Parma, 30 November 2011

Agreed joint report of EFSA and ANSES

according to Article 30 of the Regulation (EC) No 178/2002

on Bisphenol A (BPA)

On 5 October 2011 the European Commission sent a letter to EFSA stating: “The European Commission asks 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 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 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 divergence or to prepare a joint document clarifying the contentious scientific issues and identifying the relevant uncertainties in the data.”

A meeting between EFSA and ANSES was held on 7 November 2011 and the agreed minutes of this ANSES-EFSA bilateral meeting are in Annex 1. The present document aims at identifying possible divergences as requested by the Commission.

A. CONCLUSIONS

1. Aim of the respective work

ANSES report on BPA health effects dated September 2011 is meant as a first step in an ongoing risk assessment process to be completed in 2012. The approach used is consistent with that of “Hazard Identification”. This first report provides the basis for selecting the most relevant health effects to concentrate on in the future risk assessment report which will address all potential routes of exposure and not only food.

The EFSA opinions (2006, 2010) provide an assessment of the risks to human health deriving from BPA intake via food and set a Tolerable Daily Intake (TDI) for BPA from dietary sources. This TDI was set to protect the whole human population, including pregnant and breastfeeding women, infants (0-12 months) and young children (12-36 months).

Table 1. Overview of the work performed to date by ANSES and EFSA on BPA

		Latest evaluation	
Step of risk assessment	**Definition**	**ANSES**	**EFSA**
Hazard identification (1)	Identification of the inherent capability of BPA to cause adverse effects	2011[1]	2010[2] 2011[3]
Hazard characterization (2)	Qualitative and quantitative estimation of the adverse effects associated with exposure to BPA, e.g. dose–response, NOAEL, health based guidance value such as TDI	Ongoing 2012	2010[2] 2011[3]
Exposure assessment (3)	Qualitative and quantitative evaluation of human exposure (including specific subgroups at higher risk)	Ongoing 2012 (Report on BPA uses, 2011[4])	2006[5]
Risk characterization (4)	Integrates the three steps above: estimation of adverse effects likely to occur in a population given its estimated exposure	Ongoing 2012	2006[5]

2. Sources of information

The main source of information of ANSES consisted in national and international review reports and in particular the INSERM provisional report on BPA June 2010 focusing on reproductive toxicity. ANSES also reviewed original papers published between January 2010 and January 2011 (not included in the INSERM report). Papers published after January 2011 were not planned to be included in the published ANSES report. However, some primary papers published before January 2010 or after January 2011 were reviewed and included when considered relevant by the experts working group.

[1] ANSES (Agence Nationale de Sécurité sanitaire, de l'alimentation, de l'environement et du travail), 2011a. Effets sanitaires du bisphénol A. Rapport d'expertise collective. Available from: http://www.anses.fr/Documents/CHIM-Ra-BisphenolA.pdf

[2] EFSA (European Food Safety Authority), 2010. Scientific Opinion of the Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A. The EFSA Journal 8(9):1829. Available from: www.efsa.europa.eu/efsajournal.htm

[3] EFSA (European Food Safety Authority), 2011. Scientific Statement of the Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on Bisphenol A. Adopted at the CEF Panel Plenary meeting of 22-24 November 2011.

[4] ANSES (Agence Nationale de Sécurité sanitaire, de l'alimentation, de l'environement et du travail), 2011b. Connaissances relatives aux usages du bisphénol A. Rapport d'étude. September 2011. Available from: http://www.anses.fr/Documents/CHIM-Ra-BisphenolA.pdf

[5] EFSA (European Food Safety Authority), 2006. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A). The EFSA Journal 428, 1-75. Available from: www.efsa.europa.eu

In 2010, EFSA reviewed all the original studies that were published between January 2007 (date of publication of the previous EFSA risk assessment of BPA) and July 2010. EFSA has been constantly monitoring the new literature emerging on BPA since the publication of its 2010 opinion *via* a dedicated project.

3. Study inclusion criteria

Consequent to the different aims of the documents, inclusion criteria differ between ANSES and EFSA. The ANSES approach for hazard identification was to include animal studies using all routes of administration and testing single doses as well as multiple doses. The EFSA approach for hazard characterisation of dietary BPA focused on oral animal toxicity studies employing multiple doses.

In particular, ANSES collected and took note of any possible effects of BPA from the available literature, not excluding any study a priori. Particular attention was given to studies including at least one dose lower than 5 mg/kg bw/day (currently the NOAEL, EFSA; 2006, 2010). ANSES considered mostly academic, but also industry-funded studies employing all routes of administration including the subcutaneous route, both single- and multiple dose studies, and studies either complying or not with OECD test guidelines and/or GLP principles.
Human studies (about 30 studies) were also reviewed by ANSES independently of the time of publication.

For hazard characterisation of dietary BPA, EFSA focused on oral animal toxicity studies employing multiple doses and especially low doses (below the current NOAEL). Studies employing non-oral routes of exposure or single dose administration were also considered by EFSA as supplementary information (e.g. mode of action of BPA), but were not regarded as adequate for risk assessment. Indeed, the toxicokinetics of BPA markedly differs depending on the route of exposure (e.g. oral vs parenteral route), resulting in significantly different internal exposure levels to the endocrine-active form of BPA. Hence EFSA focused on oral rather than parenteral studies.

In 2010, EFSA reviewed toxicokinetic, human and animal toxicity studies, whether complying or not with OECD test guidelines and/or GLP principles. Both academic and industry-funded studies complying with these inclusion criteria were considered: full research papers in peer-reviewed journals, all human studies and for the in vivo animal toxicity studies the focus was on low dose oral studies employing several test doses including at least one <5 mg/kg bw/day and involving exposure *in utero* and/or lactation.

4. Study evaluation criteria

Different evaluation criteria between ANSES and EFSA are linked to the different scope of their reports, namely hazard identification vs. risk assessment from oral exposure.

In their hazard identification report, ANSES gave the same weight to toxicological studies using different routes of exposure, and also considered studies with some shortcomings. ANSES considered that all the studies dealing with a particular endpoint of toxicity, irrespectively of other inherent characteristics (e.g. different route of exposure, single or multiple doses, animal species, etc) were grouped according to similarity of exposure (time and duration) to BPA and were evaluated together through a decision tree to assess qualification according to their level of proof. The results from subcutaneous and oral toxicological studies were for instance evaluated together through the decision tree in this hazard identification report and were given the same weight. As the approach chosen by ANSES was a weight of evidence approach, studies with some shortcomings could be used to support related effects on the same target(s) or with similar patterns. A more detailed analysis of individual papers will be made by ANSES at a later stage of the ongoing risk assessment process.
ANSES emphasized that in some of the OECD Technical Guidelines with *in utero* exposure, specific effects in offspring such as effects on the mammary gland for example are not sufficiently evaluated. Therefore, the absence of effect for this particular endpoint in regulatory guideline is not considered by ANSES as a proof of absence of effects.

EFSA did not consider useful for the purpose of risk assessment studies with methodological weaknesses (e.g., single dose studies) and/or not meeting the inclusion criteria (e.g. non-oral studies). In its opinion of 2010 EFSA evaluated each original study individually against quality criteria (sufficient sample size, adequacy of control procedures, inclusion of positive controls when applicable, assessment of correlation between morphological and functional changes, and consideration of litter or dam as the appropriate statistical unit) in order to assess the validity and/or applicability of the individual findings to human risk assessment. Some of the studies evaluated by ANSES in the hazard identification as showing proven effects in animals and suspected effects in humans were already evaluated by EFSA in 2010. Given their methodological weaknesses and/or the fact that they did not meet the inclusion criteria, these studies could not be considered to derive a new TDI.

Effects on mammary gland were regarded by EFSA in 2010 as deserving further attention in view of mechanistic plausibility (see section 5.2.2.3 of EFSA, 2010[2]). However, because of the shortcomings in the design and reporting of the two studies where the effects on mammary gland were explored, EFSA concluded that these results could not be used for the derivation of a TDI.
Based on the quality criteria mentioned above, the Panel considered a valid multi-generation study exploring the effects of BPA also at low doses as the pivotal study for the derivation of the TDI[2].

5. Window of enhanced sensitivity

ANSES gives high importance to the window of enhanced sensitivity to BPA (window of exposure) in different periods of life (prenatal, early life and adults). Considering that, ANSES considers the possibility that a threshold approach for each endpoint, in relation to windows of

exposure linked to specific sensitivity, would be more suitable to BPA risk assessment than the TDI approach.

EFSA considers that the available database on BPA includes studies covering pre-, peri-, and postnatal life stages (developmental toxicity studies, multigeneration studies), which address the particular susceptibilities of these life stages. Also considering the toxicokinetics data in rodents and primates including humans, the TDI would be protective for the whole human population, including pregnant and breastfeeding women, infants (0-12 months) and young children (12-36 months).
The TDI originally set by EFSA in 2006 was reconfirmed in 2008 and 2010 after a comprehensive review of recent studies.

B. OVERALL CONCLUSIONS

ANSES and EFSA agree that they have covered different stages of the risk assessment process: ANSES a hazard identification and EFSA a hazard characterisation (2010) and a full risk assessment (2006) from dietary exposure to BPA (2006).

This represents one of the reasons for the divergences between their respective work in 2011 and 2010. They recognize that their selection of critical effects is not based on the same study evaluation criteria (e.g. routes of exposure).

ANSES and EFSA agree to collaborate in the near future and exchange views, information, and documents concerning BPA.

ANNEX 1

Parma, 23 November 2011

BILATERAL MEETING BETWEEN EFSA and ANSES

According to Article 30 of the Regulation (EC) No 178/2002

Bisphenol A (BPA)

Agreed minutes of the meeting of 7 November 2011

The report below does reflect the common understanding of EFSA and ANSES of the meeting held in the context of Article 30(4) of Regulation (EC) No 178/2002.

Participants

ANSES :	Christophe Rousselle and Claire Beausoleil (Chemical hazards and evaluation Unit), Jean-Nicolas Ormsby (Deputy Director, Risk Assessment Directorate), Claude Emond and Elisabeth Elefant (Anses ED- experts working group)
EFSA CEF Panel:	Iona Pratt (Chair of the Panel), Trine Husøy, Wim Mennes and Detlef Woelfle
EFSA CEF Unit:	Per Bergman[6] (Chair, Acting Director of REPRO Directorate), Alexandre Feigenbaum (Head of CEF Unit), Anna F. Castoldi, Andrea Terron and Anne Theobald (CEF Unit), and Laura Ciccolallo (Scientific Assessment Support Unit)
European Commission	Annette Schaefer and Josiane Houins-Roulet (DG Sanco)

The Chair of the meeting, Per Bergman, welcomed the participants of this EFSA-ANSES bilateral Meeting. He expressed his gratitude to the ANSES participants for their availability to liaise with EFSA with such a short notice. The objective of the meeting was to exchange scientific views on the health effects of bisphenol A (BPA) in order to identify and possibly clarify potential divergences and contentious scientific issues. The meeting notes were taken by EFSA and the current meeting minutes were agreed upon by EFSA and ANSES for agreement.

The Chair introduced the terms of reference that EFSA received from the European Commission (EC) in relation to the two ANSES reports published on 27 September 2011 dealing with BPA health effects and BPA uses, respectively. EFSA clarified that during this meeting only the ANSES report on BPA health effects was going to be discussed, whereas the report on BPA uses, although part of the mandate, was considered as not having any impact on the risk assessment performed by EFSA..

[6] P. Bergman left the meeting at 3 pm and was replaced in chairing by A. Feigenbaum.

On 5 October 2011 EFSA was asked to provide scientific advice to the EC by 15 October 2011 in relation to possible divergences between the conclusions of the latest EFSA Scientific Opinion on Bisphenol A of 2010 and those in the ANSES report "Effets sanitaires du bisphénol A". EFSA was in particular asked 1) to analyse if any elements in this report would support the need for a revision of the EFSA opinion of 2010; 2) 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.

The Chair presented EFSA's reply to this request dated 13 October 2011 proposing the following actions to be carried out by 30 November 2011:
- a meeting between EFSA and ANSES' respective experts including the Chair of the CEF Panel and the rapporteurs of the EFSA opinion adopted in September 2010;
- publication of the meeting minutes meant to be an agreed EFSA-ANSES joint document in the spirit of Article 30 of Regulation (EC) No 178/2002 and to be discussed by the CEF Panel during its next Plenary (20-22 November 2011)
- publication of a CEF Panel statement where the Panel might consider the reasons for possible diverging views between ANSES and EFSA and address whether a revision of the EFSA opinion from 2010 is needed.

ANSES emphasized that their report on BPA health effects is meant as a first step in a continuing risk assessment process. The approach used is consistent with that of "Hazard Identification". This first report provides the basis for selecting the most relevant health effects to concentrate on in the coming risk assessment report due by the end of 2012.

ANSES presented their selection criteria for the database. The main source was that of recent national and international reports (EU-RAR, 2002-2008; JRC, 2010; NTP-CERHR, 2008; Health Canada, 2008; OEHHA, 2009; AFSSA, 2010; Chapel Hill, 2007, EFSA, 2010; FAO/WHO, 2010) and in particular the INSERM provisional report on BPA June 2010[7] focusing on reproductive toxicity. EFSA opinion of 2010 relied on the review of all the original studies that were published after the 2008 EFSA opinion.
ANSES also considered papers published between January 2010 (not included in the INSERM report) and January 2011. Papers published after January 2011 are not included in the published ANSES report.
ANSES explained the methodology underlying the work done on hazard identification, which has been that of collecting and taking note of any possible effects of BPA from the available literature. To ensure that none of the BPA effects was overlooked, no study was excluded *a priori.* ANSES considered mostly academic-, but also industry-funded studies, studies employing all routes of administration including the subcutaneous route, both single- and multiple dose studies, and studies either complying or not with OECD test guidelines and/or GLP principles. Particular attention was given to epidemiological studies (about 30 studies) and low dose experimental studies (below the current NOAEL of 5 mg/kg/day, EFSA; 2006, 2010).

[7] Rapport INSERM, 2011, Reproduction et environnement – Expertise Collective

Regarding evaluation criteria, ANSES experts explained that all the studies dealing with a particular endpoint of toxicity, irrespectively of other inherent characteristics (e.g. different route of exposure, single or multiple doses, animal species, etc) were grouped according to similarity of exposure (time and duration) to BPA and were evaluated together through a decision tree to assess qualification according to their level of proof. The results from subcutaneous and oral toxicological studies were for instance evaluated together through the decision tree in this hazard identification report and were given the same weight. As the approach chosen by ANSES was a weight of evidence approach, even studies with some shortcomings could be used to support related effects on the same target(s) or with similar patterns. A more detailed analysis of individual papers will be made at a later stage.

EFSA posed several questions to ANSES on toxicological endpoints which were considered by ANSES as “proven effects” in animal studies or “suspected effects” in human studies, in particular concerning male and female reproduction, lipogenesis, cancer, neurotoxicity and immunotoxicity. Further questions to ANSES were related to pharmacokinetics and non linear dose-response relationships.

Some of the studies evaluated by ANSES and considered as showing “proven effects” in animals were also evaluated by EFSA in 2010. EFSA had then concluded that these studies had methodological flaws or/and did not meet the criteria established by CEF for risk assessment, and therefore they could not be taken into account for risk assessment.
ANSES like EFSA reviewed all the available human epidemiological studies and both organisations identified many shortcomings limiting the usefulness of such data for either hazard identification as well as for risk assessment. Nevertheless, ANSES concluded that effects seen in the Mok Lin (2008) study on female fertility and in Fujimoto et al., 2011 represent “suspected effects” of BPA. In 2010, the CEF Panel had concluded that due to its limitations, the study by Mok-Lin (2008) could not be used for risk assessment. At that time, the study of Fujimoto was not available.

Concerning the non linear dose-response relationships, ANSES said that this concept was mentioned in the report but that they would need to spend more time on this issue before coming to a conclusion. In 2010 the CEF Panel concluded that it was not aware of any clearly reproducible adverse effect *in vivo* expressed specifically at low BPA doses only.

ANSES emphasized that they gave high importance to the “window of exposure” in different periods of life, i.e. the time of exposure in relation to windows of enhanced sensitivity to BPA. , Studies with continuous exposure were also considered by ANSES and when negative results were obtained with this kind of protocol, effects observed with a particular period of exposure were not dismissed. ANSES emphasized that in some of the OCDE Technical Guidelines with *in utero* exposure, specific effects in offspring such as effects on the mammary gland for example are not sufficiently evaluated. Therefore, the absence of effect for this particular endpoint in regulatory guideline is not considered by ANSES as a proof of absence of effects.
EFSA’s approach for hazard characterization is based on setting a TDI. The pivotal study used to derive a TDI was a multi-generation study with continuous exposure to a broad dose range

including low doses.This TDI is to protect all human population, including the most vulnerable groups, such as as pregnant and lactating women, infants and young children. The TDI was first set by EFSA in 2006 and reconfirmed in 2008 and 2010 after a comprehensive review of recent studies

Conclusions on EFSA-ANSES possible divergences

The ANSES report is a preliminary work on hazard identification of BPA from all possible exposure routes (including dermal) and not a risk assessment report. In contrast the EFSA opinion provides a risk assessment of BPA from food-related uses and sets a TDI from dietary sources. Consequently the criteria used by the two organisations in considering the applicability of studies used to assess the safety of BPA are different. As an example, for hazard identification ANSES included animal studies using all routes of administration and testing single doses as well as multiple doses. For risk assessment of dietary BPA, EFSA selected only oral animal toxicity studies employing multiple doses to allow assessment of dose-response relationships related to oral exposure.

The majority of studies evaluated by ANSES as showing “proven effects” in animals and “suspected effects” in humans were already evaluated by EFSA in 2010. EFSA then concluded that these studies had methodological flaws or/and did not meet the criteria established for utility for risk assessment, and therefore they could not be taken into account.

ANSES’ main source of scientific information on BPA was provided by recent national and international reports, in particular the INSERM report of June 2010, as well as by scientific papers published between January 2010 and January 2011. The EFSA opinion of 2010 relied on the review of all the original studies that were published between January 2007 (date of publication of the 2006 EFSA opinion) and July 2010.

ANSES underscored the high importance given to the window of enhanced sensitivity to BPA (window of exposure) in different periods of life (prenatal, early life and adults). In the light of this, ANSES considers the possibility that a threshold approach for each endpoint in relation to specific windows of exposure would be more suitable to BPA risk assessment than the TDI approach. This approach differs from that of EFSA. EFSA considered - as the pivotal study for setting the TDI for BPA - a multi-generation study with continuous exposure to a broad dose range including low BPA doses. This TDI is to protect all human population, including the most vulnerable groups, such as pregnant and lactating women, infants and young children. The TDI was first set by EFSA in 2006 and reconfirmed in 2008 and 2010 after a comprehensive review of recent studies.

EFSA and ANSES agreed to collaborate in the near future and exchange views, information and documents concerning BPA.