

## **Minutes of EFSA-ANSES Expert Meeting on Bisphenol A (BPA)**

### **Art. 30 Regulation (EC) No 178/2002**

**Held on 3 December 2014, Paris (France)**

#### **Participants**

- **ANSES Experts**  
Claude Emond by phone (Chair of ED-WG)  
Luc Belzunces (Member ED-WG)  
Martine Applanat (Member ED-WG)
  
- **ANSES Staff**  
Dominique Gombert (Director of Risk Assessment Department)  
Jean-Nicolas Ormsby (Deputy-Director of Risk Assessment Department)  
  
Gilles Rivière (Head of Risk Assessment of Chemicals in Food Products Unit)  
Christophe Rousselle (Head of Hazard and Risk Assessment of Chemicals Unit)
  
- **EFSA Experts**  
Vittorio Silano (Chair CEF Panel)  
Ralph Pirow (Member CEF Working Group BPA Toxicology)  
Detlef Woelfle (Vice-chair CEF Panel, Member CEF Working Group on BPA Toxicology)
  
- **EFSA Staff**  
Juliane Kleiner (Acting Head of Regulated Products Department)  
Claudia Heppner (Head of Food Ingredient and Packaging Unit)  
Anna F. Castoldi (Senior Scientific Officer Food Ingredient and Packaging Unit)

#### **Background**

ANSES received on 20 November 2014 the version of the draft opinion on Bisphenol A (BPA) which was distributed to the members of the CEF Panel for discussion at the 51<sup>st</sup> CEF Plenary meeting held on 25-27 November 2014. It was noted that this meeting will not be recorded. The minutes will be taken jointly by Mr Jean-Nicolas Ormsby and Ms Claudia Heppner and the aim is to agree on the key points at the end of the meeting. The minutes of the meeting should be agreed one week after the meeting.

#### **1. Opening and objectives of the meeting**

The chairs (Juliane Kleiner and Dominique Gombert) welcomed the participants, who shortly introduced themselves. Apologies for absence were received from Trine Husøy (Member CEF Panel and Chair CEF Working Group BPA Toxicology). The meeting was called under Art. 30 of Regulation (EC) No 178/2002. The chairs presented the objectives of the meeting which are: to outline and discuss the respective approaches of ANSES and EFSA to the risk assessment of BPA in order to possibly identify potential sources of divergences and if divergences are identified, to try to reconcile them, or alternatively to explore how to effectively explain them. In addition, the participants agreed on the following procedural aspects: a joint report in form of minutes will be published together with the EFSA's CEF Panel opinion on BPA. The publication is foreseen for 20 January 2015. It was agreed that DG SANTE will receive the report earlier. EFSA's BPA opinion is scheduled for possible adoption at the 52<sup>nd</sup> CEF Plenary meeting which will take place from 10 to 11 December 2014. In case substantial changes to the opinion occur at the plenary meeting, another meeting between

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EFSA and ANSES is needed. ANSES informed the participants on ECHA's ongoing activities and timelines related to BPA. ANSES submitted a dossier to ECHA where a restriction of BPA in thermal paper is proposed. As ECHA's RAC committee has to come to a final conclusion by March 2015, ECHA would appreciate receiving access to EFSA's CEF Panel opinion on BPA, particularly as an *ad hoc* meeting with different stakeholders is scheduled on 29 January 2015.

## 2. Exposure assessment of BPA

### EFSA presentation

Anna Federica Castoldi presented the terms of reference of the self-task of the CEF Panel i) to assess the risks to public health related to exposure to BPA from foodstuffs, ii) to evaluate the toxicity of BPA for humans (general population and subgroups of the population), and iii) to carry out an exposure assessment considering BPA from dietary and non-dietary sources. EFSA considered chronic exposure to different sources (diet, thermal paper, air, dust, toys, cosmetics) and routes (dietary, oral non-dietary, dermal, inhalation). As dose-metric, the external exposure, the internal exposure to total BPA and the aggregated exposure were considered. Due to route- and source-dependency different absorption fractions were applied: ingestion: 1 (100%), inhalation: 1 (100%) and dermal: 0.1 (10%) for thermal paper and 0.5 (50%) for cosmetics. A plausibility check was carried out: internal exposure to total BPA levels (from all sources by means of forward modelling) should be comparable to urinary total BPA levels from all sources, i.e. data from biomonitoring studies ("backward modelling approach"). For the aggregated exposure, BPA contributions from oral and dermal exposures were converted into a toxicologically relevant dose metric, i.e. the area under the curve for the serum concentration of unconjugated BPA, by means of PBPK modelling. External dermal exposures (thermal paper and cosmetics) were converted into oral human equivalent doses (HED) and added to the external oral exposures (diet, house dust). Age groups with highest estimated dietary intake of total BPA were infants (> 6 mo) and toddlers (1-3 yrs) with an average exposure to BPA of 375 ng/kg bw per day and high exposure to BPA of 857 ng/kg bw per day. The main dietary BPA sources were canned food and non-canned meat and meat products. Analytical/experimental BPA concentration data in and from non-food sources were combined with behaviour patterns (e.g. number of fingers handling conditions of thermal paper) to estimate non-dietary exposure. These were limited data and many assumptions were made which led to a high uncertainty. The main non-food source is thermal paper for children (3-10 yrs), adolescents and adults with average exposure estimates of 69, 94 and 59 ng/kg bw per day, respectively, and high exposure estimates of 550, 863 and 542 ng/kg bw per day, respectively. Based on the comments received during the public consultation on part I of the draft BPA opinion (exposure assessment) the following revisions were carried out: no major changes in the external and internal exposure estimates; the methodology is better outlined; the dermal absorption fraction was reduced from 0.3 (30%) to 0.1 (10%), inhalation exposure is now 3-4 fold lower, dust ingestion rate was also revised, the latter two changes in line with ANSES' comments during the public consultation. External exposure to BPA via different routes is not anymore summed up. The sum of exposure from various routes is now only provided for internal exposure to total BPA and for aggregated exposure to unconjugated BPA. Revised exposure estimates for babies were calculated.

Following questions were asked:

- Was sedimented dust in inhalation figures included? This needs to be clarified by EFSA.
- The absorption factor of 0.5 for cosmetics was questioned and a value of 1 was proposed in line with the default value used by the SCSS in the absence of data. EFSA explained the value could lay between a range and has thus selected 0.5. Participants agreed that a factor of 0.5 or 1 would not change the overall exposure figures very much.
- No distinction between sexes were made for cosmetics. Indeed EFSA used the highest amount of cosmetic for the whole body, and thus is very conservative.
- Dermal absorption factor of 10% - would this need specification on the length of the exposure? Clarification on this is given part II of appendices. A key study was chosen and the dermal absorption was included in the PBPK modelling.

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## ANSES presentation

Gilles Rivière presented the exposure estimates of the ANSES BPA risk assessment from 2013. Dietary exposure was based on 1320 samples (from 2007-2009) from the French total diet study which have been re-analysed for BPA. In addition, 336 samples of bottled and tap water were considered. A probabilistic approach was used for the exposure estimates. ANSES used three different age groups, whereas EFSA assessed all age groups. It was noted that no big differences in the dietary exposure estimates carried out by both organisations were found (for details see slide 3). In addition, ANSES informed on its ongoing activities to elucidate the findings of elevated levels of unconjugated BPA in products of animal origin (app. 20% of the overall dietary exposure). In a 1<sup>st</sup> step, sampling of products of animal origin (about 300 samples) will be conducted to determine if the current contamination levels are comparable with the results from 2007-2009. EFSA informed ANSES that similar activities are planned in this area. ANSES will explore if the sampling plan can be shared with EFSA to avoid duplication of work and possibly initiate complementary work.

Non-dietary exposure from indoor and outdoor air and house dust was considered in the exposure assessment and expressed as internal exposure (cosmetic products were not considered). For the scenario thermal paper high uncertainties were identified and a separate scenario using probabilistic modelling was developed. The internal BPA levels in the general adult population exposed via thermal paper were estimated to be 54.2 ng of total (unconjugated plus conjugated) BPA /kg bw per day (high exposure scenario for 18-45y females) by EFSA and 80 ng of unconjugated BPA /kg bw per day by ANSES (this is the 95<sup>th</sup> percentile of the internal dose distribution for consumer exposure to BPA in thermal paper).

The following questions were asked:

- What were the assumptions related to dermal percutaneous absorption flux based on a dynamic transfer of a substance across the skin (unit e.g. ng/cm<sup>2</sup>/min)? ANSES explained that the rationale related to the scenarios was taken from datasets available in public literature;
- ANSES compared biomonitoring data with the modelling data – how was the fit? The modelled data for consumer exposure were at the lower range of the measured biomonitoring data, but did not take into account dietary exposure.

## Conclusions

- Although both organisations used different methodologies (deterministic vs. probabilistic approach) to calculate the exposure to BPA and different assumptions had to be made especially for the non-dietary exposure scenario for the lack of data, resulting in high uncertainties, no major differences in the exposure estimates were identified.
- Possible cooperation related to the occurrence of BPA in animal products was proposed.

## 3. Hazard assessment and risk characterisation of BPA

### EFSA presentation

Anna Federica Castoldi presented the main changes on the hazard identification, the hazard characterisation including the respective uncertainty analysis, the derivation of the temporary Tolerable Daily Intake (t-TDI), the risk characterisation and the draft conclusions after having taken into account the comments received during the public consultation on part II of the draft BPA opinion. No changes occurred in relation to the hazard identification using the Weight of Evidence approach (WoE), this means the three endpoints liver and kidney weight changes in mice (considered as general toxicological adverse effects) and mammary gland proliferation were considered as “likely effects”. The other endpoints such as neurotoxicity, reprotoxicity (below a cut off oral equivalent dose of 3.6 mg/kg bw per day), immune (classified from **As Likely As Not** (ALAN) to likely, cardiovascular, and metabolic toxicity), genotoxicity and carcinogenicity were also assessed, however, only the three endpoints which were considered as fully “likely effects” were brought forward for hazard characterisation, and benchmark dose modelling was carried out for these three endpoints. In addition, during the public consultation process the individual data on kidney weight for mice were submitted by Industry which allowed a re-analysis of the Tyl et al., 2008 study for relative kidney

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weight instead of absolute organ weight (as used before public consultation). This means a BMDL<sub>10</sub> of 8960 µg/kg bw per day was calculated as compared to the previously determined BMDL<sub>10</sub> of 3633-3887 µg/kg bw per day. The individual data for the toxicokinetic study in adult mice with oral administration were made available to EFSA by FDA/NTP, which made it possible to arrive at a more realistic estimate of the internal dose metrics (i.e. the area under the curve for the serum concentration of unconjugated BPA). These data were used to determine a revised Human-Equivalent Dosimetric Factor (HEDF) of 0.068 (vs 0.03 before) for BPA which was used for the adult mice. No changes were made for the HEDF for infants. By multiplying the BMDL<sub>10</sub> of 8960 µg/kg bw per day by the revised HEDF of 0.068, a revised reference point for HED of 609 µg/kg bw per day (vs 113 µg/kg bw per day before) was calculated. This means increased kidney weight in mice was used as the critical endpoint for establishing a TDI (no changes compared to before). A new approach to take into account the uncertainties for mammary gland proliferation (classified as “likely effect”) but also the endpoints such as immunotoxicity (classified from **As Likely As Not** (ALAN) to likely) and all the other endpoints, i.e. reproductive, neurobehavioral, and metabolic effects were included in the uncertainty analysis. The uncertainty analysis comprised a 3-step approach<sup>1</sup> to judge if an extra factor is needed for the establishment of the TDI. The new uncertainty approach resulted in a re-open of the WoE table based on expert judgement. An example of the visualisation of an “uncertainty plot” for the effects of BPA exposure on the proliferative changes in the mammary gland was given. A summary of expert judgments of the likelihood that BPA has the inherent ability to cause effects in animals in different dose intervals and their human relevance (if they occur in animals) and adversity (if they occur in humans) was outlined. Based on the uncertainty analysis, an extra factor of 6 was proposed to cover for these uncertainties which resulted in an overall uncertainty factor (UF) of 150 (vs 25 before). Based on the HED of 609 µg/kg bw per day and the UF of 150 a revised t-TDI of 4 µg/kg bw per day (vs 5 µg/kg bw per day) was established. In the risk characterisation oral exposure from dietary vs non-dietary sources were taken into account. All age groups including the age groups with highest estimated dietary intake of total BPA (infants and toddlers with average exposure to BPA of 375 ng/kg bw per day and high exposure to BPA of 857 ng/kg bw per day, respectively) were more than 4-fold below the t-TDI of 4 µg/kg bw per day. Dermal dose expressed as equivalent oral dose for average and high exposure to thermal paper and/or cosmetics was calculated based on PBPK modelling. Due to limited data many assumptions had to be made leading to a high degree of uncertainty.

Concerning aggregated average dietary vs. average non dietary exposure, for all age groups the major contribution comes from the diet. The aggregated high dietary and high non-dietary (oral plus dermal) exposure was 1.258 µg/kg bw per day for children aged 3-10 years and 1.449 µg/kg bw per day for adolescents (10-17 years). In the latter group and under this high-high exposure scenario thermal paper contributed 73% of dietary-non-dietary aggregated exposure.

The overall draft conclusions are that for all age groups including infants and toddlers the estimates for high dietary exposure are more than 4-fold below the t-TDI of 4 µg/kg bw per day. Health concerns for BPA is low at the current level of exposure. These conclusions also apply to the offspring of mothers exposed during pregnancy and to the elderly.

Following questions were asked:

- Why did EFSA consider exposure to thermal paper from 3-10 years old? Data indicate that this group is exposed to BPA via thermal paper;
- More details on the uncertainty analysis including the time spent by experts was asked. EFSA explained that each Working Group expert carried out an independent analysis, then the outcome was presented to group and after discussions experts were given to possibility to revise their assessment if wanted. The time to conduct the analysis varied, depending on whether or not the experts had already gained experience with this procedure. For the mammary gland, which was done first, the uncertainty assessment took around one day. For the other endpoints much less time was needed.
- Editorial remarks on “uncertainty plot” was given.

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<sup>1</sup> (i) to judge the likelihood that BPA exposure is associated with a certain outcome in animals at each dose interval, for 1 or more combination of animal species, exposure period and measurement time;  
(ii) to judge the relevance of this effect to humans  
(iii) to judge its adversity in humans, if it occurs

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## ANSES presentation

Christophe Rousselle supported by Luc Belzunces and Martine Applanat presented the toxicological assessment including hazard identification, the methodology used to identify key studies which were selected as point of departure, the derivation of internal toxicological values and the risk characterisation. In addition, ongoing work on BPA was outlined. It was noted that both organisations used similar terminology to classify the hazard. The following endpoints, based on recognised effects in animals were used as endpoints for the risk characterisation: effects on female reproductive system, effects on the brain, effects on metabolism and obesity, and effects on mammary gland. An overview of EFSA's conclusions "as likely as not" was given on these endpoints (female reproductive system, central nervous system, metabolism and obesity) which were not selected in the hazard characterisation by EFSA. The two key studies selected by ANSES related to effects on brain and behaviour (Xu et al., 2010) and effects on mammary glands (Moral et al., 2008) have also been appraised by EFSA. A detailed discussion followed related to EFSA's assessment of these studies' weaknesses. As regards mammary gland it was pointed out that the NTP 2013 study report (now published as Delclos et al., 2014) was not available to ANSES, when their BPA risk assessment was conducted and ANSES experts raised questions as to the quality of this study. EFSA pointed out that the overall database concerning BPA effects on mammary gland proliferation (and also other toxicological endpoints) was considered in the overall uncertainty analysis that led to determine the extra factor for the derivation of the t-TDI. Thus, this individual study on mammary gland did not have *per se* a high impact on the setting of the t-TDI and overall outcome of EFSA's risk assessment. ANSES selected as the more sensitive endpoints the effects on brain and mammary gland and outlined the derivation of an internal point of departure (application of an oral bioavailability factor of 3% of unconjugated BPA to derive internal NOAELs) from these two studies/endpoints as well as the derivation of the internal toxicological values. Internal toxicological values were also derived for the effects on the female reproductive system and the metabolism. An additional UF of 3 to take into account residual uncertainties was added to the default UF of 100, resulting in an overall UF of 300. Based on this approach internal toxicological values by application of a safety factor of 300 to the internal NOAELs were 0.005 µg/kg bw per day for brain and behaviour and 0.0025 µg/kg bw per day for mammary gland. In addition, it was noted that ANSES considered the risk only for pregnant women among consumers and workers, whereas EFSA considered the whole population and subgroups of the population. Claude Emond presented details on the development of a new PBPK model for unconjugated and conjugated BPA which would allow to take into account data from all species to improve the confidence in the model.

The following questions were asked:

- What would be a reasonable level of exposure for setting a TDI with the new model?
- How was the dermal uptake modelled? It was agreed that both organisations used the 1<sup>st</sup> order kinetics for dermal absorption, so no difference in the modelling part were identified.
- Claude Emond pointed out that if different PBPK models are used, it should be checked that both models predict the same surrogate profile concentration used. EFSA responded that two different PBPK models were used in the EFSA opinion, that the differences in model predictions were quantified, and the impact of these differences is evaluated in the overall uncertainty assessment.

Discussions focused on the questions why the organisations did not consider the same effects as likely and why not the same studies and effects were selected as reference point/point of departure.

## Conclusions

- ANSES published the report on BPA in 2013 and considered studies up to 2012, whereas EFSA considered in its current risk assessment all the studies up to December 2012 and some additional relevant studies up to March 2014 (closing date of public consultation of Part II)
- Both organisations considered that there is not a robust epidemiological study available which could be used as a point of departure.
- Different approaches and methodologies were developed to select key studies and reference points to assess the risks to public health related to exposure to BPA.

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- ANSES based the hazard identification on a decision tree for the selection of key studies, whereas EFSA used a WoE approach to hazard identification. ANSES focused on studies investigating effects at doses below the NOAEL from the Tyl study used previously by EFSA to derive the TDI (5 mg/kg bw/d)
  - ANSES selected four endpoints (brain, metabolism/obesity, female reproductive system mammary gland) based on specific studies reporting adverse effects (e.g. Xu et al., 2010 for neurotoxicity and Moral et al., 2008 for mammary gland effects), whereas EFSA considered for each endpoint both the negative and positive evidence as a whole, via the weight of evidence approach. EFSA selected effects on liver and kidney weight in mice (Tyl et al., 2008) and on mammary gland as reference endpoints. The in vivo data on mammary gland, although indicating “likely” effects, were not suitable to derive a reference point due to the lack of dose responses in most studies. ANSES did not examine the changes in liver or kidney weight reported in the study by Tyl et al., 2008, as these effects were already considered in the TDI derived previously by EFSA for BPA.
  - EFSA and ANSES agreed that BPA effects on mammary gland are critical effects for the safety assessment of BPA.
  - EFSA considers the database as regards neurotoxicity as insufficient to draw conclusions on this effect, whereas ANSES considered the database as sufficient to draw conclusions.
  - Both organisations agreed that the differences related to the hazard characterisation and selection of reference point/point of departure are mainly related to expert judgement on whether a scientific conclusion can be drawn from a specific study to derive a health based guidance value and on the relevance (and adversity) of specific outcomes in animals to humans.
  - ANSES and EFSA tried to accommodate uncertainties identified in the toxicological database, however, different methodological approaches were used.

## Outlook

- Both ANSES and EFSA will continue their work on BPA and will ensure close co-operation of forthcoming activities of their respective scientific panels.
- Development of a review protocol for BPA hazard assessment focusing on the endpoints of toxicity that are the subject of more uncertainties. This protocol should encompass the whole process of gathering, selecting and appraising the evidence. Possible collaboration with Member States can be foreseen by openly discussing this review protocol in a dedicated Stakeholder meeting to be held before the protocol implementation, or by undertaking a public consultation on it. This would certainly be beneficial in terms of agreeing on the review methodology and on the criteria chosen to appraise the evidence.
- Research needs were identified to clarify the origin of high levels of BPA in uncanned animal products such as meat and fish. ANSES has some ongoing analyses on a larger number of French samples. EFSA would like to support research in this area also considering the European perspective.
- Any new exposure data resulting from on-going projects will be exchanged.

## Concluding remarks

The chairs thanked all participants for their availability and contributions. In case both organisations will be tasked to assess BPA again in the near future a close co-operation at the start of the risk assessment process is essential.