

The Director General

Maisons-Alfort, 25 mars 2013

OPINION **of the French Agency for Food, Environmental** **and Occupational Health & Safety**

on the assessment of the risks associated with bisphenol A
for human health, and on toxicological data and data on the use of
bisphenols S, F, M, B, AP, AF and BADGE

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

On 4 June 2009, the Directorate General for Health (DGS) made a formal request to ANSES (Request no. 2009-SA-0331) for an expert appraisal on the health risks, to the general population, related to Category 3 reprotoxic substances and/or endocrine disruptors found in products and/or articles on the market, including bisphenol A (BPA). The Agency received an additional formal request on 18 February 2010 (Request no. 2010-SA-0197), from the Directorate General for Risk Prevention (DGPR), for an expert appraisal specifically on BPA and its potential alternatives, taking into account all other types of toxic effects and not just reprotoxic effects and/or effects related to endocrine disruption.

1. BACKGROUND AND PURPOSE OF THE REQUEST

In 2009, the French Ministry of Health asked INSERM and various health agencies, the ANSM (formerly AFSSAPS), ANSES, the InVS and INPES, to study the issue of endocrine disruptors. ANSES's work on BPA is therefore structured within the assessment framework for about thirty potential endocrine disrupting substances (bisphenols, phthalates, parabens, perfluorinated and brominated compounds, alkylphenols, etc.) and a second request specific to bisphenol A from the French Ministry of Ecology. The Agency has been studying the issue of BPA since 2008 and has published several Opinions and documents on this topic.

Bisphenol A is a synthetic chemical that has been used for over 50 years. Its two main uses are for the manufacture of polycarbonate plastics and epoxy resins respectively. It is

also used as a component of other polymers and resins (such as polyesters, polysulfones, polyvinyl chloride and vinyl ester resins), in the synthesis of certain flame retardants and as a chemical developer in thermal paper (cash register receipts for example).

In the course of ANSES's investigation of the two requests, an industry study was conducted in 2011¹ whose objective was to systematically identify the business sectors, and ultimately the consumer products and articles likely to contain bisphenol A. Some sixty business sectors in France were identified as potential users of this substance. The study also compiled a non-exhaustive list of the uses, articles and preparations likely to contain BPA (cables, sealants, adhesives, both food grade and non food-grade containers, headlights, sporting goods, brake fluids, coolant fluids, electrical installation equipment, household appliances, medical devices and apparatus, printing inks, etc.). The list included a wide variety of products and articles likely to contain BPA.

In its reports on the health effects and uses of bisphenol A (September 2011), ANSES showed that there are 'recognized' effects in animals (effects on reproduction, on the mammary gland, on metabolism, the brain and behaviour) and other 'suspected' effects in humans (on reproduction, metabolism and cardiovascular diseases). These effects could be observed, even at low levels of exposure, during sensitive phases of an individual's development. This led to the identification of particularly vulnerable populations. This work on the uses and health effects of BPA led the Agency, in September 2011, to recommend a reduction in population exposure, mainly through BPA's substitution in food contact materials, especially for the most vulnerable populations (infants, young children and pregnant or breastfeeding women). In 2012, working on a European level in the context of the REACH² and CLP³ Regulations, the Agency also proposed revising the classification of BPA as toxic for reproduction.

The Agency's work has continued with a health risk assessment (HRA) of this substance and an inventory of potential alternatives to it, including the physico-chemical and toxicological properties of some of these alternatives. It has also begun to investigate other bisphenols (S, F, M, B, AP, AF and BADGE).

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

This collective expert work on BPA has been carried out since 2010 by the Working Group on Endocrine disruptors and Category 3 reprotoxic substances (WG ED), reporting to the Expert Committee on Assessment of the risks related to chemical substances (CES on Chemicals).

Since September 2011, the WG ED has been conducting a risk assessment in response to the two requests. Other ANSES Expert Committees were involved in responding to these two requests concerning questions falling within their spheres of competence: the CES

¹ Knowledge of the uses of bisphenol A (ANSES, September 2011)

² Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

³ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

on Assessment of the risks related to water (CES on Water), the CES on Food contact materials (CES MCDA), and the CES on Assessment of physico-chemical risks in food (CES ERCA).

This Opinion is based on the WG ED's collective expert reports relating to the BPA HRA and the synthesis of data on use and toxicity of other bisphenols, on a study report on the inventory of alternatives to BPA, as well as on a report on the social representations due to uncertainty about the endocrine disruptors issue. This last report was prepared following public hearings with stakeholders and/or scientists on the topic of endocrine disruptors.

These reports were submitted to the CES Chemicals, which adopted the summary and conclusions note from the collective expert appraisal at its meeting on 21 February 2013. This note summarises the main results of the expert appraisal on BPA and the other bisphenols. It makes recommendations with a view to reducing the risks associated with exposure to BPA, and acquiring knowledge on the toxicity of BPA and exposure to BPA relevant to the HRA. The CES Chemicals also issued recommendations on the other bisphenols and/or alternatives to BPA.

3. ANALYSIS AND CONCLUSIONS OF THE EXPERT APPRAISAL

This expert appraisal assessed the risks to human health associated with exposure to BPA while taking into account the various documented sources and media of exposure⁴. The assessment included exposure through food, by dermal contact or by inhalation, for all the "chemical" forms of bisphenol A (free and conjugated bisphenol A)⁵.

For the purposes of the expert appraisal, specific BPA analysis campaigns were conducted at the request of ANSES, especially in foods, water intended for human consumption (from the public water supply and from bottled water), in the air and dust of housing, and on thermal paper receipts. The results of these campaigns were used to model exposure as internal exposure doses according to a probabilistic approach, to better take into account the variability in the target populations.

The analysis of scientific articles on the effects of BPA published before July 2012 and based on experimental data in animals, helped identify the critical effects deemed to be relevant to the unborn children of exposed pregnant women. The effects of BPA were classified by organ or system, both in humans and in animals, depending on the periods of exposure, according to recognized effects, suspected effects, controversial effects and effects for which the available data are inconclusive. With no recognized effects having been identified in humans, despite the numerous epidemiological studies, the experts chose to refer to effects considered to have been recognized in animals and/or suspected in humans for the risk assessment, as is conventional practice.

Then, on the basis of the available data, the experts were led to select the health effects and the key studies to be used for the risk assessment, which would enable toxicological benchmark doses to be determined for the effects, in the same way as they were led to make methodological choices for the risk assessment strategy.

⁴ Cosmetics and medical devices have undergone assessment by the ANSM, whose results are provided in the Annex to the collective expert report.

⁵ Total bisphenol A = Free (or unconjugated) bisphenol A + Conjugated bisphenol A. Conjugated bisphenol A is glucuronidated or sulfated bisphenol A.

Ultimately, it was only possible to assess risks to the unborn children of pregnant women, due to the lack of toxicological benchmark doses for the other populations or age groups of interest (young children, adolescents, etc.). The risk assessment was conducted for exposure by the dietary, inhalation and dermal routes.

With respect to dermal exposure, and despite the fact that bisphenol A is likely to be found in a large number of consumer articles or products, only exposure via cash register receipts could be sufficiently documented and therefore taken into account to assess the risks associated with handling them.

An analysis of the uncertainties completed the overall hazard and exposure assessment process. In particular this helped identify the different sources of uncertainty in the expert appraisal, the main challenge being to better qualify the confidence levels assigned to the final results, by ranking them as "high", "moderate" or "limited".

For characterising the risks, toxicological values (TV) based on the critical doses selected were derived for each effect considered. These correspond to:

- the application of a bioavailability factor according to the route of exposure considered in the study or studies having identified the NOAELs or LOAELs⁶ selected for the risk characterisation. On the basis of toxicokinetic studies primarily evaluating bioavailability parameters after oral administration of BPA to several animal species, a 3% absolute bioavailability factor by oral route was chosen by the experts due to a significant effect of hepatic first-pass metabolism (Doerge *et al.* 2010a, Farbos, 2012). This factor is therefore used to convert the NOAELs/LOAELs into equivalent internal doses.
- the application of an uncertainty factor of 300 if the critical starting dose is a NOAEL, and 900 if the critical starting dose is a LOAEL. This overall uncertainty factor can be separated into several factors:
 - a factor of 10 related to inter-species variability, to account for the transposition from animals to humans,
 - a factor of 10 related to inter-individual variability in the human population,
 - an additional factor of 3 related to the body of data available and the severity of the effect. This factor is justified by all the uncertainty as to the effects of BPA observed at lower doses than those selected, the existence of non-monotonic dose-response relationships, the existence of *in vitro* and *ex vivo* data in favour of the much greater sensitivity (beyond a factor of 10 already considered in the inter-species variability factor) of tissues of human origin with respect to BPA, as compared to animal tissues.
 - a factor of 3 for the adjustment from a LOAEL to an adjusted NOAEL,

⁶ NOAEL: No observed adverse effect level; LOAEL: Lowest observed adverse effect level.

Critical effects	Study reference	Route of exposure	LOAEL	NOAEL*	Internal NOAEL with a bioavailability factor of 3%	Internal TV with a Margin of Safety (MOS) of 300 on the internal NOAEL
			(µg/kg/d)	(µg/kg/d)	(µg/kg/d)	(µg/kg/d)
Brain and behaviour	Xu ⁷	oral	/	50	1.5	0.005
Female reproductive system	Rubin ⁸	oral	/	100	3	0.01
Metabolism and obesity	Miyawaki ⁹	oral	260	87*	2.6	0.009
Mammary gland	Moral ¹⁰	oral	/	25	0.75	0.0025

*: adjusted NOAEL calculated from the LOAEL.

Concerning the results of the risk assessment, taking into account all exposure media: air, settled dust and food (including water intended for human consumption), and excluding certain specific exposure situations (cash register receipts, water from refillable polycarbonate containers), the findings show that some situations of exposure of pregnant women to BPA pose a risk to the mammary gland of the unborn child. The selected effects are characterised by an increase in the number of undifferentiated epithelial structures associated with an increased susceptibility of the mammary gland to tumour transformation. There is a greater response to exposure to carcinogens when it occurs during puberty or adolescence, when the terminal end buds (TEB) and terminal channels of the mammary gland, regarded as the most susceptible structures to breast carcinogens, are still numerous.

The confidence level associated with these results was described as "moderate" by the majority of the experts. Some WG ED experts regarded this confidence level as "limited", mainly due to the model's sensitivity to the bioavailability factor. It is true that if lower human bioavailability levels were used, these situations of overexposure could be revised downwards. Concerning the other three types of effects (effects on the brain and behaviour, effect on metabolism and obesity, effect on the female reproductive system), the risk appears to be "negligible," depending on the assumptions made.

On average, food is the main contributor to internal exposure (84% for pregnant women). Regarding the main dietary sources of exposure and irrespective of the populations concerned, the expert appraisal identified three broad categories:

⁷ Xu *et al.*, 2010a

⁸ Rubin *et al.*, 2001

⁹ Miyawaki *et al.*, 2007

¹⁰ Moral *et al.*, 2008

- Products packaged in cans¹¹ which account for around 50% of the total exposure comprising:
 - 35 to 45% for vegetables;
 - 10 to 15% for mixed dishes, and meat- and fish-based products.
- Some foods of animal origin:
 - approximately 17% for meats, offal and delicatessen meats;
 - between 1 and 3% for seafood.
- A ubiquitous contamination whose origin has not been identified, which accounts for between 25 and 30% of total exposure.

With regard to the measured levels of contamination and the risk to pregnant women related to their exposure to unconjugated BPA, avoiding consumption of products packaged in cans or consuming products that are only available in non-BPA-releasing cans would lead to a significant reduction in the risk associated with BPA exposure through food, while not fully excluding it. The introduction of additional measures designed to reduce the high levels of contamination found in certain products of animal origin in addition to avoiding consumption of canned products (or only consuming products packaged in non-BPA-releasing cans) would also lead to a significant decrease in BPA exposure of pregnant women.

Water bottled in refillable polycarbonate containers is a source of exposure to BPA. Consumption can contribute to a substantial increase in internal exposure to BPA and could therefore, when combined with other sources of exposure, lead to an "additional" risk to the unborn child of an exposed pregnant woman.

Concerning the specific assessment of risks associated with the handling or use of products and/or articles intended for the general public and containing BPA, according to the results of the exposure calculations, handling thermal paper receipts leads to risk situations for the four types of effects considered: mammary gland, brain and behaviour, the female reproductive system, metabolism and obesity. According to the assumptions used, the risk concerns the unborn children of pregnant women handling thermal paper receipts as a result of their professional and/or consumption activities. The confidence level associated with these results was considered "limited" by the experts. It is certainly true that the models and assumptions used lead to overestimating internal exposure calculated in relation to handling thermal paper receipts. In the absence of reliable and specific French data, it would be useful to conduct a workplace study among women of childbearing age in order to measure urinary excretion of BPA and thereby confirm the estimated internal exposure.

Concerning the uncertainties relating to identification of the hazards and the dose-response relationship, the main sources of uncertainty identified relate to the transposition to humans of the selected critical effects, the dose-response relationship and the bioavailability factors. Concerning the extrapolation to humans of the critical effects, these have been observed in animals, mainly in rodents and, to date, the available data cannot confirm these effects as "recognized" in humans. However, according to the conventional HRA approach, in the absence of data indicating that these effects are specific to animals, it is assumed that they can be extrapolated to humans. Concerning the dose-response relationship, the conventional HRA process postulates a monotonic relationship, and yet non-monotonic dose-response relationships have been observed with BPA. Concerning the bioavailability factors, when conducting the HRA, the experts were faced with a methodological problem related to the choice of the bioavailability value for both oral and dermal exposure. The sensitivity analysis shows that this parameter has a

¹¹ With no possibility of detecting the presence or absence of a BPA-releasing coating

major impact on estimating internal exposure doses of unconjugated BPA and, consequently, on the results of the HRA. This is why the experts wished to emphasise the need to better characterise the human bioavailability value for BPA (by oral and especially dermal routes) in order to increase the levels of confidence in the results of this expert appraisal. Ongoing studies planned in the USA under a joint NTP/NIEHS programme on BPA, and the PBPK model being developed at ANSES's request, should help remove or reduce these uncertainties in the medium term.

Concerning the uncertainties regarding the assessment of exposure, the analysis highlights the extent of the lack of robust contamination data—especially French—on the various sources of exposure considered: air, dust, cash register receipts and numerous consumer articles or products. The uncertainty analysis also indicates the extent of the lack of data on human exposure factors (tidal volume, surface area of the hand, time spent indoors *versus* outdoors, and other habits, practices and customs needed to assess exposure) and a lack of knowledge on exposure by dermal contact.

Concerning alternatives to BPA, following the call for contributions issued by the Agency in 2011, a total of 17 contributions were received, related to health effects, uses and substitutions for BPA. Among these, ten concern substitutes for BPA. The Agency does not have the information needed to evaluate the degree to which these ten contributions are representative of all the global players involved in the marketing of BPA and/or its alternatives. In the study report entitled "Substitution of BPA: inventory of alternatives to BPA, identification of the hazards of potential alternatives to BPA", 73 alternatives to BPA were identified up to February 2012, including four coming directly from the industrial companies responding to the call for contributions, seven from industrial companies contacted outside of the framework of this call for contributions and 62 others from the international literature.

These contributions received by the Agency vary in nature. They include feedback on actual alternatives from industry or universities, and general contributions from organisations or trade associations. Only concrete examples of substitution have been cited in this report. There are many different ways of providing alternatives to BPA: direct substitution of BPA by another substance or substitution by another plastic material or another polymer with similar properties to the starting polymer, substitution by another material, other type of packaging or lastly substitution by a process. Depending on the information available for each alternative, the report describes various physico-chemical or regulatory information, as well as the advantages and disadvantages of some of the alternatives. In addition, toxicity data is presented for each previously identified alternative by differentiating alternatives to polycarbonates, epoxy resins, developers in thermal paper and flame retardants. This identification work made it possible to draw up an initial inventory of alternatives to BPA and substitutions for BPA by use.

Although scientific and technical information was collected for some of the alternatives identified, it is important to note that some of these are currently in use both on European and non-European markets while others are still at the research and development stage. It should also be emphasised that the list of existing alternatives identified is probably not exhaustive.

More specifically, information on food contact materials was collected under the auspices of the CES on Food contact materials up to July 2012. This information was supplemented by a description of the regulatory framework concerning food contact materials and materials from permanent facilities for the production, treatment and distribution of water intended for human consumption, in order to characterise the authorisation system for the alternatives identified.

On completion of this work, no single alternative stood out for replacing BPA for all of its uses. For this reason, it is important to reiterate that the Agency can only make an inventory of existing alternatives to BPA, without presuming as to their industrial feasibility, or validate proposals for identified or submitted alternatives, particularly in terms of health risks and most often in the absence of available data.

Nevertheless, it should be stressed that even though most of these chemical compounds have been pre-registered or registered under REACH, the compilation of available data on the toxicity of some of the potential alternatives to BPA indicates that these have not been fully tested for toxicity. This is particularly true of their effects on reproduction and/or endocrine disruptor nature. Finally, the search for alternatives is an evolving field of study and the information on this subject therefore needs regular updating.

Concerning other compounds of the class of bisphenols, the DGS's Request no. 2009-SA-0331 gave ANSES a mandate to assess the risk of compounds of the class of bisphenols, in particular the following: bisphenol A diglycidyl ether (BADGE), bisphenol B (BPB) and bisphenol M (BPM). Furthermore, as a result of the ongoing work on the BPA Request no. 2010-SA-0197, compounds such as bisphenol S (BPS), bisphenol F (BPF) and bisphenol AP (BPAP) have been identified as potential substitutes for BPA and, as such, have undergone a more complete analysis of their toxicological profile. In addition, an industry study was conducted in 2010-2011 on BPS, BADGE, BPB and BPM. All the toxicological data and data on the uses identified are presented in the collective expert report on the compounds of the class of bisphenols M, S, B, AP, AF and BADGE. The following conclusions were formulated by the experts:

Concerning the oestrogenic activity of the bisphenols assessed, an analysis of the available data shows that the chemical structure common to compounds of the class of bisphenols gives them oestrogenic properties.

Concerning the uses of these bisphenols, of the seven compounds analysed in this report, three are potential substitutes for BPA. They are BPS, BPF and BPAP. According to ANSES's study report on alternatives to BPA, these three compounds are used as substitutes for BPA as developers in thermal paper. BPS is used as a starting monomer for the synthesis of polyethersulfone (PES), which is specifically used for the manufacture of infant feeding bottles and children's tableware. The other four compounds (BPB, BPM, BPAF and BADGE) were not identified in this report as substitutes for BPA. The evidence gathered thus far suggests that BPB, BPM and BPAF are used for the synthesis of polymers. For its part, BADGE is employed in the synthesis of certain epoxy resins that may be used in the internal coating of food containers.

In conclusion, this review of the literature on other bisphenols indicates that at the present time, there is not enough toxicological data available for assessing the toxicity of bisphenols AF, AP, B, F, S, M and BADGE. Similarly, data on preparations and/or articles containing bisphenols M, B, S and BADGE, as well as those on potential environmental contamination caused by these compounds, are too fragmentary to enable the general population's exposure to be assessed. As a result, it is not possible to assess the health risks associated with the use of these compounds in consumer products, and the greatest care should be exercised with regard to substitution by these compounds.

Concerning the social representations of the uncertainties surrounding endocrine disruptors in general, about a dozen hearings were conducted in order to take the general public's views into consideration and shed light on its questions about endocrine disruptors. These hearings were specifically designed to pinpoint certain key areas of the

controversy by characterising the various certainties and uncertainties surrounding endocrine disruptors. The notion of uncertainty refers here to a situation where the available body of knowledge on a particular topic—such as the toxicological effects of endocrine disruptors—is regarded as little known or unknown, incomplete, incorrect, biased, unconvincing, etc. The aim of the hearings was to further the scientific debate on the characterisation of uncertainty and to document how the stakeholders' positions echoed the scientific questions.

Following these hearings, it became clear that the declarations of the people interviewed and the concepts they relied on to explain the sources of uncertainty all reflected the complexity of the issue of endocrine disruptors. The diversity of definitions of endocrine disruptors that co-exist already illustrates one of the difficulties of dealing with the issue. Depending on the definition adopted, the substances, effects and methods differ, along with the way the issue is understood. This lack of consensus is a problem when implementing research, the HRA and the introduction of a regulation.

The hearings highlighted the debate surrounding the effects at low doses and the non-monotonic dose-response relationships, illustrating the broader reservations concerning the toxicology paradigm. Conventionally accepted elements were discussed, such as extrapolation from animals to humans or the relevance of the tests implemented. The question of the effects of mixtures of substances emerged among the individuals interviewed, and the ways of measuring these effects were discussed and added to the uncertainties surrounding endocrine disruptors. The issue of the trans-generational effects of endocrine disruptors and, in this context, the role of epigenetic pathways was raised. These discussions led to the issue of regulatory measures, actions to be undertaken and general research methodologies.

What emerges from all the hearings is a social and scientific construct of the uncertainties, sometimes by consensus (on the lack of knowledge or lack of robustness of the available methods), and other times by opposition (concerning the scientific paradigm and associated best practices that should be applied). However, there is a certain amount of moderation and relatively little contrast between the remarks and positions, where standpoints could have been more pronounced.

Ultimately, the issue of uncertainty around endocrine disruptors is found in various schools of thought, emphasising personal and/or professional considerations and/or positions that cut across current social and political questions/debates on this topic. Thus, the primary value of these hearings has been to show that the field of endocrine disruptors now largely extends beyond the purely scientific field since it has become a widespread social, ideological and political debate.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions of the Expert Committee on Assessment of the risks related to chemical substances relating to the risks associated with BPA for human health, and on toxicological data and data on the use of bisphenols M, S, B, AP, AF, F and BADGE.

In the current state of knowledge and on the basis of the methodology adopted, these conclusions identify risk situations for the unborn child, associated with exposure to BPA during pregnancy. The risks identified for the unborn child relate to the mammary gland

and may be characterised by an increase in the number of undifferentiated epithelial structures associated with an increased susceptibility of the mammary gland to tumour transformation. The risks potentially affect children of both sexes. Given the uncertainties associated with the risk assessment exercise, the confidence level has been described as "moderate" by the Agency's experts.

The aggregate assessment taking into account the different exposures showed the predominance of dietary exposure compared to other routes. Nevertheless, the study of particular exposure scenarios during pregnancy identified specific risk situations associated with the handling of thermal paper and also with the consumption of water from refillable polycarbonate containers.

The scenario relating to handling thermal paper thus revealed, in addition to the effect on the mammary gland, risk situations involving other health effects for the unborn child. These may affect the brain and behaviour, metabolism and obesity or the female reproductive system. Given the many uncertainties associated with the risk assessment exercise, the confidence level was described by the experts as "limited".

To date, the available data are insufficient to conduct a risk assessment for other populations (infants, children, adolescents, etc.).

Besides the legislative measures already taken in France, the Agency issued a number of recommendations seeking mainly to reduce the risks associated with exposure to BPA during pregnancy, as well as to increase the confidence level in the results of the risk assessment¹². These recommendations will help *ipso facto* reduce the exposure of the general population to BPA, as previously recommended by the Agency.

- **Recommendations to reduce the risks associated with exposure to BPA**

- By dietary exposure

Considering the identification of risk situations for the unborn child of pregnant women exposed to BPA, ANSES recommends:

- reducing exposure *via* the release of BPA from food contact materials, and in particular, the internal coating made from epoxy resin of certain cans, which is the main vector for dietary exposure along with polycarbonate refillable water containers;
- assessing the impact of regulatory measures on dietary exposure to BPA under the Act no. 2012-1442 of 24 December 2012 aiming to suspend the manufacture, import, export and placing on the market of any packaging for food use containing BPA;
- the Agency also reiterates the relevance of the consumer recommendations issued in its previous Opinions.

- By handling thermal paper

Considering the identification of risk situations for the unborn child of pregnant women handling thermal paper containing BPA, especially as part of their occupational activities, ANSES recommends:

¹² The experts rated the confidence level of the results of the risk assessment into three categories: "high", "moderate", "limited".

- taking immediate measures to reduce the exposure of women handling thermal paper containing BPA or other compounds of the class of bisphenols, especially in the workplace;
- undertaking, at the first opportunity, a biomonitoring study of cashiers and tellers handling thermal paper containing BPA and/or BPS, in order to verify the results obtained from the exposure scenarios used in this work and to identify the most suitable risk reduction measures. The Agency undertakes to support such investigations.

- **Recommendations for acquiring new knowledge on the toxicity of BPA**

Considering the current data on the toxicity of BPA, ANSES recommends:

- improving the understanding of BPA's mechanisms of action.
- monitoring the scientific literature on the health effects of BPA,
- conducting further study on the effects of BPA particularly in connection with postnatal exposure and exposure during early childhood. These data are needed to interpret the results of the infant Total Diet Study (TDSi) that the Agency is also conducting among children under three years of age.

- **Recommendations for studies aimed at a better characterisation of exposure to BPA**

ANSES recommends:

- harmonising the methods for analysing free and/or conjugated BPA in different matrices: dust, biological fluids, hair, etc.
- In terms of external exposure via food
 - determining the sources of contamination of certain foods, especially sources responsible for ubiquitous contamination (in particular other than food containers);
 - identifying the other routes of contamination of certain foodstuffs of animal origin.
- In terms of external exposure via other sources of exposure:
 - assessing the exposure of populations likely to be exposed at higher levels, especially occupational populations handling BPA during its production, distribution, processing, and disposal, and when using materials that may contain it,
 - considering the fate of products containing BPA in the recycling systems for these products,
 - assessing exposure to BPA *via* poorly documented exposure sources: consumer articles and products and, in particular, medical devices;
 - confirming the data on contamination in indoor environments reported in this expert appraisal.
- In terms of estimating the internal dose and so as to better assess exposure to BPA in the unborn child:

- given the strong influence on the HRA results of the bioavailability factor of unconjugated BPA in humans by oral route, and the limited data available to confirm the 3% value used, conducting a kinetic study to determine this value in humans;
- determining the bioavailability value of unconjugated BPA in humans by dermal route,
- as soon as possible, comparing the results of the estimate of internal doses calculated in this expert appraisal with those resulting from the use of the PBPK model being developed at ANSES's request, with a view to improving the estimate of internal doses of human exposure to unconjugated BPA.

In general terms, ANSES also recommends studying the effects of co-exposure to BPA and other chemical compounds.

Lastly, ANSES recommends continuing the work to revise the classification of BPA in the European framework¹³.

• **Recommendations on other bisphenols and/or substitutes for BPA**

ANSES insists on the need for industry to assess the potential risks of BPA substitute products and other bisphenols. Concerning substances with effects at low doses or potentially endocrine disrupting effects, ANSES considers that an assessment of the potential risks should be undertaken regardless of the tonnage, when consumer exposure can be expected.

Concerning the compounds of the class of bisphenols studied in this expert appraisal, in view of the toxicological profiles, additional toxicokinetic (BPS, BPB, etc.), reproductive toxicity (BPS, BPF, BPAP, etc.) and mechanistic (BPAP, BPM, etc.) studies are needed to adequately assess the effects on human health of these other bisphenols or substitutes for BPA.

In terms of their structural similarities to BPA and their oestrogenic potential, the utmost caution is required when using the bisphenols cited above. Innovative alternatives are expected but their safety should be assessed prior to any use.

Recommendations relating to methodological issues

ANSES recommends:

- reviewing the relevance of using one or more Toxicity Reference Values (TRV) or Tolerable Daily Intakes (TDI) for substances for which non-monotonic dose-response relationships were observed and for which the periods of vulnerability are not always known;
- conducting studies on procedures for taking non-monotonic dose-effect relationships into account in the HRAs,
- continuing discussions within the Organisation for Economic Co-operation and Development (OECD) for a better consideration of the many effects related to endocrine disruption in toxicity studies,

¹³ http://echa.europa.eu/view-article/-/journal_content/title/first-substance-evaluation-results-further-information-needed-on-32-substances

- taking into account ongoing international research programmes on BPA (especially the joint NTP/NIEHS programme in the US) and other substances potentially similar to EDs, as appropriate, for reassessing the risks and particularly clarifying the differences in susceptibility to BPA between humans and animals;
- systematically including an interdisciplinary analysis of the uncertainties in the HRA process.

The Director General

Marc MORTUREUX