cereals (with respectively 69.57 and 66.94 pg.g^{-1} fresh weight for the LB). For normal foods, the highest contamination levels were observed in dairy-based desserts and cream desserts (244 pg.g^{-1} fresh weight for the LB), and margarines (105 pg.g^{-1} fresh weight for the LB).

Sum of the seven PBDEs: The highest mean levels were observed in jars of vegetables with meat or vegetables with fish, infant cereals, and dairy desserts (4.35 pg.g^{-1} fresh weight, 3.67 pg.g^{-1} fresh weight and 3.22 pg.g^{-1} fresh weight respectively for the LB).

The highest mean concentrations by food group were found in fish with 578 pg.g^{1} fresh weight (for the LB).

2.8 Assessment of dietary exposure for the population of children under the age of three in mainland France

Sum of the three HBCDDs: Mean daily exposure for the UB ranged from 0.505 ng.kg bw^{-1}day^{-1} for children aged 13-36 months to 8.27 ng.kg bw^{-1}day^{-1} for children aged 1-4 months. The 90th percentile ranged from 0.880 to 43.2 ng.kg bw^{-1}day^{-1} for the same age groups. The atypical contamination level for one of the first infant formulas explained these high exposure values for children aged 1-4 months (who consumed the milk in question).

For the most exposed children (above the 90th percentile), mean exposure for the UB ranged from 1.16 to 54.8 ng.kg bw^{-1}day^{-1}.

TBBPA: Mean daily exposure **for the UB** ranged from 0.512 ng.kg bw^{-1}.day^{-1} for children aged 13-36 months to 9.46 ng.kg bw^{-1}.day^{-1} for children aged 1-4 months for the LB and from 0.968 ng.kg bw^{-1}.day^{-1} to 9.94 ng.kg bw^{-1}.day^{-1} for the UB for the same age groups. The 90th percentile ranged from 1.44 to 31.3 ng.kg bw^{-1}day^{-1} for the LB and from 1.80 to 31.3 ng.kg bw^{-1}day^{-1} for the UB for the same age groups.

For the most exposed children (above the 90th percentile), mean exposure ranged from 2.49 to 39.2 ng.kg bw^{-1}day^{-1} for the LB and from 2.87 to 39.2 ng.kg bw^{-1}day^{-1} for the UB.

BDE 209: Mean daily exposure for the UB ranged from 1.12 ng.kg bw^{-1}day^{-1} for children aged 13-36 months to 2.62 ng.kg bw^{-1}day^{-1} for children aged 1-4 months. The 90th percentile ranged from 1.88 to 3.91 ng.kg bw^{-1}day^{-1} for the UB depending on the age group. For the most exposed children (above the 90th percentile), mean exposure for the UB ranged from 2.8 to 6.77 ng.kg $bw^{-1}day^{-1}$.

Sum of the seven PBDEs: Mean daily exposure for the UB ranged from 0.448 to 0.926 ng.kg $bw^{-1}.day^{-1}$. The 90th percentile ranged from 0.694 to 1.56 ng.kg $bw^{-1}.day^{-1}$. For the most exposed children (above the 90th percentile), mean exposure for the UB ranged from 1.32 to 1.78 ng.kg $bw^{-1}day^{-1}$ for the seven PBDEs depending on the age group.

2.9 Contribution of foods to dietary exposure for the population of children under the age of three in mainland France

Up to the age of six months, the main contributors to exposure to **HBCDDs** were first and then second infant formulas.

At the age of 5-6 months, milk drinks and infant dairy desserts also appeared as major contributors in addition to second infant formulas.
For the group of children aged 7-12 months, the contributors were the same as for children aged 5-6 months but also included jars of vegetables with meat or vegetables with fish.

In total, infant food accounted for 84% to 100% of intakes until the age of 12 months.

Lastly, for children aged 13-36 months, delicatessen meat was a major contributor. For the most exposed children, the contributors were the same as those found until the age of 12 months. However, for these most exposed children aged 13-36 months, delicatessen meats were not major contributors. On the other hand, milk drinks, infant dairy desserts and fish were major contributors in this age group.

For TBBPA, up to the age of 12 months, first and second infant formulas were the main contributors to exposure. For children aged 13-36 months, the main contributors were croissant-like pastries (56%) and growing-up milk (26%). For the most exposed children, the main contributors were the same overall, except for growing-up milk which was not a major contributor for those aged 13-36 months.

PBDEs: For the LB, the main contributors of BDE 209 were: first and then second infant formulas (with 94% of intakes for children aged 1-4 months for first infant formulas, 65% of intakes for second infant formulas for children aged 5-6 months and 45% of intakes for second infant formulas for children aged 7-12 months), infant dairy desserts (14% of intakes for children aged 5-12 months), ultra-fresh dairy products (14% for children aged 7-12 months and 33% for children aged 13-36 months) and dairy-based desserts and cream desserts (21% for children aged 13-36 months).

Seven PBDEs: Up to the age of 12 months, the main contributors to exposure were first and then second infant formulas: 97% of intakes for children aged 1-4 months for first infant formulas and 72% of intakes for second infant formulas for children aged 5-6 months (40% for children aged 7-12 months). From the age of seven months, some normal foods were major contributors to exposure to the seven PBDEs: fish (respectively 12% and 27% for children aged 7-12 months and 13-36 months) and ultra-fresh dairy products (11% for children aged 7-12 months and 16% for children aged 13-36 months).

In conclusion: Margins of safety (MOS) related to dietary exposure were calculated using EFSA's $BMDL_{10}$ for BDE 209 (1700 $\mu g.kg\ bw^{-1}.day^{-1}$). These margins ranged from 670,000 to 1,600,000 when considering mean exposure and from 450,000 to 960,000 when considering exposure at the 90^{th} percentile. These margins were thus well above the value of 2.5 proposed by EFSA.

The Tolerable Daily Intake (TDI) was not observed to have been exceeded for the sum of the seven PBDEs, irrespective of the assumption. For the UB, the 90^{th} percentile of exposure accounted for barely 15% of the TDI, regardless of the age group.

Based on the current knowledge and available data, dietary exposure in the infant population to BDE 209, the sum of the HBCDDs, the sum of the seven PBDEs, and TBBPA is considered tolerable.

2.10 Levels of polybrominated compounds in water and related environments

A scientific and technical support note relating to the presence of polybrominated compounds in inland water and drinking water was published by ANSES in 2014[4].

In addition to covering the issues of physico-chemical properties, sources of contamination, environmental fate, analytical methods and processes for treating drinking water, this note gave a summary of the literature on concentrations of PBDEs, PBBs, HBCDD and TBBPA in inland water and drinking water, documented at the national and international levels, for the period running from January 2000 to February 2014.

The analysis of the data in the international literature regarding the contamination of aquatic environments by polybrominated compounds showed that:

- there was great variability in concentrations of PBDEs, TBBPA and HBCDD in surface water depending on the site,
- concentrations of PBDEs, TBBPA and HBCDD in surface water were below 10 ng/L and two of the 24 identified publications described unusually high concentrations,
- only one study involving an analysis of these compounds in groundwater was identified,
- only one study described the detection of PBBs in inland water; the article's abstract indicates that these compounds were not quantified in the analysed samples.

Moreover, this note relied on information from French databases on water. According to the 80,481 results available in the SISE-Eaux and ADES databases for the 2000-2013 period, PBDE concentrations were below the limits of quantification in surface water and groundwater in 99% of cases. According to the SISE-Eaux database, PBDE concentrations were below the limits of quantification in all the samples taken from treatment plants and drinking water supply units.

The new data collected for the 2014-2015 period during the drafting of Volume 2 of the report on polybrominated compounds did not call into question the conclusions of the scientific and technical support note published in 2014.

It appeared that concentrations in sewage sludge and sediments varied depending on the compound. BDE 209 was the main PBDE congener found in these matrices.

In conclusion: In light of their hydrophobic and lipophilic properties and the low likelihood of them being present in drinking water, a national campaign for the sampling and analysis of PBDE, PBB, HBCDD and TBBPA brominated flame retardants in water (the resource used for the production of drinking water, drinking water from the distribution system, bottled water) is not a priority in relation to other chemical contaminants, with sediments and sewage sludge being the most relevant matrices.

[4] https://www.anses.fr/fr/system/files/EAUX2009sa0331-11.pdf

3 Biomonitoring data

3.1 Main conclusions of the INSERM collective expert appraisal report entitled "Reproduction and the Environment" (2011)

The presence of several representatives of this class of chemical pollutants in certain human fluids and biological tissues has been proven. In serum and breast milk, a few ng/g lipids are generally observed. A downward trend in concentration levels has been reported for the main PBDE congeners since the early 2000s, when the two penta- and octa-BDE industrial mixtures were phased out of production and use. However, this observation is not applicable for BDE 209, HBCDD or TBBPA; the available data for the latter two substances are extremely limited or even non-existent.

While the few most abundant PBDEs have been the subject of several studies, there is a shortage of data on compounds that currently remain authorised as flame retardants, including deca-BDE, HBCDD and TBBPA, in terms of exposure, concentrations, metabolism, pharmacokinetics, and links to certain clinical parameters.

3.2 Description of the studied French populations

The biomonitoring data relating to exposure to polybrominated flame retardants in the French population came from the two ELFE and PELAGIE cohort studies of pregnant women recruited in the 2002-2007 period.

ELFE and PELAGIE cohorts

The levels of contamination by polybrominated flame retardants (BFRs) observed in the framework of the perinatal component of the French biomonitoring programme from 2002 to 2007 were of the same order of magnitude or even lower than those measured in previous French studies. This decline may have been due to a decrease in exposure since the 2000s, when certain BFRs were brought into use, in particular to replace PBBs which were no longer produced or used in Europe. This decrease was particularly marked for BDE 209 for which restrictions on use took effect in 2008, as a result of earlier studies undertaken in France. Given the limited amount of contamination data available for HBCDDs, it was not possible to observe a potential secular trend in contamination levels in France for this class of BFRs.

4 Available data on the risks related to polybrominated flame retardants

4.1 Classification regarding carcinogenicity

Penta-BDE (commercial mixture):

Class D compound: substance not classifiable as to human carcinogenicity (Integrated Risk Information System (IRIS), US EPA, last revised in 1990).

BDE 209

Class C compound: possible human carcinogen (IRIS, US EPA, 2004).

Group 3: not classifiable as to its carcinogenicity (IARC Classification, 1999).

Lower brominated congeners are considered to belong to Class D (US EPA, 2004).

TBBPA assessed by IARC is classified as a possible human carcinogen (Class 2A, in preparation).

4.2 Classification regarding endocrine disruption

BDEs 99, 100 and 209 are classified as Category 2 endocrine disruptors according to the DHI classification[5].

4.3 Current reference values

No reference values (Toxicity Reference Value, Indoor Air Quality Guideline or Occupational Exposure Limit) have been defined by ANSES for these substances.

The reference values proposed by the main organisations and institutions recognised at the national and supranational levels available in the toxicological databases are given in Volume 3 of the report.

Regarding low-brominated PBDEs (penta-mix and octa-mix), an acute oral TRV of 0.03 $mg.kg^{-1}.day^{-1}$ was proposed based on a reduction in thyroid hormone T4 in sera (rat foetuses); in addition, a TRV for intermediate oral exposure of 0.007 $mg.kg^{-1}.day^{-1}$ was proposed based on a hepatotoxic effect observed in rats (Agency for Toxic Substances and Disease Registry, ATSDR (2015)). No TRV has been proposed for chronic oral exposure.

For exposure by inhalation, a TRV of 0.006 $mg.m^{-3}$ was proposed by ATSDR in 2015, based on a thyroid effect observed in rats.

[5] The European Commission commissioned DHI Water & Environment to establish a list of priority substances for future evaluation of their role in endocrine disruption.

Regarding deca-mix, a TRV for intermediate oral exposure of 10 $mg.kg^{-1}.day^{-1}$ was proposed by ATSDR in 2015, based on developmental toxicity observed in rats.

For seven PBDEs, EFSA (EFSA, 2011) proposed a TDI of 10 $ng.kg.bw^{-1}.day^{-1}$ for perinatal oral exposure in rats, based on neuro-developmental effects.

For HBCDD, EFSA (EFSA, 2011) proposed a TDI of 3000 $ng.kg.bw^{-1}.day^{-1}$ for oral exposure in mice, based on neuro-developmental effects.

Regarding penta-BDE (commercial mixture or penta-mix), the US EPA (1987) proposed an oral TRV of 0.002 $mg.kg^{-1}.day^{-1}$ for a threshold effect based on the induction of hepatic enzymes following subchronic exposure observed in rats.
The US EPA did not propose a TRV for exposure by inhalation and for a threshold effect.

Regarding BDE 47, the US EPA (2008) proposed an oral TRV of 0.0002 $mg.kg^{-1}.day^{-1}$ for a threshold effect, based on neuro-behavioural effects observed in mice, after a single administration by gavage.

Regarding BDE 99, the US EPA (2008) proposed an oral TRV of 0.0001 $mg.kg^{-1}.day^{-1}$ for a threshold effect, based on neuro-behavioural effects observed in mice, after a single administration by gavage.

Regarding BDE 153, the US EPA (2008) proposed an oral TRV of 0.0002 $mg.kg^{-1}.day^{-1}$ for a threshold effect, based on neuro-behavioural effects observed in mice, after a single administration by gavage.

Regarding BDE 209, the US EPA (2008) proposed an oral TRV of 0.007 $mg.kg^{-1}.day^{-1}$ for a threshold effect, based on neuro-behavioural effects observed in mice, after a single administration by gavage.

Other reference values

There are no TDIs on EFSA's ESCO[6] list.

5 Data produced since the expert appraisal reports (INSERM (2011) and EFSA (2013))

The INSERM collective expert appraisal report entitled "Reproduction and the Environment" includes a chapter on polybrominated flame retardants. EFSA also published reports on prioritised compounds (PBDE and HBCDD in 2011, TBBPA in 2013).

[6] ESCO: EFSA's scientific cooperation project

These reports helped identify the effects taken into account in the literature search, which are summarised in Volume 3 of the report: effects on reproductive function, thyroid function, metabolism, cancer, immune function, neurodevelopment, and the liver.

A summary of the abstracts published after 2010 (end of the INSERM bibliography) thus appears in Volume 3 of the report.

Recent data obtained in animals indicate that BFRs are especially toxic to hepatic, hormonal, male and female reproductive, nerve and immune functions. Certain compounds can accumulate in the body. The data on carcinogenicity are still limited, but PBDEs, PBBs and HBCDDs are not considered as being genotoxic. The epidemiological studies are difficult to interpret due to methodological limitations.

Effects on the thyroid:

Animal studies show that polybrominated compounds have effects on thyroid function and possible indirect impacts on reproductive function, given how these interact. Other studies undertaken in fish and amphibians have demonstrated that brominated flame retardants have an effect on the hypothalamic-thyroid axis. However, these effects seem to vary depending on the species, tested product or mode of exposure, posing the challenge of precisely determining at what level of the axis this interference occurs. In addition, it is not currently possible to establish a link between the developmental or reproductive effects of these compounds and the observed abnormalities of the thyroid axis.

Several studies in humans have focused on possible links between exposure to PBDEs and changes in circulating concentrations of thyroid hormones and/or TSH. Most studies have involved exposure in pregnant women or during the neonatal period. The various studies have produced inconsistent results. Quite often, only a limited population was included, thus limiting the scope of the conclusions.

It still remains difficult to characterise the chronic human toxicity of these compounds, which are often studied in the form of mixtures in experimental studies and have different mechanisms of action. Within the class of PBDEs, the toxicity and stability of compounds tend to decrease with the increase in the number of bromine atoms.

Carcinogenic effects:

A recent two-year study undertaken by the National Toxicology Program (USA) (Harvey *et al.*, 2015) found that exposure to TBBPA was associated with a sharp increase in the development of uterine tumours, in particular uterine cancers, in rats. The morphological and molecular characteristics of uterine cancers in the rats exposed to TBBPA resembled the type-1 high-grade tumours observed in women, suggesting that exposure to TBBPA may increase the risk of cancer.

Neuro-behavioural effects: Several human studies have shown relationships between exposure to PBDEs and neuro-behavioural effects. In some cases, the findings have been imprecise, due to the population, the presence of other contaminants, and simultaneous effects, on the thyroid for example. They therefore need to be corroborated.

Further research is needed to determine the neurotoxicity of PBDEs. For example, co-exposure should be taken into account. The various compounds studied are thought to have different neurotoxic effects.

3 Conclusions and outlook

Polybrominated compounds are commonly used as flame retardants in the manufacture of furniture and electronic equipment. They are lipophilic compounds that therefore tend to accumulate in biological tissues rich in lipids.

Thus, high-fat foods and fish are major sources of dietary exposure in humans. Furthermore, polybrominated compounds can be found in the indoor environment, whether they are released by volatilisation from foams or through abrasion from equipment in buildings. They are thus found in indoor air and household dust. The ingestion of dust seems to be a major route of exposure, especially in children.

The use of substances in the class of polybrominated compounds is regulated by the REACh Regulation and/or sector-specific regulations. The persistence in the environment of certain polybrominated compounds (pentabromodiphenylether, tetrabromodiphenylether, hexabromo-diphenylether, heptabromodiphenylether, HBCDD), although prohibited, may be a source of potentially long-term human exposure. The presence of certain compounds in breast milk and blood, as reported in studies in Europe, is related to the persistence of exposure sources.

The toxic effects of polybrominated compounds on humans have not been confirmed to date. Only studies in animals have shown potential endocrine disrupting, neurotoxic and carcinogenic effects. For the time being, polybrominated compounds have been proven to have only low toxicity to humans, but additional work will be necessary to better document these effects and exposure, and assess the potential health risks they entail.

In light of this analysis, the experts considered that certain brominated compounds such as BDEs 28, 47, 99, 100, 153, 154, 183 and 209, TBBPA and HBCDD may justify an assessment. As part of the 2017 National Endocrine Disruptor Strategy (SNPE 2017), BDE 47 was therefore selected for an assessment of its ED potential for humans and the environment.

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