PlasticsEurope
Association of Plastics Manufacturers

Polycarbonate/Bisphenol A group

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On 25.7.2013, EFSA published its draft exposure assessment of Bisphenol A (BPA) for public commenting. It is a comprehensive 314 page scientific document, including a 148 page report and 9 extensive data appendices.

EFSA evaluated consumer exposure to BPA based on an extensive review of existing literature as well as data provided by authorities and stakeholders[1]. In terms of methodology, EFSA used exposure modelling calculations and biomonitoring data, taking into account different age groups, food products and exposure factor.

The PC/BPA group of PlasticsEurope prepared a summary of the key contents of the report.

Note: text in *"quotation marks" and italics* is directly quoted from the EFSA preliminary opinion.
Bold is used by the authors of this document to mark specific text elements, also in quotes.

EFSA exposure assessment report: http://www.efsa.europa.eu/en/consultations/call/130725.htm

EFSA Q&A:
http://www.efsa.europa.eu/en/faqs/faqbisphenol.htm?utm_source=newsletter&utm_medium=email&utm_content=feature&utm_campaign=20130731

Scope of the EFSA assessment

- Human BPA-exposure assessment with a focus on vulnerable groups of the population
- Assessment of average and high chronic exposure through combined different sources and routes: dietary (food) and non-dietary (skin contact, inhalation)
- Dietary sources, in addition to food and drinks, include polycarbonate water reservoirs, water filters, water dispensers, electric kettles, tableware, epoxy coated water pipes
- Non-dietary sources assessed include dust, articles to be mouthed, dental materials, transfer from hands to food after touching thermal paper, rattles, pacifiers, body lotion

Key findings

1) **Diet is the main source of BPA exposure which however is extremely low**
2) **Thermal paper is the second source of total BPA exposure**
3) **Dental sealants / exposure via saliva is negligible**
4) **Biomonitoring studies confirm low exposure levels**
5) **Existence of unrecognised sources of exposure is unlikely**
6) **Specific scenarios and potential uncertainty are taken into account in the overall EFSA evaluation**

[1] For further details, please see p. 7 of this document

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1) Diet is the main source of BPA exposure which however is extremely low

Canned food is the main contributor, followed by meat and meat products as well as fish and other seafood from the non-canned sector. The exposure to BPA through diet is extremely low and in fact significantly lower than estimated by EFSA in its 2006 assessment. This is because a more detailed picture of food consumption patterns in Europe is now available, which allowed a considerable refinement of earlier exposure estimates.

- *„Diet was found to be the main source of exposure to BPA in all population groups (78-99%), but **modelled estimates were much lower than the estimates reported by EFSA in 2006.** In the previous assessment, high exposure was up to 5 300 ng/kg bw/day in toddlers and up to 11 000 ng/kg bw/day in infants aged 3 months, compared with the current estimates of up to 857 ng/kg bw/day for toddlers and up to 495 ng/kg bw/day for infants of 1-5 days.“*

- *“For infants and toddlers (aged 6 months-3 years) average exposure from the diet is estimated to amount to 375 nanograms per kilogram of body weight per day (ng/kg bw/day) whereas for the population above 18 years of age (including women of child-bearing age) the figure is up to 132 ng/kg bw/day. By comparison, **these estimates are less than 1% of the current Tolerable Daily Intake (TDI) for BPA (0.05 milligrams/kg bw/day) established by EFSA in 2006.”***

- *“In the 2006 opinion of EFSA a unique value of 5 µg/kg was considered for migration from tableware. The consumption of food in contact with tableware was extremely conservative, in particular for toddlers: 3 kg for a 60 kg adult (50 g/kg bw/day) and 2 kg for a 11 kg toddler (182 g/kg bw/day). **Estimated exposure from this source was therefore one order of magnitude higher as compared to the present assessment:** 250 ng/kg bw/day in adults and 900 ng/kg bw/day in toddlers.”*

- *„Systematic differences in BPA concentration between canned and non-canned food were observed in the large majority of food categories, with higher BPA-concentrations in the canned food.“*

These findings are consistent with data available from the US Food Drug Administration (FDA), although FDA focused only on dietary exposure and included exposure to baby bottles and canned infant formula, both applications which are no longer BPA-based. In Europe, *“according to the European Dietetic Food Industry Association (…) canned liquid infant formula is not offered in cans”.* In the US, based on the exposure estimates and recognizing the market changes for baby bottles and canned infant formula, FDA has very recently re-confirmed that BPA is safe for use in food contact packaging:

“… exposure to dietary BPA for infants, the population of most potential concern, is less than previously estimated. The initial FDA exposure estimates were 0.185 micrograms/kg-bw/day for adults and 2.42 micrograms/kg-bw/day for infants. The new estimate of average dietary exposure, based on increased data collection, is 0.2-0.4 micrograms/kg-bw/day for infants and 0.1-0.2 micrograms/kg-bw/day for children and adults.” (http://www.regulations.gov/#!documentDetail;D=FDA-2010-N-0100-0009)

March 2013: “FDA’s current assessment is that BPA is safe at the very low levels that occur in some foods. This assessment is based on review by FDA scientists of hundreds of studies including the latest findings from new studies initiated by the agency.” http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm.

	FDA average **dietary** exposure **modeling**	**EFSA** average **total** exposure, **modeling** (table 31)	**EFSA** average **total** exposure, **urine biomonitoring** (table 31)
infants	0.2-0.4 micrograms/kg-bw/day (incl. polycarbonate baby bottles and epoxy coated infant formula cans)	0.038 – 0.383 micrograms/kg-bw/day	< 0.01 – 0.02 micrograms/kg-bw/day
children	0.1-0.2 micrograms/kg-bw/day	0.314 micrograms/kg-bw/day	0.049 – 0.107 micrograms/kg-bw/day
adults	0.1-0.2 micrograms/kg-bw/day	0.145 – 0.152 micrograms/kg-bw/day	0.039 micrograms/kg-bw/day

In its Q&A related to the draft exposure report, EFSA states:

- ***"What are the main findings of EFSA´s draft assessment of exposure to BPA?***
  EFSA's scientific experts provisionally concluded that for all population groups considered diet is the major source of exposure to BPA in the European Union. For population groups above three years of age thermal paper was the second most important source of BPA exposure after the diet, potentially accounting for up to 15% of total exposure for some population groups. Total exposure for all population groups is at most a small fraction of the current Tolerable Daily Intake (TDI) for BPA of 0.05 mg/kg bw established by EFSA in 2006 (see Question 4 *above). For example,* ***estimated dietary exposure for adults (including women of child-bearing age)*** *of up to 132 ng/kg bw/day* ***is approximately 11 times lower than that estimated in 2006 and amounts to less than 1% of the current TDI."***

- ***"Why are the estimates of dietary exposure from 2006 and 2013 so different?***
  In 2006, estimates of dietary exposure to BPA were far higher due to the lack of data at that time, which led to very conservative assumptions about possible BPA levels in food and drinks. Following a call for data in 2012, EFSA reviewed over 2,500 samples to assess BPA levels in a range of food categories. In addition, EFSA can now call on its Comprehensive European Food Consumption Database, first made available in 2010, for a more detailed picture of food consumption patterns in Europe than that which existed at the time of EFSA's previous exposure assessment of BPA. ***These new data have led to a considerable refinement of exposure estimates compared to 2006."***

- ***"What are the other key findings?***

  - *Scientists found dietary exposure to BPA to be the highest among children aged three to ten. This is explained by their higher food consumption on a body weight basis.*
  - *Total exposure for bottle-fed infants aged 0-6 months was particularly low (38 ng/kg bw/day). This is likely to be the result of the European Union's decision in 2011 to ban BPA from baby bottles.*
  - *Canned food and non-canned meat and meat products were identified as major contributors to dietary BPA exposure for all age groups. Canned food is known to be a dietary source of BPA because of the substance's use in the lining of cans. BPA might be present in meat and meat products through contact with packaging, processing equipment or through other forms of contamination (e.g. environment, feed). However, EFSA's experts have not seen any firm scientific evidence to support this."*

EFSA´s non-dietary exposure assessment included inhalation (indoor air, dust), ingestion (dust, toys and other articles to be mouthed, dental materials, transfer from hands to food after touching thermal paper) and dermal absorption (thermal paper, cosmetics in the form of body lotions).

2) Thermal paper identified as second source of total BPA exposure

"*Thermal paper was the second source of total exposure in all population groups above 3 years of age whereas exposure to BPA from thermal paper was considered to be negligible under the age of 3. The contribution to the total average exposure ranged between 7 and 15 %, taking into account all population groups above 3 years of age. The uncertainty around the estimate of exposure to BPA from thermal paper was considerably higher than that around dietary exposure.*

The CEF Panel is aware of an ***ongoing study on BPA pharmacokinetic and dermal exposure*** *in cashiers sponsored by the National Institute of Environmental Health Sciences (NIEHS) under the National Toxicology Program (NTP).* ***The results of this study will be considered by the CEF Panel as*** *they will be* ***an additional source of information*** *regarding the absorption of BPA from thermal paper."*

In its Q&A related to the draft exposure report, EFSA states:

"Is exposure to BPA from thermal paper a concern?
For all population groups above three years of age thermal paper was the second most important source of BPA exposure after the diet, potentially accounting for up to 15% of total exposure in some population groups. For average and high consumers in the 10-18 year age bracket (the group with the highest level of exposure based on body weight) ***this amounts to less than 0.1% and 0.5%, respectively, of the current TDI of 0.05 mg/kg bw.*** *However, due to uncertainties around the estimates of exposure, EFSA's experts consider more data are needed (especially related to BPA skin absorption and cash receipt handling habits) to perform a more refined estimate of exposure through this source."*

3) Dental sealants / exposure via saliva is negligible

"Since the baseline level is very low (the level before treatment is the same as about 24h after treatment), it could be argued whether this value really represents exposure to dental material. Therefore, exposure to dental materials was not included in the total exposure calculation."

4) Biomonitoring studies confirm low exposure levels

- Biomonitoring study results „*can be directly related to the dose which has actually entered the systemic circulation. A number of sensitive analytical methods have been developed to measure low concentrations including trace amounts of BPA in biological samples such as urine and blood (…) Yet the detection and quantification of BPA-related biomarkers in these matrices is per se not sufficient to arrive at reliable and valid estimates of exposure.* ***What is additionally required*** *to interpret BPA biomonitoring data and to translate these data into daily exposure estimates* ***is a detailed understanding of the potential analytical/methodological pitfalls*** *(see Appendix I)* ***and of the toxicokinetics of BPA"****.*

- *(…) BPA is rapidly removed from circulation via conjugation* [metabolisation] *and subsequent renal excretion (…). Toxicokinetic studies with oral administration of stable isotope-labelled (deuterated)* [marked] *BPA in humans have shown that BPA is almost completely excreted in*

urine in the conjugated form and that the elimination process is essentially complete within 24 h after exposure (…). ***Urine is therefore the matrix of choice for biomonitoring, and the urinary concentration of total (unconjugated plus conjugated) BPA is the biomarker of choice to estimate BPA exposure*** *(…). Information on the presence and concentration of unconjugated and total BPA in serum* [blood] *is useful, (…), in order to inform toxicological risk assessment. However, given the exposure in the ng/kg bw range, the high first-pass metabolism in the liver, and the elimination characteristics of BPA,* ***low serum*** **[blood]*concentrations of unconjugated and total BPA are to be expected*** *. In addition, it has been shown that* ***generally less than 1 % of total serum BPA is in the unconjugated*** *form after oral administration (…). Hence,* ***the detection of unconjugated serum BPA becomes an analytical challenge that is additionally complicated by contamination and the instability of BPA conjugates*** *….)*

- ***"For the European studies, the GM*** **[geometric mean]** ***of the total BPA concentrations is in general localised in the range between 1.1–3.6 µg/l (…), which is in agreement with the results of the large-sized North-American surveys NHANES and CHMS"***

- *"The detectability and concentration range of serum BPA is one of the most controversially discussed topics in the scientific literature on BPA (Dekant and Völkel, 2008; Vandenberg et al., 2010; Hengstler et al., 2011; Teeguarden et al., 2012; vom Saal et al., 2012; Vandenberg et al., 2013)."*

- *(…) "the Panel noted that even peak serum concentrations would be expected to be below 0.1 µg/l for the toxicologically relevant, unconjugated BPA.* ***The Panel considered that detection of such low concentrations of unconjugated BPA without interferences from contamination is an analytical challenge.*** *However, a significant uptake through the dermal route would increase the proportion of unconjugated BPA in the total BPA serum concentration, so that higher peak serum concentrations of unconjugated BPA are to be expected****. In a general population having average-to-high daily BPA uptakes of 50–1 000 ng/kg bw/day, serum concentrations of conjugated or total BPA would only infrequently be expected to exceed a level of 1 µg/l."***

- *"Given the findings of the controlled exposure study in human volunteers (Teeguarden et al., 2011), with unconjugated BPA being undetectable and total BPA being detectable in only 27 % of the 320 serum samples collected from the 20 volunteers,* ***the Panel considered detection rates close to 100 % for conjugated and/or total BPA in serum, as an implausible result. High detection rates for unconjugated BPA in serum are even more implausible."***

- With reference to studies that *"appear to indicate (i) that* ***the detection of total BPA in a sample made the parallel detection of unconjugated BPA very likely, and (ii) that all serum BPA (if detected) was essentially unconjugated. The Panel considered that this is extremely unlikely*** *given the findings of the toxicokinetic studies mentioned above, in which stable isotope-labelled BPA (deuterated) was administered to avoid any interference by possible contamination of samples with free BPA from environmental sources and medical devices. "*

- *"To summarise,* ***the estimates for the average total exposure as obtained by modelling and biomonitoring methods agree with each other within an order of magnitude.*** *More specifically, the modelling approach gave estimates which were approximately 4-fold higher (38–383 ng/kg bw/day vs. <10–107 ng/kg bw/day) than those obtained by the biomonitoring approach."*

5) Existence of unrecognised sources of exposure is unlikely
„Biomonitoring estimates based on urinary BPA concentrations are in good agreement with modelled BPA exposures from all sources, suggesting that no major exposure sources have been missed for the modelled exposure assessment."

6) Specific scenarios and potential uncertainty are taken into account in the overall EFSA evaluation

For each individual exposure scenario, EFSA describes in explicit details the assumptions made, their reasoning for doing so, the values taken for calculation and the specific age-/use-related handling conditions etc.. and generally takes the more conservative/worst case scenario. e.g.: kettles (page 45) or mouthed articles (pacifier, toys - page 59).

- *"Exposure to BPA from further sources was assessed in **specific populations groups** or in consumers with specific consumption patterns. The aim was to identify possible additional sources of exposure to BPA which could lead to levels of exposure significantly higher than those estimated for the general population (….)**In most cases, exposure from these further sources was less than 20 % of the estimated high exposure for the age class.** In a few cases, exposure from these further sources was higher. It was the case for infants fed using old PC baby bottles and infants living in buildings with old water pipes repaired with epoxy resins and fed with formula reconstituted with tap water."*

Uncertainties affecting the exposure assessment were evaluated systematically by EFSA:

- *„in order to be protective for the whole of Europe, international calculations should provide exposure estimates that are equal to or greater "than the best estimates carried out at national levels" (…)*
- *"Uncertainty in the assessment of total exposure was therefore analysed in detail for the four following groups: women of child bearing age, toddlers, breastfed infants in the first few days of life and formula-fed infants"*
- *"Modelling and biomonitoring provide independent estimates of the real high exposure."*
- *"Overall the Panel concludes that all values covered by the combined uncertainty intervals for the two estimates remain plausible."(…)*
- *"The uncertainty around the estimates of dietary exposure based on the EFSA comprehensive database was judged as relatively low."*

EFSA also put their findings into context with other existing exposure assessments, undertaken by the WHO/FAO, the French ANSES, the Belgian authorities and in the framework of the European Commission -funded FACET project. In this respect EFSA concludes:

- *„Exposure to BPA carried out by the FAO/WHO Expert Meeting on Bisphenol A are far higher than others due to the use of a conservative model diet*
- *Other exposure estimates are in the same order of magnitude*
- *Only EFSA and ANSES estimated exposure to BPA by summing up different sources*
- *Only EFSA considered all routes; whereas only diet and thermal paper were considered by ANSES*
- *Exposure from canned food is one of the major contributors to dietary exposure to BPA for all age groups*
- *Exposure levels are higher in children aged over 3 years"*

Next steps

- Based on the exposure assessment report, EFSA will release a second opinion on characterization of human health risks
- The second opinion will also be open for public consultation possibly in early 2014 with a view to release the final opinion in the 2nd quarter of 2014

Data base

- Literature
  - Scientific studies published between 2006 (last full EFSA assessment of BPA) and December 2012
  - EFSA comprehensive European Food Consumption Database with consumption data from 32 different dietary surveys carried out in 22 Member States and covering more than 67 000 individuals
  - Reference to "important toxicological studies on BPA to be published shortly" and pharmacokinetic and dermal exposure studies currently undertaken by the US authorities, which will be included into the assessment on characterization of human health risks

- Inputs from previous EFSA call for data (Appendix III):
  Contributions were received from the following European countries: France, Ireland, Spain, Germany, Switzerland, Finland, Norway, the UK.
- The consumption data covered
  - canned food categories: 638 samples, 342 from literature, 296 from the call for data
  - non-canned food categories: 1.883 samples, 246 from literature, 1.637 from the call, 88% of which came from France (1.433 samples)

  Contributions from non-European countries were provided by Singapore, Japan, Korea, Canada, the USA, FAO/WHO

- Literature quality table for occurrence of BPA in food (Appendix IX)
  containing ca. 240 studies, there-of ca. 35 included in the basis of the assessment, rest excluded mainly because of non-European database but used as reference/comparison to set into context

- Literature quality table for methodology used in biomonitoring studies (Appendix I)
  with list of quality criteria (recovery, repeatability, limit of detection/limit of quantification, selectivity of method, consideration of background contamination, use of appropriate matrix, analytical method, extraction and migration measuring methods, instrumental methods)

Method

- Assessment of different age groups: 0-5 days, up to 3 months, 4-6 months, 6-12 months, up to 3 years, 3-10 years, 10-18 years, 18-45 years, 45-65 years, over 65 years

- Assessment of 17 food groups, based on the type of packaging (canned and non-canned)

- Exposure modeling calculations, urinary biomonitoring data, comparison.
  Total exposure to BPA was assessed via two different procedures independent from each other: one was based on exposure modelling calculations and the other on urinary biomonitoring data. Exposure modelling involves the assessment of exposure to BPA through food and non-food sources (thermal paper, air, dust, toys, cosmetics, dental sealants) and routes (diet, inhalation and skin contact) in the EU population. This method allows for the estimation of exposure from all sources which could be identified and quantified individually. Urinary biomonitoring data (levels of BPA found in the urine) were used to cross-check/confirm the Panel's estimates of overall BPA exposure and to ensure that no major source of exposure was missed.

- Absorption factors used: 1 for oral, 1 for inhalative, and 0.3 for dermal

- For the calculation of total exposure the contributions of dust, toys, indoor air, thermal paper and cosmetics were summed up for the respective age groups.