

## SCIENTIFIC OPINION

### Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary<sup>1</sup>

#### EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)<sup>2,3</sup>

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#### ABSTRACT

This opinion describes the assessment of the risks to public health associated with bisphenol A (BPA) exposure. Exposure was assessed for various groups of the human population in three different ways: (1) external (by diet, drinking water, inhalation, and dermal contact to cosmetics and thermal paper); (2) internal exposure to total BPA (absorbed dose of BPA, sum of conjugated and unconjugated BPA); and (3) aggregated (from diet, dust, cosmetics and thermal paper), expressed as oral human equivalent dose (HED) referring to unconjugated BPA only. 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). The highest aggregated exposure of 1.449 µg/kg bw per day was estimated for adolescents. Biomonitoring data were in line with estimated internal exposure to total BPA from all sources. BPA toxicity was evaluated by a weight of evidence approach. "Likely" adverse effects in animals on kidney and mammary gland underwent benchmark dose (BMDL<sub>10</sub>) response modelling. A BMDL<sub>10</sub> of 8 960 µg/kg bw per day was calculated for changes in the mean relative kidney weight in a two generation toxicity study in mice. No BMDL<sub>10</sub> could be calculated for mammary gland effects. Using data on toxicokinetics, this BMDL<sub>10</sub> was converted to an HED of 609 µg/kg bw per day. The CEF Panel applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) to establish a temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg bw per day. By comparing this t-TDI with the exposure estimates, the CEF Panel concluded that there is no health concern for any age group from dietary exposure or from aggregated exposure. The CEF Panel noted considerable uncertainty in the exposure estimates for non-dietary sources, whilst the uncertainty around dietary estimates was relatively low.

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#### KEY WORDS

Bisphenol A, BPA, exposure, toxicity, health risks, TDI, food contact materials

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## BACKGROUND AS PROVIDED BY EFSA

Bisphenol A (BPA) is used as a monomer in the manufacture of polycarbonates and epoxy resins and as an additive in plastics. Polycarbonates are used in food contact materials such as reusable beverage bottles, infant feeding bottles, tableware (plates and mugs) and storage containers. Epoxy resins are used in protective linings for food and beverage cans and vats.

BPA is authorised for use as a monomer in plastic food contact materials, in accordance with Commission Regulation (EU) No 10/2011/EU on plastic materials and articles intended to come into contact with foodstuffs<sup>4</sup>. Its use is subject to a specific migration limit SML of 0.6 mg/kg. In addition, Commission Implementing Regulation (EU) No 321/2011<sup>5</sup> places a restriction on the use of BPA in the manufacture of polycarbonate infant feeding bottles.

EFSA has already issued scientific opinions on BPA in 2006, 2008 and in 2010 (EFSA 2006a, 2008; EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2010).

In its opinion of 2006, EFSA performed a risk characterisation for BPA, including a dietary exposure assessment and a hazard characterisation. In this opinion, EFSA established a tolerable daily intake (TDI) for BPA of 0.05 milligram per kilogram (mg/kg) body weight per day, based on the no adverse effect level of 5 mg/kg body weight per day in multi-generation rodent studies and applying an uncertainty factor of 100.

A new opinion on the toxicokinetics of BPA was adopted by EFSA in 2008. Here, EFSA reaffirmed the TDI established in 2006, concluding that age-dependent toxicokinetics differences of BPA in animals and humans would have no implication for the assessment of BPA previously carried out by EFSA.

In 2010, the CEF Panel performed a new hazard characterisation of BPA, based on a comprehensive evaluation of more recent toxicity data. The CEF Panel concluded that no new scientific evidence had been published since the EFSA opinions of 2006 and 2008 that would call for a revision of the current TDI. However, it emphasised that there were uncertainties concerning some BPA-related effects of possible toxicological relevance, in particular biochemical changes in brain, immune-modulatory effects and enhanced susceptibility to breast tumours emerging from studies on developing animals. Given several methodological shortcomings in the studies showing these effects, the CEF Panel concluded that the relevance of these findings for human health could not be assessed, but that it would reconsider its opinion should any new relevant data become available. A CEF Panel member expressed a minority opinion based on those uncertainties.

In 2011, EFSA was asked to provide scientific advice in relation to possible divergences between the conclusions of the EFSA Scientific Opinion on BPA of September 2010 and those in the reports on BPA published in September 2011 by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). On 1 December 2011, EFSA published a Panel statement on BPA (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011a) in which the information in the ANSES report was considered not to change the views that the CEF Panel expressed in 2010. However, concerning additional data in recent literature, the CEF Panel stated that it would need further time for a more in-depth review of the new studies. The CEF Panel also underlined that there are ongoing low-dose studies at National Center for Toxicological Research/FDA and at National Toxicological Program/National Institute of Environmental Health Sciences which aim to address, at least in part, the current uncertainties regarding the potential health effects of BPA.

<sup>4</sup> Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1 – 89.

<sup>5</sup> Commission Implementing Regulation (EU) No 321/2011 of 1 April 2011 amending Regulation (EU) No 10/2011 as regards the restriction of use of Bisphenol A in plastic infant feeding bottles. OJ L87, 2.4.2011, p. 1 – 2.

The ANSES risk assessment of BPA (including exposure assessment from the diet as well as from other routes) was finalised during the preparation of this scientific opinion and was published in April, 2013 (ANSES, 2013).

After its 2011 scientific advice on BPA, EFSA noted that its latest exposure assessment to BPA through dietary sources dates back to 2006, and needed to be updated in the light of the data since then available. The relevance of a dietary exposure assessment versus a more general exposure assessment via various routes of exposure should also be explored. Also, in line with the 2011 conclusions of the CEF Panel, it is advisable for EFSA to undertake a full re-evaluation of the safety of BPA, based on all the most recent experimental evidence.

### **TERMS OF REFERENCE AS PROVIDED BY EFSA**

In accordance with Article 29 (1) of Regulation (EC) No 178/2002<sup>6</sup>, the European Food Safety Authority asks its Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) to provide by December 2014 a scientific opinion on the risks for public health related to the presence of bisphenol A in foodstuffs.

In particular, the opinion should:

- evaluate the toxicity of BPA for humans, including specific (vulnerable) groups of the population (e.g. pregnant women, infants and children, etc.) and considering all the relevant toxicological information available;
- carry out an exposure assessment on the basis of the occurrence data available in the public domain and other occurrence data that may be available, and quantify as far as possible not only dietary exposure but also exposure from non-dietary sources;
- consider specifically the exposure situation for the supposedly most vulnerable groups of the population (e.g. pregnant women, infants and children, etc.) and take into account, if available, biomonitoring data when assessing the exposure and compare the results with the calculated exposure; and
- characterise the human health risks of BPA taking into account specific groups of the population.

### **INTERPRETATION OF THE TERMS OF REFERENCE AS PROVIDED BY EFSA**

A three-step approach has been taken by the CEF Panel in developing this full risk assessment of BPA. As a first step, the CEF Panel endorsed its draft exposure assessment in July 2013 and released it for public consultation (25 July – 15 September, 2013; <http://www.efsa.europa.eu/en/consultationsclosed/call/140117.htm>). Secondly, on 12 December 2013 the CEF Panel endorsed its draft assessment of BPA health risks addressing specifically BPA hazard assessment and risk characterisation, and subsequently issued it for public consultation (17 January – 13 March, 2014; <http://www.efsa.europa.eu/en/consultationsclosed/call/130725.htm>). Following the comments received during the two public consultations the CEF Panel has now completed and adopted the full opinion on the risk assessment of BPA. In addition, EFSA has compiled a technical report listing all the comments received both on the draft BPA exposure assessment and the draft assessment of BPA health risks, and has explained whether and how they have been taken into account in the final opinion.

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<sup>6</sup> Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L31, 1.2.2002, p. 1–24

## SUMMARY

This scientific opinion deals with the assessment - by the EFSA CEF Panel - of the risks to public health associated with BPA exposure. It consists of three separate documents:

- Executive summary, which includes the sections in the opinion relevant to both Parts I and II, i.e. abstract, background, terms of reference (ToR), interpretation of the ToR and summary of Parts I and II;
- Part I - Exposure assessment, exposure conclusions, list of references and appendices.
- Part II - Toxicological assessment and risk characterisation, their conclusions, list of references and appendices.

### 1. Part I – BPA exposure assessment

Part I of this opinion addresses the second and third part of the terms of reference. It presents an exposure evaluation to BPA based on the occurrence data available in the public domain and other occurrence data that have been collected through a call for data. Furthermore it includes a quantification not only of the dietary exposure, but also of the exposure from non-dietary sources. Particular focus is on the exposure for subgroups in the human population, based on different age classes. The opinion also considers biomonitoring data to support the exposure estimates obtained by calculation, based on the information on occurrence.

#### 1.1. BPA uses

BPA (chemical formula  $C_{15}H_{16}O_2$ , CAS No 80-05-7 and EC No 201-245-8) is an organic chemical used in the manufacture of polycarbonate (PC) plastics, epoxy resins and other polymeric materials and also for certain paper products (thermal paper e.g. for cash receipts). PC is used for manufacturing food and liquid containers, such as tableware (plates and mugs), microwave ovenware, cookware and reservoirs for water dispensers, as well as for non-food applications, such as toys and pacifiers with PC shields. BPA-based epoxyphenolic resins are used as protective linings for food and beverage cans and as a coating on residential drinking water storage tanks and supply systems. Additionally, BPA may be used upstream in the process of manufacturing of some raw materials, which are then used to produce food contact materials. BPA is also used in the manufacturing of a number of non-food-related applications, e.g. epoxy resin-based paints, medical devices, surface coatings, printing inks and flame retardants.

#### 1.2. EU Regulatory framework for BPA

BPA is authorised for use as a monomer in plastic food contact materials, in accordance with Commission Regulation (EU) No 10/2011/EU on plastic materials and articles intended to come into contact with foodstuffs<sup>7</sup>. Its use is subject to a specific migration limit (SML) of 0.6 mg/kg. In addition, Commission Implementing Regulation (EU) No 321/2011<sup>8</sup> placed a restriction on the use of BPA in the manufacture of PC infant feeding bottles which was introduced in 2011 on the basis of the precautionary principle.

#### 1.3. Potential exposure sources for the general population

The general population can be exposed to BPA via food/drinking water and/or via the use of non-food consumer products such as thermal paper, toys, etc.. Environmental sources can include surface water (during swimming) and outdoor air (inhalation of aerosols). In addition, BPA from epoxy-based floorings, adhesives, paints, electronic equipment and printed circuit boards may be released into

<sup>7</sup> Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1 – 89.

<sup>8</sup> Commission Implementing Regulation (EU) No 321/2011 of 1 April 2011 amending Regulation (EU) No 10/2011 as regards the restriction of use of Bisphenol A in plastic infant feeding bottles. OJ L87, 2.4.2011, p. 1 – 2.

indoor air (including airborne dust) and dust. Environmental sources can potentially contribute to oral and dermal exposure, as well as inhalation to BPA.

#### 1.4. General approach for the exposure assessment

This opinion presents a detailed analysis of data on food consumption and BPA occurrence in food that have become available since the previous EFSA evaluation in 2006. Unlike the opinion adopted in 2006, the present opinion also addresses the contribution of non-food sources to the overall exposure to BPA.

Average and high total chronic BPA exposures were assessed in different age classes, including consideration of those groups that may be more vulnerable: infants, children and women of childbearing age (in order to address potential exposure in the fetus and in breastfed infants), whereas the assessment of BPA exposure in specific disease states, occupational exposure of workers handling BPA containing products, or acute exposure to BPA were not developed in this opinion.

The exposure assessment involved the estimation of consumer exposure in terms of the following three different metrics:

- External exposure to BPA (in Part I – Exposure assessment)

The assessment of external exposure considered the different routes (ingestion, inhalation, dermal uptake) and sources (e.g. diet, drinking water, air, thermal paper). It estimated the source-specific doses reaching the physical barriers in the gastrointestinal and respiratory tracts and of the skin. Route-specific external exposures to BPA were calculated via the so-called forward modelling approach by multiplying source concentrations with the corresponding use frequencies (e.g., food intake, handling of thermal paper).

- Internal exposure to total BPA (in Part I – Exposure assessment)

The assessment of internal exposure to total BPA considered the route- and source-specific absorption fractions to estimate the doses that passed the physical barriers to enter the body. For this purpose exposure from all sources and over all routes were combined.

These internal doses are expressed as doses of total BPA (as no differentiation is made between the unconjugated and conjugated BPA). As BPA is completely eliminated via urine, the sum of these internal doses is directly comparable to exposure estimates obtained by the so-called backward modelling approach from urinary biomonitoring data.

- Aggregated exposure to unconjugated BPA (in Part II – Toxicological assessment and risk characterisation)

The assessment of aggregated exposure used physiologically based pharmacokinetic (PBPK) modelling to translate the contributions from the relevant sources (diet and house dust for the oral route, thermal paper and cosmetics for the dermal route) into a toxicologically relevant dose metric, the area under the curve (AUC) for the serum concentration of unconjugated BPA. A translation into AUC is necessary because, in contrast to dermally absorbed BPA, orally (i.e. gastrointestinally) absorbed BPA is subjected to the first-pass metabolism before entering the systemic circulation. Based on the AUC information, external dermal exposures (thermal paper, cosmetics) were converted to equivalent oral exposures which could then be summed up with the external oral exposures (diet, house dust) to obtain aggregated exposure estimates.

#### 1.5. Methods

*Literature sources.* A thorough literature search was performed by an independent contractor to retrieve scientific studies relevant to the following categories: analytical methods for BPA in food,



human biomonitoring of BPA, occurrence of BPA in drinking water, food contact materials, food, non-food materials (such as indoor air, dust, thermal printed paper, dental materials and medical devices) and in the environment. The search using the terms “bisphenol”, “BPA” alone or combined with “food” or “migration” or “water” was conducted on these databases: ISI Web of Knowledge-Web of Science, Elsevier Science Direct, Elsevier Scopus, EBSCOhost—OmniFile Full Text Select (H.W. Wilson), SpringerLink, Taylor & Francis online, Wiley Interscience. In addition, members of the CEF Panel’s Working Group on BPA Exposure searched the scientific literature for additional relevant information, e.g. parameters used to estimate skin absorption and physiological data, etc..

The publications were then screened against the following eligibility criteria: (i) only primary research studies, (ii) language (at least abstract in English), (iii) publication date between January 2006 and December 2012 (papers published outside this period were considered only if they provided data in areas where no or very few data were available (e.g. data on human milk) or to complete the European dataset (e.g. biomonitoring data); (iv) geographical origin of the samples and sample type (only European data were used if available); (v) quality of the analytical methods employed. Also grey literature was considered as specified in the methodology of Part I of this opinion.

*EFSA call for data.* Data were also retrieved through a call for data that EFSA launched in July 2012 in relation to (i) the occurrence of BPA in food and beverages; (ii) BPA migration from food contact materials; and (iii) BPA occurrence in food contact materials. Details on the eligibility and inclusion of data received from the call for data are given in Appendix B of Part I of this opinion.

## **1.6. Assessment of BPA exposure**

### **1.6.1. External exposure to BPA**

#### **1.6.1.1. Dietary exposure**

Dietary exposure to BPA has been estimated in different population groups by combining information on BPA occurrence in food with the corresponding consumption levels. Average exposure was assessed based on average concentration and average consumption data, while high exposure was based on average concentration and high consumption.

A total of 2 516 samples (many of which were pooled samples from the French total diet study) of food and beverages were selected as the basis to assess BPA concentrations in the different food categories. Data on BPA concentrations from the literature and from the call for data did not show major differences and were therefore merged for each food category to be used in the exposure calculations.

Left-censored data, i.e. from samples with concentrations below the limit of detection (LOD) or quantification (LOQ), were handled through the substitution method. The lower bound (LB) was obtained by assigning a value of zero to all the samples reported as less than the left-censoring limit, the middle bound (MB) by assigning half of the left-censoring limit, and the upper bound (UB) by assigning the left-censored limit (LOD or LOQ) as the sample result.

Significant differences in BPA concentration between canned and non-canned food were observed in a large majority of food categories, with higher BPA concentrations in the canned food. Seven out of 17 canned food categories presented a MB average BPA concentration above 30 µg/kg (“Grain and grain-based products”, “Legumes, nuts and oilseeds”, “Meat and meat products”, “Fish and other seafood”, “Herbs, spices and condiments”, “Composite food”, and “Snacks, desserts, and other foods”). Lower levels were found in other categories. The average (MB) BPA concentration was lower than 3 µg/kg in canned beverages (water, alcoholic and non-alcoholic beverages, fruit and vegetables juices). Among the 19 non-canned food categories, the highest levels of BPA were found in the categories “Meat and meat products” and “Fish and other seafood” with average (MB) BPA concentrations of 9.4 and 7.4 µg/kg, respectively. When comparing European with non-European concentration data for food, average BPA levels were mostly in the same range.

Biomonitoring studies suggested higher levels of BPA in colostrum (produced during the first five days after delivery) compared with mature human milk. Due to the very limited availability of European data on colostrum, the CEF Panel took into account also the data from a Japanese study, despite its severe limitations (analytical determination of BPA by ELISA and long storage time of samples). Overall, an average total BPA concentration of 3 µg/L and a modelled high concentration estimate of 5.8 µg/L in colostrum were used for exposure assessment during the first five days of life. Based on different studies, the average and high concentrations of total BPA in mature human milk were estimated to be 1.1 µg/L and 4.0 µg/L, respectively.

BPA migration data from food contact materials into food simulants, retrieved from the literature and EFSA's call for data, were used to assess the exposure of specific groups of consumers. In particular, average BPA migration levels were derived for the following PC articles: water coolers with PC reservoirs (0.81 µg/L in water), PC water kettles (0.11 µg/L in warm water), PC filters (0.04 µg/L in water), PC tableware and cookware (0.09 and 0.29 µg/L, respectively, in foods that can be consumed hot).

Data from the EFSA Comprehensive European Food Consumption Database (hereafter called the Comprehensive Database) were used to assess dietary exposure to BPA in all age groups, excluding infants aged 0 to 6 months. Consumption data observed in toddlers were used as an estimate of consumption in infants aged 6 to 12 months since no data were available for the latter age class. Consumption data from a total of 32 different dietary surveys carried out in 22 different Member States covering more than 67 000 individuals are included in the Comprehensive Database. In the present assessment the adult age group has been broken down in the following subgroups, comprising women from 18 to 45 years (child-bearing age), men from 18 to 45 years, adults from 45 to 65 years, and elderly and very elderly (65 years and over). Only a limited number of dietary surveys in the Comprehensive Database have information on the type of packaging (canned or non-canned, in particular).

In the case of infants a consumption of 150 g/kg bw per day was used as a standard for both human milk and infant formula with the exception of breastfed infants over their first five days of life for whom the consumption was assumed to be 75 g/kg bw per day.

Two scenarios were developed to consider the higher levels of BPA in canned foods compared with non-canned foods. In scenario 1 only foods specifically codified as canned in the dietary survey are assigned the corresponding occurrence level for BPA. In scenario 2 any food category (at the lowest available level of food category classification) which has been codified as canned in at least one survey is always considered to be consumed as canned in all dietary surveys included in the Comprehensive Database.

Due to a low percentage of left censored samples, in particular among canned foods, the techniques used to model data below the LOD or LOQ had a small impact on the average concentration in the different food categories and, consequently, on the exposure. Therefore, middle bound average BPA concentration values were used in the final exposure assessment.

#### *Dietary exposure for the population groups older than 6 months*

The modelled dietary exposure (MB) obtained by scenario 2, for infants (6 to 12 months), toddlers (12 to 36 months) and other children (3 to 10 years) ranged from 290 to 375 ng/kg bw per day for the average exposure and from 813 to 857 ng/kg bw per day for the high exposure, respectively. Additional dietary exposure from a number of food contact articles was also assessed in specific population groups. The highest estimated high exposure from PC tableware and cookware was observed for infants and toddlers (14 ng/kg bw per day for PC tableware and 46 ng/kg bw per day for cookware). The highest estimated exposures to BPA migrating from water coolers with PC reservoirs and PC filters into drinking water were also observed in infants and toddlers (22 ng/kg bw per day for water coolers and 3.8 ng/kg bw per day for PC filters). High estimated exposure in residents of



buildings with old water pipes repaired with epoxy resins was up to 29 ng/kg bw per day in infants and toddlers.

The modelled dietary exposure obtained by scenario 2, for adolescents, adults (including women of childbearing age) and elderly/very elderly, ranged from 116 to 159 ng/kg bw per day for the average exposure and from 335 to 388 ng/kg bw per day for the high exposure, respectively. Additional dietary exposure from a number of food contact articles was also assessed in specific population groups within this population. Estimated exposure from PC kettles ranged from 2 to 3.2 ng/kg bw per day with the highest values being observed in adults and the elderly due to their higher consumption of coffee and tea.

Under scenario 1, non-canned “meat and meat products” turned out to be a major contributor to BPA average exposure in the large majority of countries and age classes. Canned foods contributed to less than 50 % to the average exposure for all age classes. “Vegetables and vegetable products” was the only canned food category that contributed up to 25-50 % exposure in some population groups.

Under scenario 2, canned products dominated in all surveys, with canned “vegetables and vegetable products”, “meat and meat products” and “composite food” being the major sources of average BPA exposure. The contribution of BPA from non-canned foods ranged from 10 to 25 % exposure, with “Meat and meat products” being the major contributor among the non-canned food categories as for scenario 1.

Exposure from non-canned meat and meat products and fish had not been anticipated until the 2013 report of ANSES on concentrations of BPA in French food. Investigation of these findings is currently underway in France (see <https://info.agriculture.gouv.fr/gedei/site/bo-agri/instruction-2014-994>), but until further results are available there is no substantiated explanation for the presence of unconjugated BPA in foods of animal origin. It may be due to migration from any food contact materials or from articles used in the processing of the product or deconjugation of conjugated BPA occurring during processing of the sample. The CEF Panel considered that accumulation of BPA in animal tissues was not a likely explanation, given the extensive data showing rapid metabolism and elimination of BPA in various animal species.

Overall, among the population older than 6 months, infants and toddlers presented the highest estimated average (375 ng/kg bw per day) and high (857 ng/kg bw per day) dietary exposure. The CEF Panel considered that this was mainly due to their higher consumption of foods and beverages per kg bw.

#### *Dietary exposure for infants aged 0-6 months*

For breastfed infants, the estimated average dietary exposure was 225, 165 and 145 ng/kg bw per day for infants in the first five days of life, infants from 6 days up to 3 months and infants 4-6 months, respectively. The estimated high dietary exposure was 435, 600 and 528 ng/kg bw per day, respectively. The CEF Panel noted that, due to the lack of recent European data related to colostrum, the estimated dietary exposure in the first five days of life was based on BPA concentration in samples collected in Japan in 2000 and generated using ELISA methodology. The CEF Panel noted these severe limitations and the resulting uncertainties in the estimates for this age group.

Average and high additional exposure to infants that would derive from the consumption of herbal tea prepared with water heated in a PC kettle would be as low as 6 and 12 ng/kg bw per day, respectively.

In the case of formula-fed infants (0-6 months), the estimated average and high exposures were 30 and 80 ng/kg bw per day, respectively. These estimates are based on the assumption that non-PC baby bottles and water containing low BPA levels were used to reconstitute the infant formula. Additional dietary exposure may occur in specific population groups due to the use of old PC bottles bought before the 2011 ban (estimated high exposure: 731 ng/kg bw per day). The percentage of infants to

which these cases would apply is unknown. If this percentage was higher than 5 % in some countries, it would lead to a high dietary exposure which is significantly higher than 80 ng/kg bw per day.

Dietary exposure from further sources in other specific population groups of infants was also assessed: exposure for infants fed powdered formula reconstituted with water heated in PC kettles was 53 ng/kg bw per day (average) and 94 ng/kg bw per day (high).

Compared with the assessment of dietary exposure to BPA estimated by EFSA in 2006 (up to 11 000 ng/kg bw per day in infants aged 3 months in one of the scenarios considered), the current estimate in the population 0 to 6 months is far lower, due to the improvement of data compared with 2006, which previously led to very conservative assumptions in relation to BPA concentration in infant formula and to BPA migration from PC bottles.

#### 1.6.1.2. Non-dietary exposure

The non-dietary sources considered for this assessment were thermal paper, indoor/outdoor air (including air-borne dust), dust, toys and articles which may be mouthed, and cosmetics. An average and a high scenario were made for all sources. For the average scenario, average values for all parameters, including parameters describing frequency of use, were chosen. For the high scenario, the same average parameters were used for absorption rates and occurrence data, but the frequency of use parameters was modified to account approximately for the highest 95<sup>th</sup> percentile among the EU population, in line with the methodology used to assess dietary exposure.

Data on occurrence, migration and transfer of BPA from non-food sources are scarce. The following concentration data were selected from the scientific literature and other risk assessment reports to calculate exposure in the EU: for air 1 ng/m<sup>3</sup>; for dust 1 460 µg/kg, and for cosmetics (such as body wash, and body lotions, etc.) 31 µg/kg. A migration of 0.14 µg/toy product into saliva over a 24 h period was assumed. The transfer of BPA from thermal paper to fingers was estimated to be 1.4 µg/finger considering 10 s of contact with paper. Handling events were assumed as 1 per day for adolescents and adults to assess average exposure and as 4.6 per day to assess high exposure. For children the handling events were assumed as 0.5 time per day for average exposure and 2 times per day for high exposure. The thermal paper was assumed to be handled mainly by the fingertips of three fingers of one (average exposure) or two hands (high exposure).

The estimates of external non-dietary exposure according to source and exposure route are as follows:

*Dust ingestion:* for the average scenario the derived exposure values ranged from 0.6 ng/kg bw per day in adults to 8.8 ng/kg bw per day in infants. The CEF Panel considered that these are likely to be overestimated, because in the original studies soil and dust ingestion rates could not be determined separately, and so conservative assumptions were made when deriving the dust ingestion rates. In the high exposure scenario the exposure ranged from 1.0 ng/kg bw per day (adults) to 14.6 ng/kg bw per day (infants).

*Mouthing of toys:* exposure values of 0.2 and 0.01 ng/kg bw per day for the average exposure scenario and 0.6 and 0.01 ng/kg bw per day for the high exposure scenario for infants' and toddlers' exposure, respectively, to rattles (as a proxy for PC mouthing toys) were derived.

*Air inhalation:* the average exposure values ranged from 0.2 (adults) to 0.7 ng/kg bw per day (toddlers and infants), whereas high exposure levels ranged from 0.3 (adults) to 1.4 ng/kg bw per day (infants).

*Dermal exposure to thermal paper:* this scenario applied only to subjects older than 3 years. From average assumptions, exposures of 68.8, 93.8 and 58.9 ng/kg bw per day were derived for children, adolescents and adults, respectively. For the high exposure, values ranged from 542 (adults) to 863 ng/kg bw per day (adolescents).

*Dermal exposure to cosmetics:* average exposure ranged from 2.0 (adults) to 4.8 ng/kg bw per day (infants). High exposure ranged from 4.0 (adults) to 9.4 ng/kg bw per day (infants).

The CEF Panel noted that the average values for dust and thermal paper differed by a factor 10 from the respective high values. This is due to highly conservative assumption for dust ingestion and frequency of and number of fingers handling thermal paper when assessing high exposure.

### 1.6.2. Internal exposure to total BPA

The external exposure values to BPA as derived by forward calculation were transformed into internal exposure levels by applying route- and source-specific absorption fractions, namely 100 % absorption for both ingestion and inhalation, 10 % for dermal absorption of BPA from thermal paper and 50 % for dermal absorption of BPA from cosmetics. The internal levels of total BPA summed up over different routes were only used to validate external exposure estimates, by means of a comparison with daily urinary excretion of total BPA from biomonitoring studies. Internal levels of total BPA were not used for risk characterisation, which only focuses on the toxicologically active unconjugated fraction of BPA.

By forward modelling, the average internal exposure (expressed as ng/kg bw per day) to total BPA ranged from 42 to 387 for the overall age class “Infants”, and amounted to 384 for toddlers and 301 for children 3–10 years old. For the adolescents, women of childbearing age, and all the adult populations internal total BPA exposures were estimated to be in the range of 124 to 172 ng/kg bw per day. The high internal exposure to total BPA for the overall class of infants ranged from 101 to 878 ng/kg bw per day, and for toddlers and children 3–10 years old it was estimated around 870 ng/kg bw per day. Lower levels were estimated for adolescents, women of childbearing age, and all the adult populations (between 393 and 473 ng/kg bw per day).

The estimates for the average and high internal exposure to total BPA in the general population, as obtained by the forward modelling approach, were compared with the biomonitoring estimates. The focus is on total BPA (conjugated plus unconjugated) in order to provide validation for the external exposure levels.

A relatively large amount of information on urinary BPA concentration was available for Europe covering all age classes: children (except 1–3-year-old toddlers), adolescents, and 18–75-year-old adults.

Average and high urinary concentrations of total BPA were multiplied by age-specific urinary output rates to obtain estimates of daily urinary excretion for the different age groups. Since absorbed BPA is rapidly removed from circulation via conjugation and subsequent renal excretion, the estimates of daily urinary excretion can be used as estimates of daily BPA exposure.

For the average exposure, the following biomonitoring estimates (expressed as ng/kg bw per day) were derived: <10 (infants 1–2 months old), 107 (children 3–5 years old), 49 (children 5–10 years old), 48 (adolescents), 39 (adults including women of childbearing age), and 56 (the elderly). The biomonitoring estimates (expressed as ng/kg bw per day) for high BPA exposure were 161 (infants 1–2 months old), 676 (children 3–5 years old), 380 (children 5–10 years old), 256 (adolescents), 290 (adults including women of childbearing age), and 203 (the elderly).

By comparing estimated internal exposure with biomonitoring data, the forward modelling approach gave about 4-fold higher estimates (42–387 vs. <10–107 ng/kg bw per day) than the biomonitoring approach for average exposure, and about 2-fold higher for high exposure, demonstrating quite a good agreement between these two approaches. The different statistical procedures used to derive central tendencies and the scenarios for modelling the dietary and non-dietary exposure may contribute to the observed differences. The CEF Panel also noted that there are considerable uncertainties in both estimates.

### 1.6.3. Conclusions

The assessment of external exposure to BPA from all sources showed that diet is the main source in all population groups. Specifically, canned food and non-canned meat and meat products are the two main dietary contributors to external BPA exposure in the large majority of countries and age classes.

While canned food as a main source of dietary exposure to BPA is confirmed by the data presented in this opinion, exposure from non-canned meat and meat products and fish had not been anticipated until the 2013 report of ANSES on concentrations of BPA in French food (see above). Investigation of these findings is currently under way, but, until further results are available, there is no substantiated explanation for the presence of unconjugated BPA in foods of animal origin.

Among the population older than six months, infants (6-12 months) and toddlers had the highest estimated external average (0.375 µg/kg bw per day) and high (0.857 µg/kg bw per day) dietary exposure. This was mainly due to their higher consumption of foods and beverages per kilogram body weight. The modelled dietary exposure for adolescents, adults (including women of childbearing age) and elderly/very elderly ranged from 0.116 to 0.159 µg/kg bw per day for the average external exposure and from 0.335 to 0.388 µg/kg bw per day for the high exposure, respectively. Dietary exposure to BPA estimated by EFSA in 2006 in the population older than six months was far higher (up to 5.3 µg/kg bw per day in toddlers) compared with the current assessment (up to 0.857 µg/kg bw per day for the high exposure of toddlers), owing to the lack of data at that time which led to the use of very conservative assumptions in relation to both the level of consumption of canned food and the estimated BPA concentration in these foods.

The current much higher data availability than in 2006 has made it possible for the CEF Panel to carry out a more refined dietary exposure assessment for infants. According to the current estimate, BPA exposure for infants up to six months (0.03 to 0.225 µg/kg bw per day for average external exposure) is much lower than that estimated by EFSA in 2006 for infants within six months of age ( $\leq$  11 µg/kg bw per day). This was due to the use at that time of very conservative assumptions in relation to BPA concentration in infant formula and to BPA migration from PC bottles to account for the lack of data.

Dietary external exposure in women of childbearing age (0.132 and 0.388 µg/kg bw per day for average and high exposure, respectively) was similar to that of men of the same age (0.126 and 0.335 µg/kg bw per day for average and high external exposure, respectively). The minimal differences may be related to women consuming different food items, as reported in the individual surveys.

The uncertainty around the estimates of dietary exposure was judged as relatively low compared to non-dietary sources of exposure such as thermal paper.

Thermal paper was the second largest source of external exposure in all population groups above three years of age. The modelled estimates for 3–10-year-old children, adolescents, adults (including women of childbearing age) and elderly/very elderly ranged from 0.059 to 0.094 µg/kg bw per day for the average exposure and from 0.542 to 0.863 µg/kg bw per day for the high external exposure, respectively. The CEF Panel considers that more data would be needed for BPA absorption through the skin, on skin metabolism and for patterns of thermal paper handling by the general population in order to provide a refined estimate of exposure through this source to reduce the uncertainty in the estimate.

In children under the age of three years (except for infants in the first few days of life) dust was the second largest source of external exposure to BPA and ranged from 0.009 to 0.015 µg/kg bw per day for average and high external exposure, respectively.

Average external exposure to BPA from non-dietary sources such as toys and cosmetics was estimated to be less than 0.001 µg/kg bw per day and 0.005 µg/kg bw per day, respectively, in all population groups.

For the four age classes covering infants from 1 day up to 6 months, the average internal exposure to total BPA, as estimated by forward modelling, ranged from 0.042 µg/kg bw per day to 0.226 µg/kg bw per day. The average internal exposure for the population older than six months ranged from 0.301 to 0.387 µg/kg bw per day in children aged 3 to 10 years and infants aged 6 to 12 months and from 0.124 to 0.172 µg/kg bw per day in the elderly/very elderly and adolescents.

For the four age classes covering infants from 1 day up to 6 months the high internal exposure to total BPA ranged from 0.101 µg/kg bw per day to 0.621 µg/kg bw per day. The high internal exposure for populations older than six months ranged from 0.873 to 0.878 µg/kg bw per day in toddlers and infants aged 6 to 12 months, and from 0.393 to 0.473 µg/kg bw per day in men and adolescents.

Internal exposures to total BPA, as estimated by forward modelling, are in good agreement with the backward-modelling estimates obtained from urinary biomonitoring, suggesting that it is likely that no major exposure sources have been missed for the forward-modelled exposure assessment. It is, however, important to highlight the fact that the internal exposure estimation of total BPA includes conservative assumptions resulting in likely overestimation of exposure that could in theory have hidden other possible sources of exposure. The CEF Panel noted also that there are considerable uncertainties in the forward and backward estimates of internal exposure.

The CEF Panel additionally carried out an assessment of aggregated dietary and non-dietary exposure to unconjugated BPA using PBPK modelling. This aggregated exposure assessment included diet and house dust (the main oral-route sources) as well as thermal paper and cosmetics (the main dermal-route sources).

## **2. Part II – BPA toxicological assessment and risk characterisation**

Part II of this opinion addresses the first and the fourth part of the terms of reference, i.e. BPA hazard assessment, and the risk characterisation for human health associated with BPA exposure.

### **2.1. Methods**

*Literature sources:* A thorough and extensive literature search was outsourced by EFSA to cover the period from August 2010 to December 2012. The publications were searched on five online databases—namely PubMed, ScienceDirect, Scopus from Elsevier, Web of Knowledge/Science from the Institute for Scientific Information, and the Directory of Open Access Journals (DOAJ)—using the search strings “bisphenol” or “BPA” (without any additional search terms). Additional sources of information were the list of published scientific studies on BPA submitted by Réseau Environnement Santé to the European Commission (EC) and received by EFSA on 19 February 2013; pre-(July)2010 studies previously identified as key studies by various risk assessment bodies including EFSA; pre-(July)2010 studies not previously evaluated by EFSA because they did not match the inclusion criteria established for the 2010 opinion, e.g. non-oral studies, single-dose studies, studies addressing BPA exposure only during adult age and genotoxicity studies (searched from 2006 onwards); and some studies available in 2013 (as per the literature search carried out by an EFSA contractor) selected on a case-by-case basis (based on expert judgement) based on their relevance to critical review questions and/or their methodological soundness. The literature cited in the comments of the public consultation and therefore published by the closing date of the consultation (17 March 2014) was an additional source of evidence.

The studies used for the hazard identification and characterisation of BPA were then grouped according to 10 macro-areas of interest, including toxicokinetics and metabolism, general toxicity, reproductive and developmental effects. The studies grouped by macro-area were assigned to the working group on BPA toxicology for evaluation, including appraisal of their strengths and



weaknesses. *In vitro* studies and studies on the mechanisms of action of BPA were used primarily as supplementary information for the toxicological evaluation.

## 2.2. Hazard identification

For the hazard identification of BPA, the Weight of Evidence (WoE) approach was structured in such a way as to facilitate consistent treatment of the evidence and to document this in a tabular format, as described in more detail in Appendix A of this opinion. The WoE evaluation for each toxicological endpoint was divided into one or several parts addressing different questions considered by the CEF Panel to be relevant for hazard identification of BPA, e.g. “Is there an association between BPA exposure and reproductive effects in humans?”. As already indicated, the conclusions of earlier assessments by EFSA in 2006 and/or 2010 were taken as a starting point for each question. Subsequently, for each question, the relevant publications were organised into a number of “lines of evidence”, addressing different findings or considerations that provide an answer to the question concerned. The strengths and weaknesses of each line of evidence, and of the evidence underpinning the earlier assessments, were briefly summarised in a tabular format, to facilitate a conclusion to be drawn on the likelihood that exposure to BPA was associated with a particular effect. This conclusion was categorised depending on the strength of the overall experimental evidence for the effect, as follows. Note that, on this scale, “As likely as not” means a level of likelihood between “Unlikely” and “Likely”, where it is about equally likely that BPA causes, or does not cause, the effect.

### Box 1. Set of standard terms used for expressing the overall likelihood in the WoE tables.

<b>Likelihood</b>
Very likely
Likely
From “-as likely as not- to likely”
As likely as not
From “unlikely to –as likely as not-”
Unlikely
Very unlikely

The CEF Panel would like to underline that this classification applies solely to BPA hazard identification and not to the assessment of human risks from BPA exposure.

This approach was adopted independently for (1) human studies reporting effects of BPA, (2) animal studies and (3) *in vitro* studies, where considered appropriate. An overall conclusion was then drawn regarding the likelihood that BPA could be associated with the effect in question in the human population, based on a WoE approach in humans, animals and/or *in vitro* studies.

The toxicokinetics of BPA were similarly reviewed using the conclusions of previous evaluations and the results of new toxicokinetic studies on BPA published since the 2010 EFSA opinion on BPA. In this case, however, a WoE approach was not found to be necessary to reach an overall conclusion on the toxicokinetics of BPA in humans and experimental animals.

The conclusions of the CEF Panel on the hazard identification step for BPA in relation to each endpoint considered are summarised in the following sections.

### 2.2.1. Toxicokinetics

- Species- and life-stage dependent differences in the toxicokinetic profile of BPA must be considered when comparing toxicokinetic data from different species.
- Conjugation to BPA-glucuronide is the major metabolic pathway of BPA in humans, non-human primates and rodents. Glucuronidated BPA is a biologically inactive form of BPA at the oestrogen receptors (ERs); however it cannot be excluded that the glucuronidated form

may have effects at ER independent sites. BPA can also be conjugated via sulfation to a lower extent.

- The oral systemic bioavailability of unconjugated BPA in adults is: 2.8 % in rats, 0.45 % in mice and 0.9 % in monkeys, based on oral versus intravenous toxicokinetic data.
- Unconjugated BPA and BPA-conjugates are observable at low concentrations in the amniotic fluid of rats and monkeys in comparison with serum levels. In early pregnancy exposure of the fetus might be greater compared with later pregnancy after i.v. exposure to BPA.
- BPA is present in rat milk from BPA-treated dams in both unconjugated and conjugated forms. In rat milk, BPA-glucuronide comprises about 80 % of the total BPA concentration. Pup exposure via lactation is low, i.e. about 1/300 of the maternal dose. Unconjugated BPA has also been reported in human milk.
- BPA-conjugating enzymes (UDP-glucuronyl-transferases (UGT) and sulfotransferases (SULT)) are polymorphic in humans. The default intraspecies uncertainty factors used to derive a health-based guidance value are considered sufficient to account for possible differences in rates of metabolism of BPA between human individuals.
- A solid base of toxicokinetic studies in various laboratory animal species provides internal dose metrics for neonatal-to-adult stages and for different routes of exposure. Moreover, PBPK models have been developed to predict the internal exposures in laboratory animals and humans in a route-specific manner.
- Overall, this body of information permits extrapolation to humans and the application of the human equivalent dose (HED) concept for providing HEDs for points of departure derived from critical animal data. This was achieved by estimating human equivalent dose factors (HEDF) from the ratio of the Area Under the Curve (AUC) for the test species and AUCs for humans.
- Available experimental evidence indicates a 24-h percutaneous penetration of BPA across human skin of 2.3–8.6 %. For exposure scenarios with dermal contact to thermal paper, the CEF Panel used a conservative value of 10 % dermal absorption. The CEF Panel did not consider skin metabolism (conservative decision). For scenarios with aggregated oral and dermal exposures, PBPK modelling was used to estimate the internal dose metrics (AUCs) for unconjugated BPA, with which equivalent oral exposures were subsequently calculated.

### 2.2.2. General toxicity

- BPA was found to affect kidney and liver weight in parental animals and in all the generations of rats and mice examined in multi-generation studies. These effects were considered by EFSA (2006, 2010) as relevant systemic effects for the identification of a NOAEL. In mice the increased kidney weight was associated with nephropathy at the highest BPA dose. Liver weight was increased in rats (relative weight) and mice (both absolute and relative weight). The latter species also showed hepatocellular hypertrophy.
- The CEF Panel re-confirmed that the changes in the kidney and liver are critical endpoints in BPA toxicity and therefore took them forward for hazard characterisation.

### 2.2.3. Reproductive and developmental effects

- Only limited conclusions can be drawn from human studies on the likelihood of associations between BPA exposure during pregnancy and disturbed foetal growth, or maternal and infant decreased thyroid function. The evidence is not sufficient to infer a causal link between BPA exposure and reproductive effects in humans.

- Data considered in previous EFSA opinions show that BPA is a reproductive toxicant at high dose levels. On balance, the evidence from new lower dose (below 3.6 mg/kg bw per day, that corresponds to the NOAEL for general toxicity transformed in HED) animal studies for changes in reproductive function arising from in utero exposure to BPA remains contradictory and highly variable between studies. Furthermore, the biological relevance to humans of some of the effects of BPA exposure observed in some animal studies (e.g. reduced ano-genital distance in females) is not well understood. The CEF Panel noted that there is some evidence for effects of BPA exposure on several parameters indicative for changes in the reproductive system in adult male animals at dose levels below 3.6 mg/kg bw per day, although these effects were modest. It is not possible to conclude that these changes are reflective of changes in reproductive performance, since the studies rarely included a forced/continuous breeding phase in adulthood to establish reduced fertility. However, in several multi-generation studies no effects were observed at dose levels as low as 3 µg/kg bw per day up to at least 50 mg/kg bw per day.
- The CEF Panel re-confirmed that BPA is a reproductive toxicant at high dose levels.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “as likely as not” to reproductive and developmental effects of BPA at low doses (below the HED of 3.6 mg/kg bw per day). Since the likelihood level for this endpoint is less than “likely” (see Box 1), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation.

#### 2.2.4. Neurological, neurodevelopmental and neuroendocrine effects

- There are indications from prospective studies in humans that prenatal BPA exposure (BPA exposure during pregnancy) may be associated with altered child behaviour in a sex-dependent manner. 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. The associations reported do not provide sufficient evidence to infer a causal link between BPA exposure during pregnancy or childhood and neurodevelopmental effects in humans.
- A number of new studies report changes that may indicate effects of BPA on brain development (effect on neurogenesis and on gene expression, neuroendocrine effects, effects on the morphology of certain brain regions, etc.). Whether such changes are mechanistically related to the neurobehavioral responses reported following exposure is attempted addressed by some studies but with inconsistent results.
- Several new animal studies investigated anxiety-like behaviour, learning and memory, social behaviour and sensory-motor function. Some studies report changes in anxiety-like behaviour after BPA exposure. Some, but not all, studies reported significant impairment of either learning and/or memory capacities. A few studies also report effects on social behaviour and sensory-motor function. However, the studies present methodological shortcomings, such as small sample size, lack of consideration of the litter effect, not properly controlled variability of exposure through diet and inadequate statistics. Moreover the results from different studies are inconsistent.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “as likely as not” to neurological, neurodevelopmental and neuroendocrine effects of BPA. Since the likelihood level for this endpoint is less than “likely” (see Box 1), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation.

### 2.2.5. Immune effects

- Based on recent studies, there are indications that BPA exposure may be linked to immunological outcomes in humans, although these studies had limitations and confounding factors may have been present. A causal link between BPA exposure during pregnancy or in childhood and immune effects in humans cannot be established.
- Studies in animals lend support to the possibility of immunological effects of BPA. However, most of these studies suffered from shortcomings in experimental design and reporting. Although dose-responses could not be confidently established in most studies, a dose-related effect was observed for allergic lung inflammation.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “-as likely as not- to likely” to immunotoxic effects of BPA. Since the likelihood level for this endpoint is less than “likely” (see Box 1), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation.

### 2.2.6. Cardiovascular effects

- All but one study, among the newly considered human studies in relation to cardiovascular effects since the 2010 EFSA opinion, are cross-sectional and thus unsuitable to study BPA exposure-disease associations on their own. There are indications from one prospective study that BPA may be associated with such effects but overall a causal link between BPA exposure and cardiovascular effects in humans cannot be established.
- There are insufficient animal data to suggest that BPA has an effect on cardiac function or causes cardiotoxicity.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “as likely as not” to cardiovascular effects of BPA. Since this likelihood level is less than “likely”, this endpoint was not taken forward for risk characterisation. It cannot be ruled out that the observed association between exposure to BPA and cardiovascular effect in the epidemiological studies is confounded by diet or other concurrent exposure factors. This association does not provide sufficient evidence to infer a causal link between BPA exposure and cardiovascular effects in humans. Since there is also a lack of information on the dose-relationship for this association, and since there were only very limited number of animal studies on this endpoint, this endpoint was not included in the uncertainty analysis.

### 2.2.7. Metabolic effects

- 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. Inconsistent with the results of cross-sectional studies one prospective study found that a higher BPA concentration in maternal urine during pregnancy was associated with a lower level of obesity in daughters. A causal link between BPA exposure and metabolic effects in humans cannot be established.
- A number of studies in pre- and postnatally exposed rats and mice indicate that BPA exposure could have an effect on metabolic function as evidenced by effects on glucose or insulin regulation or lipogenesis, and body weight gain (short-term studies). However, based on the results from other studies with a longer duration (e.g. 90 days) there is no convincing evidence that BPA is obesogenic after intrauterine exposure or in longer-term studies.

- Using a WoE approach, the CEF Panel assigned a likelihood level of “as likely as not” to metabolic effects of BPA. Since the likelihood level for this endpoint is less than “likely” (see Box 1), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation.

#### **2.2.8. Genotoxicity**

- The available data support that BPA is not mutagenic (in bacteria or mammalian cells), or clastogenic (micronuclei and chromosomal aberrations). The potential of BPA to produce aneuploidy in vitro was not expressed in vivo. The positive finding in the postlabelling assays in vitro and in vivo is unlikely to be of concern, given the lack of mutagenicity and clastogenicity of BPA in vitro and in vivo.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “unlikely” to BPA genotoxicity.

#### **2.2.9. Carcinogenicity**

- Very few epidemiological studies published to date have investigated a possible association between exposure to BPA and incidence of certain cancers, specifically breast cancer and meningioma. These studies do not allow any conclusion to be drawn regarding the carcinogenicity of BPA in humans.
- BPA was not carcinogenic in two standard oral carcinogenicity studies in rats and mice. In a more recent study, female but not male mice, exposed to approximately 10 mg/kg bw per day BPA from *in utero* up to postnatal day (PND) 21, developed significantly more hepatocellular tumours (adenomas and carcinomas together) with or without preneoplastic lesions after a stop-exposure period of 10 months. Additional rodent studies on perinatal exposure to BPA investigated the potential carcinogenic effect in mammary gland. Due to weaknesses in these studies the results do not provide convincing evidence that BPA is carcinogenic to the liver during adult life or in mammary gland following perinatal exposure.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “unlikely to - as likely as not -” to carcinogenic effects of BPA. Since the likelihood level for this endpoint is less than “as likely as not” (see Box 1), this endpoint was not taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation.

#### **2.2.10. Proliferative and morphological changes potentially related to carcinogenesis**

- Earlier evidence for BPA effects on cell proliferation and differentiation in the mammary gland and other tissues (e.g. prostate or testis) has been supported by recent studies. The proliferative changes in the mammary gland reported in these new studies, including a non-human primate study, are however insufficient to conclude that there is a link to cancer development, although there might be a possible role of BPA in increasing the susceptibility to mammary gland carcinogenesis later in life.
- The proliferative responses and possibly enhanced sensitivity to mammary gland carcinogens seen in animal studies might be of relevance for human health and are therefore included in the risk assessment.
- Using a WoE approach, the CEF Panel assigned a likelihood level of “likely” to BPA induced proliferative changes in the mammary gland. Therefore, this endpoint was brought forward for hazard characterisation and for uncertainty analysis.



- The CEF Panel considered that the evidence for proliferative changes induced by BPA in other organs (e.g. prostate or testis) is currently too limited to reach any conclusion.

### 2.2.11. Mechanistic studies with BPA including epigenetic effects

- Mechanistic studies published since 2010 continue to support the conclusion that BPA affects a number of receptor-dependent and independent signalling pathways, resulting in effects on hormone homeostasis and gene expression as well as in cytogenetic and epigenetic effects.
- The CEF Panel confirmed its conclusion in its opinion of 2010 that no single clearly defined mode of action of BPA can be identified that can contribute substantially to the understanding of the potential effects of BPA in humans.

## 2.3. Hazard characterisation

The WoE approach to hazard identification has been used to identify the critical toxicological effects for BPA, following prenatal or postnatal exposure, or both. The subsequent step in the risk assessment, namely hazard characterisation, was carried out for only those endpoints for which the overall likelihood for the specific effect was considered as “likely”. Dose-response relationships (hazard characterisation) were examined for the studies considered by the CEF Panel to be the most reliable, in order to provide a reference point for the derivation of a health-based guidance value.

The CEF Panel considered that the “likely” effects indicative of general toxicity in rats and mice that were already described in the EFSA 2010 opinion should be maintained as a critical endpoint for risk assessment of BPA. Additionally the CEF Panel concluded that BPA-induced effects on the mammary gland of rats, mice and monkeys exposed pre- or perinatally were “likely” effects. These latter conclusions resulted from the CEF Panel’s evaluation of new evidence published since EFSA’s previous risk assessment in 2010 and of earlier studies using the subcutaneous route of administration (not considered in the EFSA 2010 opinion). The CEF Panel also considered that recent scientific literature has provided additional indications (compared with its 2010 evaluation) of reproductive and developmental effects at doses of BPA below the NOAEL for general toxicity as well as neurological/neurodevelopmental/neuroendocrine, immune-modulatory and metabolic effects. In light of the methodological shortcomings identified in the evaluated studies, the CEF Panel considered that none of these effects could be considered as “likely” by the WoE approach. Instead, they were considered in a thorough and structured uncertainty analysis, the results of which were taken into account in hazard and risk characterisation.

The CEF Panel has carried out dose-response (Benchmark Dose [BMD]) modelling on the data for general toxicity and for the proliferative changes in the mammary gland. The analysis of the mammary gland data revealed large differences in the BMD estimates obtained with the various models and wide BMD confidence intervals obtained with some of the models. These estimates could not be used for the derivation of a health-based guidance value. Therefore, the proliferative changes in the mammary gland were taken into account in the evaluation of uncertainty for hazard characterisation and for risk characterisation.

The CEF Panel therefore used only the endpoint “general toxicity” for risk characterisation, specifically the mean relative kidney weight in a two-generation study in mice, and calculated a BMDL<sub>10</sub> of 8 960 µg/kg bw per day.

Subsequent to the 2010 opinion, new toxicokinetic data have become available which allow a more accurate substance-specific extrapolation of data from animals to humans, using the human equivalent dose (HED) approach. The human equivalent dose factor (HEDF) of 0.068 for oral exposure of adult mice was applied to the BMDL<sub>10</sub> of 8 960 µg/kg bw per day, which results in a HED of 609 µg/kg bw per day. The CEF Panel decided to use the HED value of 609 µg/kg bw per day as the reference point for establishing a health-based guidance value for BPA.

The CEF Panel also developed criteria<sup>9</sup> for nonmonotonic dose responses (NMDRs) and reviewed studies reporting a NMDR for BPA. None of the studies fulfils these criteria. Overall the CEF Panel concluded that the available data do not provide evidence that BPA exhibits a NMDR for the endpoints considered (reprotoxicity/development, neurotoxicity/behavioural effects, metabolic effects, proliferative changes in mammary gland).

### 2.3.1. Uncertainties in hazard characterisation

The overall uncertainty evaluation included the effects on the mammary gland as well as on the reproductive, metabolic, neurobehavioural and immune systems. The CEF Panel concluded that the health-based guidance value should cover the lowest dose in the dose range for which the likelihood approaches “likely” from the overall uncertainty evaluation, taking into account uncertainty of all the evaluated endpoints as well as their relevance and adversity to humans. The uncertainty evaluation approached “likely” in the (HED) dose range of 100–1000 µg/kg bw per day. The CEF Panel therefore decided that the uncertainty regarding the above mentioned effects at the HED of 100 µg/kg bw per day and higher should be taken into account when establishing a health-based guidance value by including an extra factor in establishing the TDI. Thus, as the reference point was 609 µg/kg bw per day based on the mean relative kidney weight and the lower end of the dose-range for which the uncertainty evaluation for other endpoints approached “likely” is 100 µg/kg bw per day, a factor of 6 was applied.

### 2.3.2. Health-based guidance value

In deriving a health-based guidance value, the CEF Panel used an uncertainty factor of 2.5 for inter-species differences (1 for toxicokinetics and 2.5 for toxicodynamics, reflecting the fact that toxicokinetic differences have been addressed by use of the HED approach) and an uncertainty factor of 10 for intra-species differences. In addition, the CEF Panel considered that the extra factor of 6 should be included to take into account the uncertainty in the database, i.e. mammary gland and reproductive, neurobehavioural, immune and metabolic systems.

The CEF Panel applied, therefore, an overall uncertainty factor of 150 to the HED of 609 µg/kg bw per day and established a temporary Tolerable Daily Intake (t-TDI) for external oral exposure to BPA in humans of 4 µg/kg bw, based on the mean relative kidney weight effect in mice. The CEF Panel designated the TDI as temporary, pending the outcome of the long-term study in rats involving prenatal as well as postnatal exposure to BPA, currently being undertaken by NTP/FDA.

## 2.4. Risk characterisation

The following table shows the aggregate exposures figures that were used for the risk characterisation.

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<sup>9</sup> (i) at least two adjacent doses departing from monotonicity or support for the NMDR from a similar study (same species, similar treatments, similar sampling time) on the same effect (this criteria is relevant to reduce the chance for an incidental finding).

(ii) a plausible underlying mode of action/overarching concept;

(iii) the reliability of the study and the relevance of the effect for human health should be considered as medium or high (as expressed in Appendix B and C); the reliability of the study results should also include an appropriate statistical treatment of the reported data

**Table 1:** Summary table on average (A) and high (H) exposure ( $\mu\text{g}/\text{kg}$  bw per day) from dietary and non-dietary sources to BPA in the different age groups of the general population. Dermal doses are expressed as equivalent oral doses as obtained by PBPK modelling.

Age group	Exposure level	Dietary	Non-dietary			Sum of non-dietary
		Oral	Oral	Dermal		
		Food & beverage	Dust & Toys	Thermal paper	Cosmetics	
Infants 1-5 days (breastfed)	A	0.225	-	-	-	-
	H	0.435	-	-	-	-
Infants 6 days - 3 months (breastfed)	A	0.165	0.009	-	-	0.009
	H	0.6	0.015	-	-	0.015
Infants 4-6 months (breastfed)	A	0.145	0.009	-	-	0.009
	H	0.528	0.015	-	-	0.015
Infants 0-6 months (formula fed)	A	0.03	0.009	-	-	0.009
	H	0.08	0.015	-	-	0.015
Infants 6-12 months	A	0.375	0.009	-	-	0.009
	H	0.857	0.015	-	-	0.015
Toddlers 1-3 years	A	0.375	0.007	-	-	0.007
	H	0.857	0.012	-	-	0.012
Children 3-10 years	A	0.290	0.003	0.053	0.008	0.064
	H	0.813	0.005	0.424	0.016	0.445
Adolescents 10-18 years	A	0.159	0.002	0.113	0.015	0.13
	H	0.381	0.003	1.036	0.029	1.068
Women 18-45 years	A	0.132	0.0006	0.071	0.012	0.084
	H	0.388	0.001	0.650*	0.024*	0.675*
Men 18-45 years	A	0.126	0.0006	0.071	0.012	0.084
	H	0.335	0.001	0.650	0.024	0.675
Other adults 45-65 years	A	0.126	0.0006	0.071	0.012	0.084
	H	0.341	0.001	0.650*	0.024	0.675*
Elderly and very elderly 65 years and over	A	0.116	0.0006	0.071	0.012	0.084
	H	0.375	0.001	0.650*	0.024*	0.675*

\* It is assumed that the dermal exposures as expressed as equivalent oral doses for the age group men 18-45 years also are representative for the age groups women 18-45 years, other adults 45-65 years, and elderly and very elderly 65 years and over, assuming that the toxicokinetics are not significantly different between these age groups.

Comparison of the estimates for high dietary exposure for all age groups with the t-TDI of  $4 \mu\text{g}/\text{kg}$  bw per day showed that the dietary exposure in all age groups (including the most exposed groups, i.e. 6-12 months infants and toddlers with levels of  $0.857 \mu\text{g}/\text{kg}$  bw per day) was more than 4-fold below the t-TDI, indicating no health concern from dietary exposure alone. The additional contribution from other oral sources, like dust and toys mouthing (high exposure up to  $0.015 \mu\text{g}/\text{kg}$  bw per day), did not change this conclusion.

Comparison of the aggregated estimates for exposure to dietary and non-dietary sources of “children 3-10 years” and adolescents with the t-TDI showed that even when the high exposure estimates for dietary and non-dietary sources are combined, the aggregated exposure for children 3-10 years ( $0.813 + 0.445 = 1.258 \mu\text{g}/\text{kg}$  bw per day) and adolescents ( $0.381 + 1.068 = 1.449 \mu\text{g}/\text{kg}$  bw per day) will be approximately 3-fold below the t-TDI.

The aggregated high dietary and non-dietary exposures (including oral and dermal sources) for women ( $0.388 + 0.675 = 1.063 \mu\text{g}/\text{kg}$  bw per day) and men ( $0.335 + 0.675 = 1.010 \mu\text{g}/\text{kg}$  bw per day) are mostly identical and they are lower than those for adolescents and children 3-10 years. The CEF Panel considered that the exposure estimates (up to approximately  $1 \mu\text{g}/\text{kg}$  bw per day) for men and for women including pregnant women and prenatally exposed children, will be approximately 4-fold below the t-TDI of  $4 \mu\text{g}/\text{kg}$  bw per day.

Having evaluated the overall uncertainty of this assessment, the upper bound of the uncertainty interval for dietary BPA exposure alone did not exceed the t-TDI for any age group. Upper bounds for the uncertainty of high but not average aggregate exposure estimates to BPA exceed the t-TDI but the lower bounds are considerably lower than the t-TDI. The wide uncertainty intervals are caused by uncertainty about the magnitude of external exposure to BPA from thermal paper, about the proportion of the amount of BPA which is absorbed through the skin, and about the choice of PBPK model for converting dermal exposures to oral equivalents.

## OVERALL CONCLUSIONS

The CEF Panel concludes that the dietary exposure to BPA for the highest exposed groups, which includes infants, children and adolescents, is below the t-TDI of 4 µg/kg bw per day, indicating that there is no health concern for BPA at the estimated levels of exposure. These conclusions also apply to prenatally exposed children and to the elderly.

In addition, the CEF Panel concludes that the central estimates for aggregated exposure to BPA via the dietary and non-dietary sources (dust, toys, cosmetics and thermal paper) for the highest exposed groups, which includes infants, children and adolescents, is also below the t-TDI of 4 µg/kg bw per day, indicating that the health concern for BPA is low at the estimated levels of exposure. However, the CEF Panel noted that there is a considerable uncertainty in the exposure estimate for the non-dietary sources.

## RECOMMENDATIONS

Reflecting the uncertainties surrounding this risk assessment of BPA as outlined in the previous Section, the CEF Panel considers that further research in the following areas would be useful:

- Further work to refine the Human Equivalent Dose approach used in this opinion to extrapolate from experimental results in animals to humans, including further refinement of the toxicokinetics of unconjugated BPA in mice
- Further refinement of the human PBPK modelling applied in the opinion
- Further studies on the frequency and extent of dermal contact with BPA containing materials
- Further studies on the extent of dermal absorption following exposure to BPA by the dermal route in humans and the toxicokinetics of BPA following dermal absorption in humans and experimental animals.
- Mechanistic studies in the kidney to determine the mode of action of BPA in this organ
- Further research on the significance of proliferative and morphological changes in mammary gland following exposure to BPA and the possible relevance for the development of breast cancer
- Further research on the potential adverse health effects of BPA for which there are uncertainties and that were therefore not definitely considered as “likely” in this opinion, in particular reproductive, neurobehavioural, immunological and metabolic endpoints, using validated, robust methodology
- Further investigations designed to explore the occurrence of non-monotonic dose responses following in vivo exposure to BPA
- Investigations to clarify the extent and the sources of unconjugated BPA in meat and fish