AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

AFSSA – Request no. 2010-SA-0041
Related Request no. 2009-SA-0270

Maisons-Alfort, 7 June 2010

# OPINION

## of the French Food Safety Agency regarding exposure to bisphenol A in the French population and maximum levels of bisphenol A in foods

THE DIRECTOR GENERAL

## 1. CONTEXT OF THE REQUEST

On 17 February 2010, the French Food Safety Agency (AFSSA) received a request from the Directorate General for Health (DGS) for an Opinion firstly on study proposals to assess bisphenol A exposure and contamination in the French population and secondly on maximum levels of bisphenol A in foods.

## 2. CONTEXT

Following the publication of the AFSSA Opinion of 29 January 2010 on the critical analysis of the results of a developmental neurotoxicity study of bisphenol A together with other recently-published data on its toxic effects, the DGS requested AFSSA to provide additional information, particularly regarding concentrations of bisphenol A in foods and exposure to bisphenol A in populations.

First, clarifications were made further to this Opinion of 29 January 2010 (Opinion of 2 March 2010).

Second, AFSSA undertook an expert assessment to respond to Request 2010-SA-0041. It had the following characteristics:

**- Questions examined:**

AFSSA will propose a study schedule to assess bisphenol A exposure and contamination in the French population and will estimate the study cost. It will provide information in response to the question on maximum levels of bisphenol A in foods.

Therefore, the subject of the request entailed:

- the description of bisphenol A concentrations in marketed foods to characterise the variability of these concentrations food by food in order to identify possible improvements to reduce exposure in populations.
- initial exposure studies in young children under the age of 3, children and adults based on daily dietary intakes of bisphenol A.
- lastly, recommendations for additional studies on both dietary exposure and biomonitoring, i.e. measurement of concentrations of bisphenol A in human biological media.

This request does not examine infant exposure through breastfeeding, which was already studied in Opinion 2009-SA-0270.

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## 3. EXPERT ASSESSMENT METHOD

An internal expert assessment of the dossier was undertaken by the AQR-PC unit of the DERNS Scientific Risk Assessment Support Unit (PASER) with validation by the AFSSA Scientific Panel on 'Physical and Chemical Contaminants and Residues'.

This expert assessment was based on data published in Europe on bisphenol A concentrations in foods and on original French data from professionals and consumer associations combined with food consumption data taken from the INCA2 (AFSSA, 2009) and Bébés-SFAE 2005 (Fantino and Gourmet, 2008) surveys. On this occasion, AFSSA created a database of BPA concentrations in foods.

Recommendations for additional exposure and contamination studies were drawn up by conducting a critical analysis of the international literature and by referring to previous AFSSA opinions. The toxicological studies that were taken into account in AFSSA Opinion 2009-SA-270 are not mentioned when they do not involve human populations.

## 4. DESCRIPTION OF DATA AND WORKING HYPOTHESES

### 4.1. Contamination data

#### 4.1.1. French data

In order to gather data needed to assess bisphenol A (BPA) concentrations in foods and to estimate the French population's exposure to BPA, AFSSA contacted authorities, consumer associations and various professional organisations. The analytical results received came from the following sources:

- The French National Association of Food Industries (ANIA), n=5 data
- The French Association of Food-Processing Companies (ADEPALE), n=66 data
- The French Soft Drink Association (SNBR), n=144 data
- The UFC-Que Choisir Consumers' association (May 2010), n=67 data
- The French Brewers' Association, n=5 data
- The French National Trade Association for Fruit Juices and Nectars (UNIJUS), n=9 data
- L'Alliance 7, n=23 data

These 319 data covered various bottled or canned food products that were grouped into major food categories which corresponded to the classification commonly used in food studies.

Overall, BPA concentrations in the analysed products varied from the limit of detection (<LOD) or the limit of quantification (<LOQ) to 128 µg/kg for the highest value in a canned mixed dish, i.e. a maximum value around 4 to 5 times lower than the Specific Migration Limit (SML) set in Europe at 600 µg/kg of food. 4.4% of values were not detected and 58.6% were not quantitated. Often, the only information that was available concerned non-quantification. The LOD[1] and LOQ[2] values received varied according to the analysis from 0.1 to 10 µg/kg and are described in Annex 1.

Maximum values varied perceptibly between the various food categories: 17 µg/kg for canned beverages and soft drinks, 39 µg/kg for canned cooked pasta such as ravioli, 80 µg/kg for canned fish, 93 µg/kg for canned vegetables, and 128 µg/kg for canned cooked dishes such as cassoulet. In light of the sample numbers, which were sometimes small (only 6 samples of canned cooked dishes), these maximum values are estimates only.

[1] LOD=Limit of Detection
[2] LOQ=Limit of Quantification

Within the food categories, BPA levels for the same food can vary by a factor of 2 or even a factor greater than 10. However, since the measured concentrations were not accompanied by information on the corresponding processing techniques used, it was not possible to make a correlation between process characteristics and measured levels. A percentage of the concentration variability was also due to analytical uncertainties.

#### 4.1.2. European data

A literature review of recent European publications (2000 to present) related to BPA levels in foods was also conducted, particularly for foods or food categories for which no data had been obtained in the French study. With the exception of several publications on BPA migration from plastic baby bottles, few other infant food products have been studied in scientific publications.

A base of 372 foods analysed for their BPA content was therefore created.

These literature data were taken into account only when French data were lacking or insufficient (less than 5 samples available) for a given food category. In the end, 181 data from the European literature were selected based on these criteria.

The various BPA levels measured in the food products under study ranged from the limits of detection or quantification to 420 µg/kg. The latter value, which was taken from an English study on canned meat products, is still lower than the regulatory specific migration limit of 600 µg/kg. LODs and LOQs varied respectively, according to the analysis and food, from 0.1 to 2 µg/kg and from 0.2 to 7 µg/kg and are described in Annex 1. 15.9% of values were not detected and 1.3% were not quantitated[3].

All of the data that were used to estimate the population's exposure are summarised in Tables 1 and 2.

[3] The unusual fact that there is a larger percentage of non-detected values than non-quantitated values is due to the fact that, in many cases, only the LOD or LOQ was given and not both.

**Table 1. Summary of contamination data used for the low exposure estimate (Scenario 1)**

| | French data (in µg/kg) | | | | | | European literature data (in µg/kg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **food group** | **n** | **mean** | **SD** | **min.** | **p50** | **max.** | **n** | **mean** | **SD** | **min.** | **p50** | **max.** |
| water heated in baby bottles | 36 | 0.5 | 0.8 | 0.0 | 0.0 | 3.4 | . | . | . | . | . | . |
| baby food | 23 | 2.0 | 3.8 | 0.0 | 0.0 | 15.8 | . | . | . | . | . | . |
| powdered milk | 3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 8 | 0.1 | 0.1 | 0.0 | 0.0 | 0.3 |
| meat products | . | . | . | . | . | . | 12 | 128.3 | 155.7 | 16.0 | 56.0 | 420.0 |
| canned fish | 30 | 18.1 | 19.7 | 0.0 | 14.0 | 80.0 | . | . | . | . | . | . |
| canned vegetables | 32 | 26.4 | 18.2 | 0.0 | 24.5 | 93.4 | . | . | . | . | . | . |
| canned pulses | . | . | . | . | . | . | 15 | 25.5 | 8.4 | 9.0 | 26.0 | 35.0 |
| bottled water | 8 | 0.3 | 0.7 | 0.0 | 0.0 | 2.0 | . | . | . | . | . | . |
| cold, non-alcoholic beverages, soft drinks and colas | 156 | 0.5 | 2.1 | 0.0 | 0.0 | 17.3 | . | . | . | . | . | . |
| soups | 1 | 77.6 | . | 77.6 | 77.6 | 77.6 | 32 | 13.1 | 12.5 | 0.0 | 9.8 | 37.6 |
| desserts | 1 | 29.0 | . | 29.0 | 29.0 | 29.0 | 8 | 18.6 | 12.4 | 0.0 | 21.4 | 29.7 |
| canned mashed and cooked fruits | 1 | 13.0 | . | 13.0 | 13.0 | 13.0 | 19 | 13.8 | 11.3 | 5.0 | 6.8 | 38.0 |
| sauces | 6 | 13.4 | 6.7 | 2.4 | 14.0 | 21.0 | . | . | . | . | . | . |
| milk | . | . | . | . | . | . | 8 | 1.5 | 0.7 | 1.0 | 1.2 | 2.6 |
| condensed milk | . | . | . | . | . | . | 2 | 12.5 | 2.1 | 11.0 | 12.5 | 14.0 |
| wine | . | . | . | . | . | . | 59 | 0.4 | 0.4 | 0.0 | 0.3 | 2.1 |
| beer, cider | 6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 11 | 0.5 | 0.8 | 0.0 | 0.0 | 1.5 |
| mixed dishes | 6 | 86.5 | 40.1 | 35.0 | 100.5 | 128.0 | . | . | . | . | . | . |
| cooked pasta | 10 | 30.1 | 6.9 | 21.0 | 29.5 | 39.0 | 7 | 15.4 | 17.0 | 0.0 | 9.0 | 41.0 |

**Table 2. Summary of contamination data used for the high exposure estimate (Scenario 2)**

| | French data (in µg/kg) | | | | | | European literature data (in µg/kg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **food group** | **n** | **mean** | **SD** | **min.** | **p50** | **max.** | **n** | **mean** | **SD** | **min.** | **p50** | **max.** |
| water heated in baby bottles | 36[4] | 0.8 | 0.6 | 0.5 | 0.5 | 3.4 | . | . | . | . | . | . |
| baby food | 23 | 6.4 | 4.7 | 0.1 | 8.6 | 15.8 | . | . | . | . | . | . |
| powdered milk | 3 | 10.0 | 0.0 | 10.0 | 10.0 | 10.0 | 8 | 1.6 | 0.8 | 0.3 | 2.0 | 2.0 |
| meat products | . | . | . | . | . | . | 12 | 128.3 | 155.7 | 16.0 | 56.0 | 420.0 |
| canned fish | 30 | 19.2 | 18.9 | 2.0 | 14.0 | 80.0 | . | . | . | . | . | . |
| canned vegetables | 32 | 26.7 | 17.8 | 7.0 | 24.5 | 93.4 | . | . | . | . | . | . |
| canned pulses | . | . | . | . | . | . | 15 | 25.5 | 8.4 | 9.0 | 26.0 | 35.0 |
| bottled water | 8 | 0.5 | 0.7 | 0.1 | 0.1 | 2.0 | . | . | . | . | . | . |
| cold, non-alcoholic beverages, soft drinks and colas | 156 | 1.8 | 2.1 | 0.5 | 2.0 | 17.3 | . | . | . | . | . | . |
| soups | 1 | 77.6 | . | 77.6 | 77.6 | 77.6 | 32 | 14.0 | 11.6 | 2.0 | 9.8 | 37.6 |
| desserts | 1 | 29.0 | . | 29.0 | 29.0 | 29.0 | 8 | 18.9 | 12.0 | 2.0 | 21.4 | 29.7 |
| canned mashed and cooked fruits | 1 | 13.0 | . | 13.0 | 13.0 | 13.0 | 19 | 13.8 | 11.3 | 5.0 | 6.8 | 38.0 |
| sauces | 6 | 13.4 | 6.7 | 2.4 | 14.0 | 21.0 | . | . | . | . | . | . |
| milk | . | . | . | . | . | . | 8 | 1.5 | 0.7 | 1.0 | 1.2 | 2.6 |
| condensed milk | . | . | . | . | . | . | 2 | 12.5 | 2.1 | 11.0 | 12.5 | 14.0 |
| wine | . | . | . | . | . | . | 59 | 0.5 | 0.4 | 0.1 | 0.3 | 2.1 |
| beer, cider | 6 | 8.5 | 3.7 | 1.0 | 10.0 | 10.0 | 11 | 2.3 | 1.6 | 1.5 | 2.0 | 7.0 |
| mixed dishes | 6 | 86.5 | 40.1 | 35.0 | 100.5 | 128.0 | . | . | . | . | . | . |
| cooked pasta | 10 | 30.1 | 6.9 | 21.0 | 29.5 | 39.0 | 7 | 16.7 | 15.8 | 2.0 | 9.0 | 41.0 |

A total of 500 data were used for this Opinion to assess the French population's exposure to BPA.

[4] These 36 data were taken from the UFC-Que Choisir study that examined 18 plastic baby bottles including 13 polycarbonate bottles heated for either one minute or three minutes in a microwave.

With respect to censored data (≤LOD or ≤LOQ), the following rules were applied:

- Scenario 1, low estimate: all non-detected (≤LOD) and non-quantitated (≤LOQ) values are set at 0 (Table 1).
- Scenario 2, high estimate: all values ≤ LOD are set at the corresponding LOD and all values ≤ LOQ are set at the corresponding LOQ (Table 2).

Scenario 2 will end up over-estimating product contamination and consequently consumer exposure, with the goal of protecting the population.

## 4.2. Consumption data

This Opinion uses consumption data relating to the general population (children aged 3 to 17 years and adults aged 18 years and older) and the population of infants and young children under the age of 36 months. To that end, two studies were used:

### 4.2.1. Bébés-SFAE 2005 study

The study was conducted in the field from 12 January to 10 March 2005 by TNS-SOFRES for the French Association for Children's Food, a member of Alliance 7 (Fantino and Gourmet, 2008). Consumption data were collected in the homes of 713 children (between the ages of 15 days and 36 and a half months), using the food diary technique, on three consecutive days, meal by meal. They were noted by the children's caregivers (usually the mother and/or nanny, with the father's participation).

This study included infants and young children who were not breastfed (exclusively or partially) and who did not attend a day nursery or a school in the three days following recruitment. This is because the amount of milk consumed by breastfed babies is difficult to assess. Given the fact that the composition of breast milk varies, the dietary consumption of fully or partially breastfed children would have required a specific protocol and an analysis of each woman's breast milk, possibly even at each feed. Breastfed children were therefore excluded by TNS-SOFRES.

Seven food diaries had to be excluded from the nutritional analysis because they were too incomplete to be taken into consideration. Moreover, the body weight was not provided in one case. Calculations were therefore performed for 705 children.

This consumption study's classification included 32 main food categories with sub-categories (e.g. the cereals category included infant cereals and breakfast cereals).

### 4.2.2. INCA2 consumption study

The consumption data used to calculate BPA intakes in the general population were taken from the individual and national survey of food consumption (INCA2) for the 2005-2007 period (AFSSA, 2009) that was representative of the French population. This study's survey base was the INSEE census.

In total, more than 4,079 people were surveyed, with 4 study waves from December 2005 to April 2007, including 1,455 children aged 3 to 17 years and 2,624 adults aged 18 years or older. In order to avoid underestimating exposure, under-reporters were excluded from the calculations.

Consumption data were gathered using 7-day diaries and a manual of photographs to assess portion sizes that distinguished between 1,342 different foods.

## 4.3. Exposure assessment methodology

In order to estimate exposure levels, individual consumption data were cross-referenced with mean contamination levels for each food category. BPA intake was estimated by assigning a contamination value to a food category that was broader than the foods that were actually sampled and analysed. Indeed, food container types were not always specified in the consumption studies.

This approach was preferred in order to produce more conservative scenarios.

For example, bisphenol A concentrations in canned soft drinks were applied to all soft drinks, irrespective of their packaging type, whereas the market share of cans in soft drink consumption totals around 18% (source: SNBR).

## 5. RESULTS OF THE ESTIMATE OF BPA EXPOSURE IN THE FRENCH POPULATION

The detailed calculation results are presented in Annex 1.

### 5.1. Infants and children under the age of 36 months

#### 5.1.1. Scenario 1: low estimate

Exposure in young children is 0.1 µg/kg on average and 0.4 µg/kg at the 97.5$^{th}$ percentile. With a 99.6% consumer rate, the results are similar between consumers and the entire population. Because it is consumed in large quantities, milk (other than infant formulas) is the leading contributor (40% of total mean intakes), although bisphenol A concentrations in standard milk are often lower than the limit of quantification. Baby food and canned fruits are also contributors that respectively account for 25% and 14% of total mean intakes.

#### 5.1.2. Scenario 2: high estimate

In the worst-case scenario, exposure is 0.2 µg/kg on average and 0.5 µg/kg at the 97.5$^{th}$ percentile. The food categories that mainly contribute to the total mean intake are baby food (41% of intake), milk excluding infant formulas (21%) and infant formula (16%).

The food categories that contribute the most to intake differ between scenario 1 and scenario 2, which shows that there are lingering uncertainties in this regard.

For infants under the age of 3 months and under the age of 6 months respectively, in its Opinion 2008-SA-0141, AFSSA had mentioned maximum exposure levels of 11 µg/kg b.w./day and 13 µg/kg b.w./day through conservative scenarios estimated by EFSA. Taking data on the highest bisphenol A concentration level in water heated for three minutes in a microwave in a polycarbonate baby bottle that was published by UFC-Que Choisir, which corresponds to a considerable overestimate of heating practices, with the same consumption data (1060 ml water per day for 6.1 kg body weight, data from the study by (Kersting *et al*, 1998)), we obtain an exposure level of 0.6 µg/kg b.w./day. With heating for one minute, maximum exposure is only 0.09 µg/kg b.w./day, which shows the significance of limiting microwave heating time in order to keep exposure as low as possible. In the AFSSA Opinion 2009-SA-0270, infant exposure, via bottles and formula, had been estimated at 0.5 µg/kg b.w./day on average with a maximum estimate of 2.2 µg/kg b.w./day and a minimum estimate of 0.22 µg/kg b.w./day. At the time, there were no French data on BPA concentrations in formulas and exposure was calculated on the basis of Canadian data from (Cao *et al*., 2009) on canned liquid formulas with a theoretical consumption scenario. The data given in this Opinion are perceptibly lower as they reflect the French situation in which the vast majority of marketed formulas are powdered milks, and liquid milks are marketed not in metal tins but in plastic bottles.

### 5.2. Adults, women of childbearing age and children aged 3 to 17 years

#### 5.2.1. Scenario 1: low estimate

Exposure in children aged 3 to 17 years is 0.2 µg/kg b.w./day on average and 0.5 µg/kg b.w./day for high consumers (97.5$^{th}$ percentile).

For adults, average exposure is 0.1 µg/kg b.w./day and 0.3 µg/kg b.w./day for high consumers.

For women of childbearing age (aged 18 to 44 years), average exposure is 0.1 µg/kg b.w./day and 0.3 µg/kg b.w./day for high consumers.

The rate of consumers is 100% in the 3-17-year-old population, 99.6% in the adult population and 99.9% in women of childbearing age, and so the results are the same for the general population and consumers only. It is therefore not necessary to differentiate the "consumers only" category.

#### 5.2.2. Scenario 2: high estimate

For children aged 3-17 years, the high estimate of BPA exposure is 0.2 µg/kg b.w./day on average and 0.6 µg/kg b.w./day at the 97.5$^{th}$ percentile.

For the adult population, exposure is 0.1 µg/kg b.w./day on average and 0.3 µg/kg b.w./day at the 97.5$^{th}$ percentile.

For women of childbearing age, average exposure is the same as for the adult population as a whole (0.1 µg/kg b.w./day and 0.3 µg/kg b.w./day at the 97.5$^{th}$ percentile).

In both scenarios, the exposure estimates are comparable for adults, women of childbearing age and children.

For the adult population, the main food groups that contribute to exposure are canned mixed dishes (42 to 44% according to the scenario), followed by canned soups (around 14%), meat products (around 8.5%) and canned vegetables (around 8%).

The breakdown is the same for women aged 18 to 44 years: mixed dishes make up 43 to 46% of total exposure, soups 9.5% and canned meat products and vegetables around 8% each.

For children, this breakdown is fairly similar. Mixed dishes contribute the most to total exposure (37 to 39% according to the scenario), followed by desserts (around 10.5%), soups (9.8%), canned vegetables (around 8.5%), canned cooked pasta (around 8%) and canned meat products (6%). It should be noted that these are maximum contributions since foods that can potentially be canned were considered to be canned foods.

Intakes due to migration from polycarbonate tableware or kitchen utensils could not be estimated due to a lack of data on the frequency at which these recipients are used. Data on migration from polycarbonate baby bottles to water show concentration levels in water (or milk) that are lower than those observed in several canned foods. It is therefore possible to consider that the order of magnitude for total exposure was not underestimated due to the conservative hypotheses that were taken into account regarding the consumption of canned foods. However, these first exposure estimates would need to be supplemented by taking into account migration from polycarbonate recipients and utensils or PVC film.

## 6. BPA CONTAMINATION AND EXPOSURE, INVENTORY OF EXISTING DATA AND STUDY PROPOSALS

A literature review of exposure and contamination studies was conducted (Annex 2).

Two types of studies were mainly found in the literature:

- **Studies on external exposure** through food and possibly via other routes of exposure based on bisphenol A levels in foods, supplemented with data in media and combined with information on exposure factors such as food consumption. The exposure study presented in the previous section is an example of an external exposure study. These studies are relatively rare internationally and very few examine non-dietary exposure. In the study by (Wilson *et al*, 2007) and in the case of young children, dietary exposure was estimated to be the most common. (Stahlhut *et al*, 2009), in the NHANES study, were unable to make a correlation between urinary excretion of BPA and the time elapsed between the last meal and the sample. The latter study suffered however from methodological limitations. The contribution of dietary exposure to total exposure has not been sufficiently documented. AFSSA therefore recommends collecting further data on BPA concentrations in foods and information on heating practices for foods in polycarbonate containers or in contact with PVC film to estimate dietary exposure. AFSSA will include bisphenol A in the next French exposure study, the so-called total diet study for infants (EAT). To estimate non-dietary exposure, AFSSA recommends collecting data on BPA concentrations in interior air and in dust and combining external exposure estimates with contamination measurements. To more precisely define useful BPA measurements in media, it will be relevant to refer to the AFSSET industry study that is in progress. The influence that the use of dental cement containing BPA has on contamination can also be studied by introducing questions on the use of this material type in biomonitoring studies.

- **Biomonitoring or bisphenol A contamination studies** with urine or blood sampling possibly combined with a more or less complex dietary questionnaire. There are many of these studies at the international level and they generally show contamination in all populations under study (Vandenberg *et al*, 2010). These contamination levels give estimated external exposure levels lower than 1 µg/kg b.w./day, i.e. levels significantly lower than EFSA's Tolerable Daily Intake (TDI) of 50 µg/kg b.w./day. Contamination levels vary by age, sex, and sometimes income, education level and other socio-demographic factors. Contamination in children is often higher than contamination in adults. Measured contamination levels are rarely correlated with indicators of dietary habits, and some authors believe this calls into question the hypothesis of a dominant dietary source. **However, it is also important to consider that, since contamination varies significantly over time, it is not always possible to link it reliably to information about subjects' dietary habits** (Mahalingaiah *et al*, 2008). In France, there are few BPA contamination data. A published study in a particular population of patients visiting hospitals in Lyon shows contamination levels similar to those observed in the general population in other countries, but these data cannot be considered representative of the French population. This type of bisphenol A contamination study therefore needs to be developed for the general population. AFSSA recommends including bisphenol A in the national biomonitoring strategy managed by the InVS. It should be noted that the AFSSA Opinion 2009-SA-0270 also recommended acquiring French data on BPA levels in breast milk.

- To supplement external exposure and biomonitoring studies that are representative of the general population, AFSSA emphasises the significance of comparing external and internal exposure levels in the framework of the same study in order to better characterise exposure sources. This type of study cannot be undertaken in the general population because the time spent simultaneously participating in both the external exposure and biological sampling components may excessively limit the participation rate. AFSSA therefore recommends developing this third study type among a limited number of volunteers (around 50 children and 50 adults), reproducing intentionally contrasting exposure scenarios. This type of study would combine a component on external exposure based on measurements in foods and in media and environments and repeated contamination measurements (at least three per participant). This third study type would characterise dietary and non-dietary routes of bisphenol A exposure for the adult and child populations with greater certainty than the two study types mentioned above. This study type's main methodological themes are presented in Annex 2.

- It should be noted, moreover, that existing toxico-kinetic studies in the human population for bisphenol A remain insufficient (AFSSA Opinion 2009-SA-0270) for linking *in vivo* effects in laboratory animals to potential effects in humans related to contamination levels.

## 7. CONCLUSION

Bisphenol A levels in foods, as analysed in 691 samples, mainly in France, are appreciably lower than the specific migration limit that has been established in Europe. The considerable variability in BPA contamination levels observed between food categories and even between foods in the same category can be linked to analytical biases, the food's physico-chemical characteristics and processing techniques, as well as to the technologies that are used to manufacture food contact materials.

Dietary exposure levels in the French population, including infants and children under the age of 3 years, are significantly lower than the TDI set by EFSA (<2%) and are comparable to those observed in other international studies.

Recent studies have reported possible toxic effects after exposure during the perinatal period in connection with BPA's endocrine disruptor properties. In its Opinion of 29 January 2010, AFSSA concluded that the consequences of these warning signs for human health remained to be established. It considers, however, that consumer exposure to BPA should be kept as low as possible, especially for the most sensitive consumers. It therefore recommends reassessing BPA's specific migration limit by using the best technologies currently available. It also recommends the systematic labelling of household utensils that are in contact with foods and that contain BPA (plastic boxes, etc.) so that they are not used to heat foods for an extended length of time.

Moreover, AFSSA recommends developing in-depth studies to better characterise BPA concentrations in foods, dietary and non-dietary exposure in the general population and contamination levels, using the biomonitoring programme provided for in the French national health and environment plan, PNSE2.

It also draws attention to the fact that BPA fits into the more general issue of endocrine disruptors and that manufacturers should be encouraged to develop BPA substitutes for food use, and that potential substitutes will have to undergo a prior in-depth assessment.

**The Director General**

**Marc MORTUREUX**

## KEYWORDS

BISPHENOL A, EXPOSURE, CONTAMINATION, BIOMONITORING

## REFERENCES

AFSSA (2008) AFSSA Opinion regarding bisphenol A in polycarbonate baby bottles likely to be heated in microwave ovens, Request no. 2008-SA-0141

AFSSA (2009) AFSSA Memo regarding the publication by Stahlhut *et al* (2009) on urinary elimination of bisphenol A in humans, Request no. 2009-SA-0177

AFSSA (2009). Individual National Study on Food Consumption (INCA2) 2006-2007. Coordinator: Lionel Lafay.

AFSSA (2010) AFSSA Opinion on the critical analysis of the results of a developmental neurotoxicity study of bisphenol A together with other recently-published data on its toxic effects, Request no. 2009-SA-0270

AFSSA (2010) AFSSA Opinion regarding clarification of the AFSSA Opinion on bisphenol A issued on 29 January 2010, Request no. 2010-SA-0040, Related Requests no. 2009-SA-0270 and no. 2010-SA-0041

Becker K *et al* (2009) GerES IV: phthalate metabolites and bisphenol A in urine of German children. Int J Hyg Environ Health 212(6):685-92

Braunrath, R., Podlipna, D., Padlesak, S. & Cichna-Markl, M. (2005) Determination of bisphenol A in canned foods by immunoaffinity chromatography, HPLC, and fluorescence detection. J Agric Food Chem, 53, 8911-7.

Braunrath, R. & Cichna, M. (2005) Sample preparation including sol-gel immunoaffinity chromatography for determination of bisphenol A in canned beverages, fruits and vegetables. J Chromatogr A, 1062, 189-98.

Brede C *et al* (2003) Increased migration levels of bisphenol A from polycarbonate baby bottles after dishwashing, boiling and brushing. Food Addit. Contam. 20:684-689

Brenn-Struckhofova, Z. & Cichna-Markl, M. (2006) Determination of bisphenol A in wine by sol-gel immunoaffinity chromatography, HPLC and fluorescence detection. Food Addit Contam, 23, 1227-35.

Calafat AM *et al* (2005) Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population, Environ Health Perspect 113(4), 391-395

Calafat AM *et al* (2008) Exposure of the US population to bisphenol A and 4-tertiary-octylphenol: 2003-2004, Environ Health Perspect, 116(1), 39-44

Carwile JL *et al* (2009) Polycarbonate bottle use and urinary bisphenol A concentrations, Environ Health Perspect, 117(9) 1368-1372

Casajuana, N. & Lacorte, S. (2004) New methodology for the determination of phthalate esters, bisphenol A, bisphenol A diglycidyl ether, and nonylphenol in commercial whole milk samples. J Agric Food Chem, 52, 3702-7.

Cao XL *et al* (2008) Levels of bisphenol A in canned liquid infant formula products in Canada and dietary intakes estimates. J Agric Food Chem. 56(17), 7919-24

EFSA (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) question number EFSA-Q-2005-100, The EFSA Journal 428, 75 pages

Ehlert, K. A., Beumer, C. W. & Groot, M. C. (2008) Migration of bisphenol A into water from polycarbonate baby bottles during microwave heating. Food Addit Contam Part A Chem Anal Control Expo Risk Assess, 25, 904-10.

Engel SM *et al* (2006) Xenobiotic phenols in early pregnancy amniotic fluid. Reprod Toxicol 21 : 110-112

Fantino M. et Gourmet E., (2008). Apports nutritionnels en France en 2005 chez les enfants non allaités âgés de moins de 36 mois. Archives de pédiatrie, 15, 446-455.

FSA 'Survey of Bisphenols in Canned Foods' (Number 13/01), March 2001. Food Survey Information Sheet. http://www.food.gov.uk/science/surveillance/fsis2001/bisphenols

Goodson A *et al* (2004) Migration of bisphenol A from can coatings, effects of damage, storage conditions and heating. Food Addit Contam 21(10): 1015-26

Goodson, A., Summerfield, W. & Cooper, I. (2002) Survey of bisphenol A and bisphenol F in canned foods. Food Addit Contam, 19, 796-802.

Grumetto, L., Montesano, D., Seccia, S., Albrizio, S. & Barbato, F. (2008) Determination of bisphenol a and bisphenol B residues in canned peeled tomatoes by reversed-phase liquid chromatography. J Agric Food Chem, 56, 10633-7.

He Y *et al* (2009) Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels, Environ Res 109, 629-633

Huyghe E, Plante P, Thonneau PF (2007) Testicular cancer variations in time and space in Europe. European Urology 51:621-628

Kaddar N *et al* (2009) Development of a radioimmunoassay for the measurement of Bisphenol A in biological samples Analytica Chimica Acta 645 : 1-4

Kang JH, Kondo F, Katayama Y (2006) Human exposure to bisphenol A, Toxicology 226, 79-89

Kamrin MA (2004) Bisphenol A : a scientific evaluation, MedGenMed 6(3) : 7

Kersting M *et al* (1998) Measured consumption of commercial infant food products in German infants: results from the DONALD study. Dortmund Nutritional and Anthropometrical Longitudinally Designed. J Pediatr Gastroentrol Nutr 27, 547-552

Lakind J S, Naiman D Q (2010) Daily intake of bisphenol A and potential sources of exposure : 2005-2006 National Health and Nutrition Examination Survey, J Expo Sci Environ Epidemiol, 1-8

Lopez-Cervantes J, Paseiro-Losada P (2003) Determination of bisphenol A in, and its migration from, PVC stretch film used for food packaging, Food Addit Contam, 20(6), 596-606

Mahalingaiah S *et al*, (2008) Temporal variability and predictors of urinary bisphenol A concentrations in men and women, Environ Health Perspect, 116:173-178

Matsumoto A *et al* (2003) Bisphenol A levels in human urine, Environ Health Perspect. 111, 101-104

Munguia-Lopez EM *et al* (2005) Migration of bisphenol A from can coatings into a fatty-food stimulant and tuna fish, Food Addit Contam 22(9), 892-898

Otaka H, Yasuhara A, Morita M (2003) Determination of bisphenol A and 4-nonylphenol in human milk using alkaline digestion and cleanup by solid-phase extraction. Anal Sci 19(12):1663-1666

Stahlhut RW, Welshons WV, Swan SH (2009) Bisphenol A data in Nhanes suggest longer than expected half-life, substantial nonfood exposure, or both, Environ Health Perspect, 117(5), 784-789

Thomson BM, Grounds PR (2005) Bisphenol A in canned foods in New Zealand : an exposure assessment, Food Addit Contam, 22(1), 65-72

Vandenberg L N *et al* (2010) Urinary, circulating and tissue biomonitoring studies indicate widespread exposure to Bisphenol A, Environ Health Perspect, http://dx.doi.org

Von Goetz *et al* (2010) Bisphenol A : how the most relevant exposure sources contribute to total consumer exposure, Risk anal, 30(3):473-87

Wilson NK *et al* (2007) An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol A, and nonylphenol at home and daycare, Environ Res 103 : 9-20

Ye X *et al* (2009) Stability of the conjugated species of environmental phenols and parabens in human serum, Environ int, 35(8) 1160-1163

Ye X *et al* (2009) Levels of metabolites of organophosphate pesticides, phthalates and bisphenol A in polled urine specimens from pregnant women participating in the Norwegian Mother and Child cohort study (MoBa), Int J Hyg Environ Health 212, 481-491

Yoshida T *et al* (2001) Determination of bisphenol A in canned vegetables and fruit by high performance liquid chromatography. Food Addit Contam 18(1): 69-75

## ANNEX 1

**Table 3. Detailed estimate of exposure to BPA in infants and children under the age of 36 months according to both scenarios (low and high estimates)**

| food group | Low estimate | | | High estimate | | |
|---|---|---|---|---|---|---|
| | mean µg/kg b.w./day | p97.5 µg/kg b.w./day | Contribution % | mean µg/kg b.w./day | p97.5 µg/kg b.w./day | Contribution % |
| Water (heated in plastic baby bottles for 1 to 3 minutes in a microwave)* | 0.00 | 0.02 | 4.0% | 0.01 | 0.03 | 3.2% |
| Canned fruits | 0.01 | 0.11 | 13.9% | 0.01 | 0.11 | 7.5% |
| Canned vegetables | 0.01 | 0.06 | 5.0% | 0.01 | 0.06 | 2.7% |
| Baby food | 0.03 | 0.11 | 24.8% | 0.08 | 0.34 | 41.2% |
| Canned mixed dishes | 0.01 | 0.10 | 5.0% | 0.01 | 0.10 | 2.7% |
| Canned fish | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| Canned soups | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| Fruit juices and nectars | 0.00 | 0.00 | 0.0% | 0.00 | 0.02 | 1.1% |
| Canned desserts | 0.00 | 0.05 | 3.0% | 0.00 | 0.05 | 1.6% |
| Infant formula | 0.00 | 0.00 | 0.0% | 0.03 | 0.10 | 15.5% |
| cold, non-alcoholic beverages | 0.00 | 0.00 | 0.0% | 0.00 | 0.01 | 0.5% |
| Sauces | 0.00 | 0.01 | 1.0% | 0.00 | 0.01 | 0.5% |
| Milk | 0.04 | 0.27 | 39.6% | 0.04 | 0.27 | 21.4% |
| Canned meat products | 0.00 | 0.07 | 4.0% | 0.00 | 0.07 | 2.1% |
| **TOTAL** | **0.10** | **0.40** | **100.0%** | **0.19** | **0.49** | **100.0%** |

*By default, in order to simulate the 'worst-case scenario' in young children, the content of water heated in a microwave in plastic baby bottles was applied to all consumed water and not only water used to prepare infant formula. However, this conservative hypothesis has little impact on total exposure.

**Table 4. Detailed estimates of exposure to BPA in adults (18 years and older), according to both scenarios (low and high estimates)**

| | Low estimate | | | High estimate | | |
|---|---|---|---|---|---|---|
| food group | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % |
| meat products | 0.01 | 0.07 | 8.9% | 0.01 | 0.07 | 8.4% |
| canned fish | 0.00 | 0.01 | 0.8% | 0.00 | 0.01 | 0.8% |
| canned vegetables | 0.01 | 0.04 | 8.1% | 0.01 | 0.04 | 7.6% |
| canned pulses | 0.00 | 0.02 | 1.6% | 0.00 | 0.02 | 1.5% |
| bottled water | 0.00 | 0.01 | 1.6% | 0.00 | 0.01 | 2.3% |
| cold, non-alcoholic beverages | 0.00 | 0.01 | 0.8% | 0.00 | 0.02 | 3.1% |
| soups | 0.02 | 0.10 | 14.5% | 0.02 | 0.10 | 14.5% |
| desserts | 0.01 | 0.04 | 6.5% | 0.01 | 0.04 | 6.1% |
| mashed and cooked fruits | 0.00 | 0.02 | 2.4% | 0.00 | 0.02 | 2.3% |
| sauces | 0.00 | 0.01 | 3.2% | 0.00 | 0.01 | 3.1% |
| milk | 0.00 | 0.01 | 1.6% | 0.00 | 0.01 | 1.5% |
| condensed milk | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| wine | 0.00 | 0.00 | 0.8% | 0.00 | 0.00 | 0.8% |
| beer, cider | 0.00 | 0.00 | 0.0% | 0.00 | 0.02 | 1.5% |
| mixed dishes | 0.06 | 0.23 | 44.4% | 0.06 | 0.23 | 42.0% |
| pasta dishes | 0.01 | 0.04 | 5.6% | 0.01 | 0.04 | 5.3% |
| **TOTAL** | **0.12** | **0.33** | **100.0%** | **0.13** | **0.34** | **100.0%** |

**Table 5. Detailed estimates of exposure to BPA in women of childbearing age (18 to 44 years), according to both scenarios (low and high estimates)**

| food group | Low estimate | | | High estimate | | |
|---|---|---|---|---|---|---|
| | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % |
| meat products | 0.01 | 0.07 | 8.4% | 0.01 | 0.07 | 7.9% |
| canned fish | 0.00 | 0.01 | 0.8% | 0.00 | 0.01 | 0.8% |
| canned vegetables | 0.01 | 0.04 | 8.4% | 0.01 | 0.04 | 7.9% |
| canned pulses | 0.00 | 0.01 | 1.7% | 0.00 | 0.01 | 1.6% |
| bottled water | 0.00 | 0.01 | 1.7% | 0.00 | 0.01 | 2.4% |
| cold, non-alcoholic beverages | 0.00 | 0.01 | 1.7% | 0.01 | 0.03 | 4.8% |
| soups | 0.01 | 0.07 | 9.2% | 0.01 | 0.07 | 9.5% |
| desserts | 0.01 | 0.04 | 6.7% | 0.01 | 0.04 | 6.3% |
| mashed and cooked fruits | 0.00 | 0.02 | 1.7% | 0.00 | 0.02 | 1.6% |
| sauces | 0.00 | 0.01 | 3.4% | 0.00 | 0.01 | 3.2% |
| milk | 0.00 | 0.01 | 1.7% | 0.00 | 0.01 | 1.6% |
| condensed milk | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| wine | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| beer, cider | 0.00 | 0.00 | 0.0% | 0.00 | 0.02 | 1.6% |
| mixed dishes | 0.06 | 0.22 | 46.2% | 0.06 | 0.22 | 43.7% |
| pasta dishes | 0.01 | 0.04 | 7.6% | 0.01 | 0.04 | 7.1% |
| **TOTAL** | **0.12** | **0.31** | **100.0%** | **0.13** | **0.31** | **100.0%** |

**Table 6. Detailed estimates of exposure to BPA in children (aged 3-17 years), according to both scenarios (low and high estimates)**

| food group | Low estimate | | | High estimate | | |
|---|---|---|---|---|---|---|
| | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % | mean (µg/kg b.w./day) | p97.5 (µg/kg b.w./day) | Contribution % |
| meat products | 0.01 | 0.08 | 6.3% | 0.01 | 0.08 | 6.0% |
| canned fish | 0.00 | 0.02 | 1.1% | 0.00 | 0.02 | 1.0% |
| canned vegetables | 0.02 | 0.07 | 8.5% | 0.02 | 0.07 | 8.0% |
| canned pulses | 0.00 | 0.03 | 1.6% | 0.00 | 0.03 | 1.5% |
| bottled water | 0.00 | 0.01 | 1.1% | 0.00 | 0.01 | 1.5% |
| cold, non-alcoholic beverages | 0.00 | 0.01 | 1.6% | 0.01 | 0.04 | 5.0% |
| soups | 0.02 | 0.12 | 10.1% | 0.02 | 0.13 | 10.0% |
| desserts | 0.02 | 0.11 | 10.6% | 0.02 | 0.11 | 10.0% |
| mashed and cooked fruits | 0.01 | 0.06 | 4.8% | 0.01 | 0.06 | 4.5% |
| sauces | 0.01 | 0.02 | 2.6% | 0.01 | 0.02 | 2.5% |
| milk | 0.01 | 0.04 | 4.8% | 0.01 | 0.04 | 4.5% |
| condensed milk | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| wine | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| beer, cider | 0.00 | 0.00 | 0.0% | 0.00 | 0.00 | 0.0% |
| mixed dishes | 0.07 | 0.31 | 39.2% | 0.07 | 0.31 | 37.0% |
| pasta dishes | 0.02 | 0.07 | 7.9% | 0.02 | 0.07 | 7.5% |
| **TOTAL** | **0.19** | **0.53** | **100.0%** | **0.20** | **0.55** | **100.0%** |

**Table 7. Limits of detection/quantification from BPA contamination data (in µg/kg):**

| Literature data | LOD | LOQ |
|---|---|---|
| Brenn-Struckhofova, 2006 | 0.1 | 0.2 |
| Casajuana, 2004 | 0.15 | - |
| Braunrath, 2005 | [0.1-7.4] | - |
| FSA, 2001 | 2 | 7 |

| French data | LOD | LOQ |
|---|---|---|
| ANIA | - | 0.1 |
| ADEPALE | 2 | - |
| SNBR | - | [0.5-2] |
| UFC-Que choisir | - | [0.5-10] |
| French Brewers' Association | 10 | - |
| UNIJUS | - | [0.1-10] |
| ALLIANCE 7 | 0.1 | 10 |

## ANNEX 2

### BPA contamination and exposure, inventory of existing data and study proposals

In its Request of 17 February 2010, the Directorate General for Healt(DGS) requested AFSSA to:

- propose relevant studies to assess bisphenol A exposure in the French population, and particularly in sensitive populations
- coordinate work on the relationships between external and internal exposure to bisphenol A, in conjunction with the work that AFSSET is coordinating on endocrine disruptors in the framework of the INSERM collective expert assessment
- submit a schedule of exposure studies and their cost and a timetable of expert assessment work

In particular, the DGS wished to determine the maximum contamination threshold to be determined in certain foods and beverages.

**This part of the response to the request aims to give an inventory of existing exposure studies and propose additional studies if necessary.** It should be noted that exposure studies are one of the four stages of a risk assessment. They assess and characterise risk if the hazard level of the agent or substance has been characterised.

#### 1. Context of the request and indication of the limits to the scope of the expert assessment

For greater efficiency and in order to focus efforts on substances requiring specific studies, exposure studies adhere to a general principle of step-by-step studies, starting with rough and yet conservative methods as they largely overestimate exposure, and conducting realistic exposure studies only when these prove to be necessary.

In the case of bisphenol A, the European Food Safety Authority (EFSA) made conservative and non-realistic exposure estimates in 2006 that it did not deem necessary to refine given that these estimates were lower than the tolerable daily intake of 50 µg BPA/kg b.w./day for all the populations under study, including breastfed and bottle-fed infants, children and adults (EFSA, 2006).

It follows that there is a difference in order of magnitude between EFSA's conservative exposure estimates, which are based on concentrations in foods, and exposure estimates based on urinary excretion of BPA. External exposure based on levels in foods vary from 0.2 to 13 µg/kg b.w./day according to age group and feeding methods in infants and young children and mean exposure totals 1.5 µg/kg b.w./day in adults. However, exposure estimates based on urinary excretion are significantly lower, with, for example, a 95$^{th}$ percentile estimated at 0.16 µg/kg b.w./day for an American adult, which corresponds to 5.18 µg/l of urine (Calafat *et al.*, 2005).

Because of these uncertainties, it is presently difficult to classify the sources of consumer exposure and particularly to identify the percentage of exposure that is related to foods and the various food groups. For infants and young children, it is considered that polycarbonate baby bottles are the main source of BPA. However, for children who eat solid foods and for adults, there is not a great deal of information that can be used to estimate the relative contribution of the various potential sources: polycarbonate kitchen utensils, canned foods, canned beverages, non-dietary routes of exposure.

In this opinion, we will examine study methodologies that would shed further light on routes of exposure to BPA, in order to identify approaches that could reduce exposure in the population and especially in the most exposed population (young children in particular).

## 2. Expert assessment method

After we review the literature on BPA exposure and particularly studies that identify and characterise the various potential sources, we will propose various study methods and will analyse their advantages and disadvantages in response to the various questions that have been raised.

The expert assessment therefore has four phases:

Analysis of questions raised and definition of study objectives,

Inventory of study methods to answer the questions,

Degree of response to questions raised and to objectives (fully, significantly, partially, not at all),

Study recommendations.

## 3. Analysis of the assessment subject using the described assessment method

### a. Analysis of questions raised

The following two questions were raised by the Directorate General for Health in terms of the proposal for exposure studies:

propose relevant studies to assess bisphenol A exposure and contamination in the French population, and particularly in sensitive populations

coordinate work on the relationships between external and internal exposure to bisphenol A, in conjunction with the work that AFSSET is coordinating on endocrine disruptors in the framework of the INSERM collective expert assessment

These information requests can be broken down into sub-questions as follows:

**SQ1 Assess external exposure to BPA in the French population, particularly in sensitive populations (young children, pregnant women)**

**SQ1 Assess internal exposure to BPA contamination in the French population, particularly in sensitive populations (young children, pregnant women)**

**SQ3 Study links between external and internal BPA exposure and BPA contamination**

**SQ4 Include this information on BPA exposure or contamination in a broader risk assessment of endocrine disruptors**

Another implicit objective can be added because it is closely connected to the questions raised and particularly the question related to maximum limits in foods:

**SQ5 Study the various sources of BPA exposure in the population (dietary and non-dietary), and in particular link BPA exposure and BPA concentrations in foods and media**

Epidemiological studies comparing BPA contamination and health effects do not fall within the scope of this Opinion, and neither do toxico-kinetic studies. These may be the subject of methodological recommendations at a later time if necessary.

### b. Inventory of study methods to answer the questions raised

Most of the questions raised deal with human populations, while questions SQ1 and SQ5 also deal with foods and media. A literature review of studies that have mainly been undertaken in the United States, Europe and Japan shows that it is however necessary to distinguish between studies in populations of volunteers subject to an experimental programme that may be complex, and the general population or large samples for which there needs to be a high participation rate and therefore less complex programmes to achieve representativeness (Vandenberg *et al*, 2010). Moreover, some of the questions raised deal with foods and media and therefore require measurements in foods and environmental compartments (air, contact with polycarbonate articles, etc.).

As the toxicological effects of BPA exposure are mainly chronic, it should be specified that the exposure to be characterised are also chronic, which represents non-negligible difficulty given the temporal variability of internal BPA exposure for the same person (Mahalingaiah S *et al*, 2008).

*In the general population*, the following exposure and contamination study methods can be implemented:

**M1 Analysis of BPA concentrations in foods and media, including everyday articles, and characterisation of these articles and media (mainly polycarbonate kitchen utensils) and estimate of oral exposure and possibly contact or airborne exposure by using exposure factors (food consumption, other exposure factors).**

**M2 Urine or blood samples to measure chronic BPA exposure in the general population through a biomonitoring programme (possibly with a questionnaire on dietary habits and behaviour).**

*In a population of volunteers*, other more in-depth studies can be undertaken.

**M3 Repeated measurement of BPA contamination through urine or blood samples, combined with food and environmental measurements to characterise and classify exposure sources.**

### c. Degree of response to the questions raised and objectives by study type

**M1 Analyses of BPA levels in foods and media including everyday articles and estimate of oral exposure and possibly airborne or contact exposure.**

Traditionally, external exposure levels are calculated by combining data on concentrations in foods, products and media with which the population is in contact with exposure factors (food consumption, time spent in the various media, frequency of contact with products that may contain BPA).

These external exposure levels can also be estimated on the basis of urinary excretion of BPA and the application of a simple approach which considers that all ingested BPA is excreted in urine within 24 hours of oral exposure in various forms, conjugates or other (EFSA, 2006; Vandenberg *et al*, 2010). For a standard volume of 2 litres of urine per 24 hours, urinary excretion of 5 µg/L of total BPA is considered equivalent to oral exposure of 10 µg/day of BPA in terms of order of magnitude (EFSA, 2006). This simplifying approach does not take into account kinetics or the distribution of various metabolites in urine.

EFSA has made conservative estimates of external dietary exposure to BPA whose order of magnitude is significantly higher than the estimate based on urinary excretion (see section entitled "context of the request and limits of the expert assessment"). EFSA notes that "the discrepancy between the levels of exposure estimated through biomarkers and the levels of exposure assessed by combining food consumption data with BPA concentration in the diet is likely to be due to the highly conservative assumptions used to estimate the latter, which are aimed at assessing exposure in the most exposed population groups" (EFSA, 2006).

Due to the risk assessment approach based on conservative 'worst-case' estimates, publications on realistic exposure to BPA are rare.

This is due to the fact that BPA measurement in foods does not generally involve all foods but rather limited food groups likely to contain BPA because of their packaging.

A realistic exposure study limited to canned foods and beverages for adults that was undertaken in New Zealand showed that the mean exposure level was 0.008 µg/kg b.w./day with a maximum exposure level of 0.29 µg/kg b.w./day (Thomson *et al*, 2005), i.e. a value close to the high exposure values of 0.3 µg/kg b.w./day that were estimated through urinary BPA excretion (Kamrin, 2004). Another study conducted in Switzerland (Von Goetz *et al*, 2010) estimates exposure in infants fed with polycarbonate baby bottles to be 0.8 µg/kg b.w./day. The study based its results on BPA concentrations in water that was heated for one hour at 100°C (Brede *et al*, 2003), which is not very realistic. In this same study, calculated external exposure for children and adults is compared with contamination data with consistent results, e.g. for adult men, calculated external exposure of 0.03 µg/kg b.w./day and external exposure based on the contamination study of 0.05 µg/kg b.w./day.

The main BPA analysis methods in foods are liquid or gas chromatography combined with simple or tandem mass spectrometry (HPLC-MS, GC-MS, GC-MS-MS). The cost of these methods can explain why analyses are focused on foods that are known *a priori* to potentially contain BPA (canned foods and beverages).

**Determinants of BPA contamination in canned and pre-packaged foods**

In 2006, Kang, Kongo and Katayma conducted an inventory of publications on BPA levels in canned foods: meat-based products, fish, fruits and vegetables, beverages, dairy products, foods for young children (Kang *et al*, 2006). It appears that BPA levels are higher in canned meat-based products (21 to 130 µg/kg on average according to the study) than in canned fruits and vegetables (6 to 42 µg/kg on average according to the study) and fish (22 to 30 µg/kg according to the study). Beverages, and mainly soft drinks, have considerably lower levels of BPA (1 to 18 µg/kg according to the study). This is due to the fact that the main determinants of BPA migration from the surfaces of cans to foods are heating times and temperatures. Some studies show that heating times have less of an impact than temperature for an aqueous medium (Kang *et al*, 2003). For sunflower oil, it has been shown that migration from a can covered with resin is significantly higher when heated for 90 minutes at 120°C (403 to 646 µg/L) than when heated for 135 minutes at 111°C (11 to 73 µg/L) (Munguia-Lopez *et al*, 2005). Storage time can also be a factor in BPA migration in canned foods (Yoshida *et al*, 2001), particularly when heating temperatures are low (Munguia-Lopez *et al*, 2005). But the storage time effect is not found in all studies (Goodson *et al*, 2004). The salt or vegetable oil content of foods can also be associated with higher BPA levels (Kang *et al*, 2003), but there are few relevant data.

One publication showed low migration levels for BPA used as an additive in PVC film to olive oil used as a fatty food simulant (3 to 31 µg per $dm^2$) whereas migration to water and acetic acid simulants was observed only for one tested film (13 µg per $dm^2$) (Lopez-Cervantes *et al*, 2003). These migration levels were lower than the specific migration limit at the time, which was 500 µg per $dm^2$ for film. The authors recommended considering foods packaged with PVC film as possible sources of dietary BPA exposure.

**Determinants of BPA contamination in foods in polycarbonate containers**

Several studies show that the use of polycarbonate containers can result in migration to foods. The effect that the temperature used to heat polycarbonate baby bottles has on levels in milk was emphasised in AFSSA Opinion 2008-SA-0141 of 24 October 2008 (AFSSA, 2008). It has been highlighted that the use of used polycarbonate baby bottles could increase migration levels in water at the same temperature, and that the water's hardness could also be a migration factor (Brede *et al*, 2003).

It would therefore be necessary to undertake a realistic exposure study taking into account all potential dietary sources and all food categories that potentially contain BPA. This study should consider the use of polycarbonate packaging, kitchen utensils and tableware as its exposure scenario to compare how these uses impact human exposure.

**Dietary and non-dietary exposure studies**

A published external exposure study took into account both dietary and non-dietary sources of exposure. The CTEPP study in 257 young children between the ages of one and a half and five years in the United States estimated exposure from the following sources: foods, beverages, interior and exterior air, dust, soil (Wilson *et al*, 2007). BPA measurements were taken in foods, beverages, exterior and interior dust and exterior and interior air. Unfortunately, no BPA assaying in urine was undertaken for this study. Median dietary exposure was estimated at 1.7 and 2.7 µg per day in each of the two study centres, airborne exposure was estimated at 14 and 7.8 ng per day and soil or dust ingestion exposure was estimated at less than 1 ng per day. Dietary exposure was therefore dominant by far. However, this result was isolated and took into account young children only. Such studies are currently lacking in Europe. Multi-source exposure studies need to be undertaken to be able to make sufficiently certain conclusions as to routes of exposure to BPA in populations. A statistical analysis showing no correlations between urinary excretion of BPA and the amount of time elapsed since the last meal in the NHANES study raised questions as to the dominance of dietary exposure (Stahlhut *et al*, 2009) and knowledge of the toxico-kinetics of BPA. However, this study relied partly on self-reported data subject to biases and its conclusions should be re-examined using observed data and more in-depth toxico-kinetic studies (AFSSA Opinion 2009-SA-0177).

***The M1 study type fully responds to questions SQ1 (exposure) and SQ5 (exposure sources), significantly helps respond to question SQ4 (integration into the issue of EDs), and does not respond to questions SQ2 (contamination) or SQ3 (link between external and internal exposure). It could be combined with an in-depth literature study of determinants of migration from packages to foods and experimental studies to identify good practices, particularly in terms of heating canned foods, to reduce migration levels. Questionnaires or observations on the home use of plastic containers, and namely polycarbonate containers, to heat foodstuffs would be useful to estimate concentration variability in consumed foods.***

**M2 Urine or blood samples to measure chronic BPA contamination (with a more or less complex questionnaire on dietary habits).**

BPA contamination is usually measured by taking urine or blood samples (Vandenberg *et al*, 2010). In order to estimate *in utero* exposure, BPA has been measured in the amniotic fluid or the placenta (Engel *et al*, 2006). BPA measurements have mainly been taken in breast milk to estimate exposure in breastfed infants (Otaka *et al*, 2003). BPA has also been measured in saliva to estimate migration from dental cement.

The substances that are usually assayed in urine are BPA and its conjugates, namely BPA-glucuronide (Calafat *et al*, 2008). It is often not possible to measure BPA and its conjugates separately, whether in blood serum or urine (Vandenberg *et al*, 2010).

An isolated urine sample cannot determine, for a given individual, chronic BPA exposure, because of its temporal variability. The positive predictive value (i.e. the probability that the subjects who are actually the most exposed will be classified as the most exposed) of urine samples to classify subjects in the highest contamination tercile increases from 0.63 to 0.85 between a single BPA measurement in urine (high tercile) and two measurements (Mahalingaiah *et al*, 2008). The number of measurements required to identify chronic BPA contamination at the individual level with a given degree of confidence is not currently documented. With the goal of acquiring knowledge of the inter-individual variability of mean contamination levels over a long period and their determinants, it is usually considered that two measurements are sufficient to statistically separate temporal and inter-individual variations. However, the rare BPA contamination studies that examine hundreds of individuals, such as the NHANES study in the United States (Calafat *et al*, 2008) and the German study in children and adolescents between the ages of 3 and 14 years (Becker *et al*, 2009) use only one urine sample per participant.

The main analytical methods that have recently been used to measure BPA in blood serum or urine are liquid or gas chromatography combined with mass spectrometry and sometimes tandem mass spectrometry (GC-MS), (GC-MS/MS), (HPLC-MS/MS). The other methods that are used include ELISA enzyme immunoassay methods, which suffer from a lack of specificity, and liquid chromatography combined with fluorescence detection. Very recently, an RIA radioimmunoassay method was published to measure BPA in blood serum with positive correlations with mass spectrometry assays (Kaddar *et al*, 2009). Various aqueous and solid phase extraction methods exist. According to the study, limits of detection vary from 0.01 to 1 µg/L, which generally means that the vast majority of results can be quantitated, except in the case of studies in populations with low contamination levels that use relatively high limits of detection such as the Chinese study by (He *et al*, 2009). Special attention needs to be given to containers before assaying. Involuntary non-contamination in the sample preparation and analysis process must be verified on a regular basis using blank tests. In general, less than 1 ml of blood or urine is required, which makes it easy to analyse BPA in the framework of general biomonitoring studies devoted to a large number of substances.

BPA contamination studies in the general population have been used to examine contamination variations by age, sex, education level and household income (He *et al*, 2009; Becker *et al*, 2009; Calafat *et al*, 2008). They have rarely highlighted associations characterising routes of exposure. Based on the American NHANES study, positive correlations were very recently highlighted (Lakind *et al*, 2010) between internal BPA exposure and frequent soft drink consumption (with no possible distinction between bottled and canned drinks), meals taken at school cafeterias (for subjects in school) and meals taken outside of the home (only for subjects aged 18 years and older). No association with the consumption of canned tuna or bottled water was highlighted. However, information about the packaging of bottled water or foods in general was generally not available. In a Chinese study, the consumption of tobacco and alcoholic beverages was associated with urinary concentrations of BPA but tobacco consumption alone was associated with blood serum concentrations (He *et al*, 2009).

Overall, it therefore appears that existing BPA contamination studies, even when they use questionnaires on dietary habits (the NHANES study, for example), have not yet thoroughly examined sources of BPA exposure.

It is difficult to know whether the limits of the obtained results are related solely to methodological difficulties, to the fact that these associations between BPA contamination and dietary habits have not yet been sufficiently studied, or to the fact that these associations are actually not very significant. However, it appears probable that the variability of BPA contamination over time makes it difficult to measure associations with dietary habits.

This temporal variability of BPA exposure also makes it difficult to study associations between BPA exposure and other endocrine disruptors, especially other disruptors whose contamination also varies over time (phthalates for example). Nevertheless, this type of study is possible since moderate volumes (around one ml) of serum or urine are needed to assay BPA, even if the associations will be underestimated due to temporal variability. The epidemiological study of the possible health effects of BPA contamination is not included in the scope of the request. However, it should be noted that due to the high geographic variability, particularly in Europe, of some health indicators that can be associated with the concept of endocrine disruption such as incidence or mortality for testicular cancer (Huyghe *et al*, 2007), it would be highly useful to have comparable data on BPA contamination in general populations at the international level.

In France, there are currently no data on BPA contamination that are representative of the population. A study among 207 hospital patients in Lyon described blood contamination levels that were mainly between 0.08 and 2 µg per litre, i.e. in the orders of magnitude observed in other international studies (Kaddar *et al*, 2009). However, this study was undertaken to develop a radioimmunoassay method and the studied population and results are not described in detail. 195 BPA analyses in the urine of pregnant women were very recently undertaken in the framework of the EDEN cohort in order to conduct a case-control study to investigate the determinants of cryptorchidism and hypospadias in the cohort and will be published in the near future (Slama R, personal communication). Other data will soon be available in the framework of the ELFE cohort pilot study.

***This M2 study type therefore fully responds to question SQ2 (internal exposure of the population), significantly helps respond to questions SQ1 (exposure in the population) and SQ4 (integration into the issue of EDs) and only partly responds to question SQ5 (exposure sources).***

*In a population of volunteers*, other more in-depth studies can be undertaken.

**M3 Repeated measurement of internal BPA exposure through urine or blood samples, combined with food and environmental measurements to characterise and classify exposure sources**

The comparison, in a population of volunteers, of human contamination levels with food contamination and consumption, such as a 'duplicated meals with biomonitoring' study, would make it possible to compare external exposure calculated using environmental measurements according to a methodology similar to that used for young children by (Wilson *et al*, 2007) and repeated internal exposure measurements over time. This methodology would therefore combine the advantages of methodologies M1 and M2 for the same subjects, repeatedly over time. Available repeated contamination studies (Mahalingaiah S *et al*, 2008) show that at least 3 successive measurements would be needed for each participant. For three days, the foods from the three main meals would be assayed by duplicated meals, separating canned foods from other foods, as would the urine from 24 corresponding hours with a sufficient time lag. The urine will need to be frozen soon enough after it is sampled to prevent degradation. Environmental measurements would supplement these food assays.

The first priority would be to implement this study type for children under the age of 3 years and for women of childbearing age, who are the priority study populations for BPA. A sample size comparable to that used in the study by (Wilson *et al*, 2007), i.e. at least 50 people per age group, would be necessary, which would give a total of 100 people. For the 50 adults or a percentage of them, a urine assay after a 48-hour fasting period would be undertaken to define a non-dietary contamination level (which would nevertheless include exposure from water). Such a study would cost around 750,000 euros including 100,000 euros for BPA analyses in urine and 400,000 euros for BPA analyses in foods and the environment. The study would last for around 2 years.

***This M3 study type fully responds to questions SQ3 (link between exposure and contamination) and SQ5 (exposure sources), significantly helps respond to questions SQ1 (exposure) and SQ2 (internal exposure) and partially responds to question SQ4 (integration into the general issue of endocrine disruptors).***