

SCIENTIFIC OPINION

Statement on the ANSES reports on bisphenol A¹

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

EFSA has been asked to provide scientific advice in relation to possible divergences between the conclusions of the EFSA Scientific Opinion on Bisphenol A of September 2010 and those in the ANSES reports on BPA published in September 2011. The EFSA CEF Panel has analysed whether the ANSES report "Effets sanitaires du bisphénol A" contains any elements that would necessitate a revision of the EFSA opinion. The approach of the ANSES report is that of hazard identification, comprising also elements which could be relevant for the safety assessment of non-dietary exposure to BPA, whereas the EFSA opinion of 2010 addresses the assessment of risk from dietary exposure to BPA. This is the main reason for divergences between the ANSES and EFSA conclusions on BPA. The Panel overall considers that the information in the ANSES report does not change the views that the Panel expressed in 2010. To further investigate the divergences between the conclusions of ANSES in 2011 and those of EFSA in 2010 and to identify the relevant uncertainties in the data, the CEF Panel has undertaken a preliminary review of the new literature emerging on BPA. For most endpoints, the Panel considers that there is no new information that would change the views of the Panel of 2010. In 2010 the Panel noted that some studies conducted on developing animals suggest certain BPA-related effects which were not sufficiently convincing to use as pivotal effects for risk assessment, but which the Panel considered could be of possible toxicological relevance. Since then, additional studies related to these effects have become available, indicating effects of BPA in rodents at dose levels below the current NOAEL of 5 mg/kg bw/day. Uncertainties regarding the relevance to humans of these toxicological effects remain to be clarified. The Panel would need more time to review in depth these new studies. The Panel will reconsider its opinion following further evaluations of new studies and of new data from ongoing low dose studies.

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KEY WORDS

Bisphenol A, BPA, CAS No. 00080-05-7, risk assessment, TDI, low dose toxicity studies

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TABLE OF CONTENTS

Summary	1
Table of contents	2
Background as provided by the European Commission.....	3
Terms of reference as provided by the European Commission ⁴	3
Evaluation.....	4
1. Introduction	4
2. Analysis of the ANSES report on the health effects of Bisphenol A	4
3. Evaluation of the new literature.....	6
Conclusions	6
References	8
Abbreviations	10

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION⁴

On 27 September 2011 the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) published two reports on Bisphenol A.

In the report "Effets sanitaires du bisphénol A" ANSES concludes that health effects have been proven in animals and suspected in humans, even at low levels of exposure that are below current regulatory thresholds. On the basis of these findings it recommends no exposure to Bisphenol A of infants, young children, pregnant and breastfeeding women which were identified by ANSES as the most susceptible populations.

On 23 September 2010 EFSA adopted its Scientific Opinion on Bisphenol A containing:

- an evaluation of a study investigating its neuro-developmental toxicity
- a review of recent scientific literature on its toxicity and
- an advice on the Danish risk assessment of Bisphenol A in which EFSA confirms the tolerable daily intake of 0.05 mg Bisphenol A per kg body weight per day.

There may be divergences between the conclusions of ANSES and EFSA in these reports.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION⁴

On 13 October 2011 the European Commission asked EFSA to provide scientific advice on the ANSES report "Effets sanitaires du bisphénol A" in relation to possible divergences between the conclusions of this report and those of the latest EFSA Scientific Opinion on Bisphenol A of 2010. The European Commission asks EFSA to analyse if the two ANSES reports contain any elements that would necessitate a revision of the EFSA opinion.

If appropriate, on the basis of the analysis of the reports, EFSA is invited to liaise with ANSES in order to either resolve the divergences or to prepare a joint document clarifying the contentious scientific issues and identifying the relevant uncertainties in the data.

EFSA should confirm that it is following up this issue and that it will provide a scientific advice by 15 October 2011⁵.

⁴ This text was adapted from a letter received from Commission on 5 October 2011.

⁵ The deadline was agreed with Commission and extended to 30 November 2011.

EVALUATION

1. Introduction

On 27 September 2011 the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) published two reports on Bisphenol A (BPA), one related to the health effects associated with exposure to BPA (ANSES, 2011a) and the other one concerning its uses (ANSES, 2011b). The ANSES report on the uses of BPA (ANSES, 2011b) has been identified to lie outside the scope of the EFSA opinion of 2010. In the report "Effets sanitaires du bisphénol A" ANSES (2011a) concludes that health effects have been proven in animals and suspected in humans, even at low levels of exposure that are below current regulatory thresholds. On the basis of these findings it recommends no exposure to BPA of infants, young children, pregnant and breastfeeding women which they identified as most susceptible populations.

In 2006, EFSA set a Tolerable Daily Intake (TDI) for BPA, of 0.05 mg BPA/kg body weight (bw)/day. The TDI was based on a No-Observed-Adverse-Effect-Level (NOAEL) of 5 mg/kg bw/day, identified in two multi-generation reproductive toxicity studies in rodents, where the critical effects were changes in body and organ weights in adult and offspring rats and liver effects in adult mice, respectively (EFSA, 2006). This TDI was set to protect the human population for life-time exposure, including sensitive groups such as pregnant and lactating women, infants (0-12 months) and young children (12-36 months). In 2008, EFSA reaffirmed this TDI, concluding that age-dependent toxicokinetics differences of BPA in animals and humans would have no implication for the default uncertainty factor of 100 and in turn for the TDI (EFSA, 2008).

In September 2010, the EFSA's Panel on food contact materials, enzymes, flavourings and processing aids (CEF) adopted a new scientific opinion on the risk assessment of BPA. The opinion globally addressed three mandates received from the European Commission: (i) to assess a dietary developmental neurotoxicity study on BPA in rats (Stump, 2009), (ii) a comprehensive review of the scientific literature published between January 2007 and July 2010 (this review included both GLP and non GLP-studies, academic as well as industry-funded studies) and (iii) an advice on the scientific risk assessment underlying the Danish ban of BPA in food contact materials for infants aged 0-3 years. Overall, the CEF Panel concluded that no new study had been identified that would call for a revision of the current TDI established by EFSA (2006). Based on all information on BPA toxicokinetics, the default uncertainty factor of 100 applied in the derivation of the TDI was regarded as conservative. However the Panel (2010) identified some toxicological effects in developing animals which need further consideration. In the opinion of 2010 a Panel member expressed a minority opinion.

On 5 October 2011 EFSA was asked to provide scientific advice to the EC in relation to possible divergences between the conclusions of the latest EFSA Scientific Opinion on Bisphenol A of 2010 and those in the ANSES reports. EFSA was in particular asked:

- to analyse if any elements in the report "Effets sanitaires du bisphénol A" would support the need for a revision of the EFSA opinion of 2010;
- to liaise with ANSES in order to either resolve the divergence or to prepare a joint document clarifying the contentious scientific issues and identifying the relevant uncertainties in the data.

2. Analysis of the ANSES report on the health effects of Bisphenol A

In formulating the current statement, the CEF Panel has considered the ANSES report (2011a) and has met with ANSES experts via a videoconference (7 November 2011). The minutes of that meeting and a joint report have been agreed upon by EFSA and ANSES and published by EFSA as an EFSA-ANSES joint document in the spirit of Article 30 of Regulation (EC) No 178/2002. Evaluation of the ANSES report and subsequent discussion with ANSES shows that the approach taken by ANSES is one of hazard identification which comprises also elements which could be relevant for the safety

assessment of non-dietary exposure to BPA, whereas the EFSA opinion of 2010 is based on assessment of risk from dietary exposure to BPA. The CEF Panel considers that this is a main reason for the divergences between the ANSES report and the EFSA opinion of 2010. ANSES will use the outcome of its hazard identification in its planned risk assessment of BPA, which is due to be concluded by the end of 2012.

The criteria used by the two organisations for inclusion of studies to be used in the evaluation of BPA are different in some respects.

ANSES included:

- National and international reports on BPA⁶ supplemented by original research papers
- all epidemiological studies
- low dose animal studies published between January 2010 and January 2011
- for animal studies all routes of administration including subcutaneous during all periods of life
- single dose as well as multiple dose studies.

EFSA's inclusion criteria were set as follows:

- original data (no reviews, discussions or others)
- full research papers published in peer-reviewed journals since the EFSA 2006 opinion (January 2007 - July 2010)
- all epidemiological studies
- for animal studies oral route of exposure, developmental exposure, i.e. pre-, peri-, and/or early postnatal exposure and several tested doses (plus a control) including at least one dose level lower than the NOAEL of 5 mg/kg bw/day (low doses)

If studies employed only doses of BPA at or higher than the NOAEL of 5 mg/kg bw/day on which the previously derived TDI was based, the EFSA CEF Panel considered that they were not relevant to risk assessment because such studies would not impact on the TDI. In formulating its scientific advice as requested by the European Commission, the CEF Panel still considers that its inclusion criteria are adequate for the purpose of risk assessment of BPA. The CEF Panel considered studies using non-oral routes of administration of BPA as supplementary information only (e.g. for toxicokinetics or mode of action).

The main difference between the ANSES and EFSA inclusion criteria is the fact that ANSES used animal studies involving all routes of administration in identifying hazard and, besides multiple dose studies, also single dose studies.

ANSES, like EFSA, has placed great emphasis on any evidence of BPA-induced effects in epidemiological studies. Both organisations have identified many shortcomings in these human studies, which limit the usefulness of these findings for either hazard identification or risk assessment. ANSES has however concluded that effects seen on oocyte maturation in women in medically assisted in vitro fertilisation are in line with animal data showing an effect on female fertility and considered that this was a suspected effect of BPA in humans that could be used for their future risk assessment. They similarly concluded that there is a suspected effect of BPA on cardiovascular disease and diabetes in humans. The CEF Panel identified significant limitations in all the human studies evaluated, including those identified by ANSES as showing suspected effects in humans, and considered it could not draw any conclusion from these studies for risk assessment. By design, these cross-sectional studies are unsuitable to establish a causal link between exposure and effect, especially chronic disease.

⁶ These included AFSSA, 2010; Aschberger et al., 2010; EC, 2010; INSERM, 2011; NTP-CERHR, 2008; OEHHA, 2009; Health Canada, 2008, also the EFSA 2010 opinion and the conclusions of the panel of experts brought together under the leadership of the FAO/WHO (FAO/WHO, 2010), Chapel Hill, 2007.

Although the ANSES conclusions on suspected effects of BPA on female fertility, cardiovascular disease and diabetes are based on human studies, the majority of the ANSES conclusions on the hazards of BPA are primarily based on animal studies. The CEF Panel notes that ANSES has concluded that there are proven effects on male and female reproduction, brain including neurogenesis, lipogenesis, mammary gland and immune system based on these animal studies.

The CEF Panel has therefore examined those studies considered by ANSES to show proven effects, reviewing them against the Panel's own opinions on these endpoints as expressed by EFSA in 2010 and also following a review of new literature published since then.

The CEF Panel notes that the majority of studies evaluated by ANSES and considered as showing proven effects on male and female reproduction, brain including neurogenesis, lipogenesis, mammary gland and immune system were also evaluated by CEF for their 2010 opinion. Given the methodological weaknesses of the studies (e.g. low numbers of animals, use of a single or a low number of doses) or the fact that they did not meet the criteria established by the Panel at that time (see EFSA's criteria detailed in section 2), these studies could not be used to derive a new TDI. However, the Panel considers that some of these studies reported effects in areas identified by the CEF Panel in 2010 as deserving further consideration.

3. Evaluation of the new literature

In order to further investigate the possible divergences between the conclusions of the ANSES report and of the latest EFSA opinion on BPA of 2010 and to identify the relevant uncertainties in the data, the CEF Panel has undertaken a preliminary review of the new literature emerging on BPA from a continuing literature monitoring project running since the 2010 opinion. Some of these new studies have also been considered by ANSES (see above), but also some additional studies were found. Several new studies on the toxicokinetics of BPA in rodents, primates and humans have been published since the 2010 opinion. In the 2010 opinion the Panel concluded that after oral administration systemic exposure to free BPA is significantly less than after parenteral administration. For that reason the Panel concluded that studies with parenteral routes of administration are less relevant for risk assessment for exposure to BPA *via* food than studies with oral administration. The information published since the release of the 2010 opinion confirmed this view of the Panel, and again demonstrated that in all species (rodents, monkeys, humans) BPA metabolism is extremely fast, resulting in virtually no free BPA in plasma after oral exposure. In perinatally exposed animals some free BPA may be found in the plasma, but in primates the amount of free BPA is considerably less than in rats.

For the majority of endpoints, the Panel considers that there is no new information in the recent literature that would change the views of the Panel expressed in the 2010 opinion. In the same opinion the Panel noted that some studies conducted on developing animals suggest other BPA-related effects of possible toxicological relevance (biochemical changes in brain, immune-modulatory effects and enhanced susceptibility to breast tumours). The Panel also noted that these studies had many shortcomings and that their relevance for human health could not be assessed at that time. Since the publication of that opinion, additional studies related to these effects have become available, indicating effects of BPA in rodents at dose levels below the current NOAEL of 5 mg/kg bw/day. Uncertainties regarding the relevance to humans of these toxicological effects of BPA remain to be clarified. The Panel has not had sufficient time to consider this. The Panel is also aware that very extensive low dose studies are ongoing at NCTR/FDA and at NTP/NIEHS exploring the whole area of uncertainties around BPA which may further clarify issues.

CONCLUSIONS

The CEF Panel overall considers that the information in the ANSES report does not change the views of the Panel expressed in the 2010 opinion. However, concerning additional data, the Panel would need more time to review more in depth the new studies.

The Panel will reconsider its opinion following further evaluations of new studies and when new data from the ongoing low dose studies become available. The Panel will consider how to best integrate in the outcome of the risk assessment the results of well-conducted studies that deal with specific endpoints that may not be fully covered by standard OECD guideline toxicity studies.

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ABBREVIATIONS

AFSSA	Agence Française de Sécurité Sanitaire des Aliments
ANSES	Agence Nationale de Sécurité sanitaire, de l'alimentation, de l'environnement et du travail
BPA	Bisphenol A
bw	Body weight
CEF	Scientific Panel on food contact materials, enzymes, flavourings and processing aids
EC	European Commission
EFSA	European Food Safety Authority
FAO/WHO	Food and Agriculture Organization/World Health Organization
NCTR/FDA	U.S. National Center for Toxicological Research/Food and Drug Administration
GLP	Good Laboratory Practice
INSERM	Institut national de la santé et de la recherche médicale
NOAEL	No-Observed-Adverse-Effect-Level
NTP-CERHR	U.S. National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction
NTP/NIEHS	U.S. National Toxicology Program/National Institute of Environmental Health Sciences
OEHHA	Office of Environmental Health Hazard Assessment California Environmental Protection Agency
TDI	Tolerable Daily Intake