Superior Health Council

PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8732

Bisphenol A – dietary and non-dietary routes of exposure

In this science-policy advisory report, the Superior Health Council of Belgium provides an expert opinion on the evaluation of the different routes of exposure (dietary and non-dietary) and alternatives to bisphenol A (BPA), especially for children under the age of three.

As BPA is an endocrine disrupting chemical, the report provides some general recommendations such as limiting the exposure of pregnant women.

7 November 2012

1. INTRODUCTION AND ISSUES

In October 2010, the Superior Health Council (SHC) received an urgent request from the Cabinet of the Minister of Public Health as well as that of the Minister for SMEs, the Self-Employed, Agriculture and Scientific Policy to issue an advisory report on the use of bisphenol A (BPA) in the manufacture of materials intended to come into contact with foodstuffs and in particular with those used for children under the age of three.

At the time, the standing working group NHFS (Nutrition and Health, including Food Safety) wrote an advisory report (SHC advisory report No. 8697 of 3 November 2010) on the basis of opinions published by various European and international bodies. In that report, the SHC advised to minimize the exposure to BPA of children under the age of 3. The report also emphasized that scientific advisory reports from European and international bodies had focused on the dietary exposure to BPA only, whereas data from the literature indicated that the contribution of non-dietary routes of exposure might be significant.

In order to examine this issue in greater detail, the NHFS working group embarked on a new project with regard to BPA, viz. that of assessing the contribution of both dietary and non-dietary routes to the overall exposure to BPA. Meanwhile, the European Union (EU) has banned the use of BPA in plastic infant feeding bottles (the ban on BPA in feeding bottles has been applicable since May 1st, 2011 as regards their manufacture and has been effective since June 1st, 2011 as regards their marketing and importing into the EU) (EC, 2011b).

The NHFS working group therefore also decided to examine the scientific literature on alternatives to BPA in plastic feeding bottles, what they are, what their toxicity is, and whether they involve any problems of migration.

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A significant number of toxicological studies as well as epidemiological studies have been published to date on the endocrine effects of BPA. There have been considerable discrepancies as regards the outcome of these studies, both with respect to the nature of the effects observed and, where reported, the levels at which they occur. This has led to controversy in the scientific community over the safety of BPA and has resulted in national authorities taking different risk management decisions (WHO, 2011). Furthermore the European Food Safety Authority (EFSA) has started working on a new risk assessment of bisphenol A in 2012 which focuses on the exposure of vulnerable groups.

So, the objectives of this advisory report are the following:

- to evaluate the various routes of exposure to BPA, in particular to assess the contribution of non- dietary routes of exposure;
- to evaluate the alternatives to BPA-releasing materials;
- to identify any deficiencies that might hamper a proper risk assessment of BPA, knowing that this compound is an endocrine disrupting chemical;
- to consider the need for reducing to exposure to endocrine disrupting chemicals;

2. CONCLUSIONS AND RECOMMENDATIONS

2.1. CONCLUSIONS

2.1.1 Hazards of exposure to BPA

Recently the French Food Safety Agency (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES) has published a comprehensive report on the health effects of BPA (ANSES, 2011a). Based on this review and other recent reports in the scientific literature on the toxicological properties and possible health effects of BPA the SHC concludes that effects below the present tolerable daily intake (TDI) value of 50 µg/kg body weight per day cannot be excluded. The reason for this concern is related to the endocrine disrupting properties of the compound. There are indications for non-monotonic dose-effect relationships as well as for specific vulnerability during particular periods of human development, so-called windows of exposure. Examples of the latter are the period of foetal development and puberty. Therefore the SHC considers it prudent to reduce the exposure to BPA and similar endocrine disrupting chemicals, also below the present TDI. This recommendation is particularly relevant for pregnant women and infants (see below).

Uncertainties about the health effects of BPA at low doses are partly due to the complexity of epidemiological studies and the subsequently difficult interpretation of the results obtained. Reasons for this complexity are:
- BPA cannot be isolated from the mixture of endocrine disrupting chemicals (EDCs) humans are exposed to.
- There is virtually no unexposed control population due to the ubiquity of BPA.
- There could be an interval of several decades between the foetal and early postnatal critical windows of exposure and delayed BPA effects, such as metabolic syndrome in adulthood.
- Long term exposure to BPA is difficult to measure as the compound has a short half-life (it is quickly metabolized after ingestion), which means that the assessment of urinary levels provides an estimate of the exposure during the few days prior to ingestion only.

2.1.2. Overview of the sources of exposure to BPA

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Based on the data in section 3, it is clear that, for most populations that have been investigated, exposure to BPA from non-dietary sources is generally lower by at least one order of magnitude compared to exposure from dietary sources.

Except in specific cases or in the event of occupational exposure, dietary ingestion accounts for over 90 % of the overall exposure to BPA for all population age groups. In normal situations, the exposure from inhaling household dust, from dental materials or skin absorption after contact with thermal paper amounts to less than 5 % of total exposure to BPA for infants, children, and adults.

Some additional sources of exposure (such as medical devices) have been identified, but in general, non-dietary exposure to BPA is less well documented than dietary exposure.

For dietary exposure, the level of exposure is generally lower than the current tolerable daily intake (TDI) of 50 µg / kg body weight / day (EFSA, 2010). Note, however, that except for infant formula, the data do not take into account food preparation (heating and cooking) prior to consumption. Preparing food in containers made of polycarbonate or with an epoxy resin coating may result in additional contamination with BPA.

The data presented in section 3 also show that biomonitoring data (measurements of the urinary concentration of BPA in humans) can provide a correct assessment of the total consumer exposure to BPA (through dietary and non-dietary routes), however, it is still necessary to collect these data for populations of different age groups (infants, children and adults).

2.1.2. Overview of the alternatives to bisphenol A

On January 28, 2011 the European Commission (EC) published a Directive restricting the use of BPA in infant feeding bottles (EC, 2011b). Moreover, the EC issued regulation Nr. 321/2011 (EC, 2011c), indicating that “BPA is not to be used for the manufacture of polycarbonate infant feeding bottles. This restriction is applicable from 1st May 2011 as regards the manufacture and from 1st June 2011 as regards the placing on the market and importation into the Union”.

Note also that infant feeding bottles can still contain bisphenol S as well as other compounds that exhibit similar endocrine disrupting properties (see section 3).

Unlike polycarbonate (PC), the polymer synthesized from BPA,, alternatives to PC have not been the subject of extensive research. Among the possible alternatives, we can mention:

- polyethylene terephthalate (PET). Potential problems linked to PET bottles are migration of phthalates or antimony into the food.
- polypropylene (PP). Some researchers have shown that there is leaching of bioactive compounds.
- 2,2,4,4-tetramethylcyclobutane-1,3-diol, an aliphatic diol used as a monomer for the synthesis of Tritan copolymer. Its specific limit of migration (SLM) is 5 mg/kg (EC, 2011a).
- poly(oxy-1,4-phenylenesulfonyl-1,4-phenylene), known as polyethersulfone (PES) and polypoly(oxy-1,4-phenylene ether-ether-sulfone), known as polyphenylsulfone (PPSU). Low amounts of diphenyl sulfone have been shown to migrate into the food simulant, but far below the regulatory limits (SLM = 0.05 mg/kg), (EC, 2011a).
- silicones. There are also reports in the literature of siloxanes migrating into food.

In conclusion, it is important to emphasize that any of these new or existing alternative materials would need to be assessed for appropriate functionality and safety using state of the art methodology and scientific knowledge, as is starting to be the case for BPA.

2.2. RECOMMENDATIONS

2.2.1. Recommendations for a relevant risk assessment of BPA

Several characteristics of BPA deserve special attention. Indeed, it is these characteristics that make it particularly difficult to make a proper risk assessment.

The main fact that needs to be taken into consideration is that BPA belongs to the category of endocrine disruptors. It has the ability to interact with oestrogen and androgen hormone receptors, thyroid hormone, peroxisome proliferator-activated receptor gamma (PPAR γ) and G protein coupled receptor GPR30.. Some endocrine disrupting chemicals (EDC), including BPA, are known for their "unconventional" toxic effects. These effects manifest themselves at low doses below pre-established ADI or TDI values that did not take endocrine disrupting events into account. Furthermore, effects due to non-monotonic dose-response relationships have been observed in toxicological studies (Vandenberg et al., 2012). Also, toxic effects can occur in children or adults, depending on specific windows of exposure, especially as regards *in utero* exposure (Diamanti-Kandarakis et al., 2009). Moreover, the combination of several EDCs may result in effects that are not simply additive.

Another difficulty is that BPA is readily metabolized, which means that there is a constant competition between the absorption and elimination of BPA by the human body. The challenge is to be able to determine whether, under such dynamic conditions, it is possible to establish a causal link between BPA exposure and (short/long term) health effects. Therefore, certain precautions need to be taken when designing biomonitoring campaigns or protocols for epidemiological studies. Special attention should be devoted to the following points:

- When selecting the target population in biomonitoring studies, choose a representative sample from the following groups and identify differences in life style and dietary habits:
  - i) adults, adolescents, infants, babies and premature babies;
  - ii) men and women;
  - iii) pregnant women;
  - iv) fertile and infertile men and women;
  - v) ethnic groups.

  Biomonitoring data are especially needed for infants and pregnant women.
- Because of the rapid urinary excretion of BPA, it is necessary to develop strategies to handle the issue of the highly variable BPA concentrations in spot urine samples. When the population studied is large enough (e.g. at the national level), the spot sampling method can provide sufficient statistical power to classify the average population exposure to BPA. For other purposes, the biomonitoring data will be enhanced by collecting several spot urine samples, especially in studies designed to assess the potential impact of BPA exposure on human health. In addition, the study design should take into account the impact of the timing of sampling (e.g. after food consumption) and last urination.
- It is necessary to focus on all routes of exposure:
  - i) occupational exposure (plastic industry);
  - ii) food contact materials containing BPA;
  - iii) other materials that can contribute to oral exposure (toys);
  - iv) household dust;
  - v) skin contact (thermal paper);
  - vi) medical equipment.
- It is important to draw a link between "windows of exposure" and "multiple effects":
  - i) exposure *in utero* can have long term effects that don't become apparent until adulthood or even in subsequent generations;
  - ii) the concentrations of BPA in the human body can vary considerably over time and repeated biomonitoring can help to monitor this variability;
  - iii) it is still unclear whether the concentrations of BPA in maternal biological samples are representative of the exposure of the foetus or infant.

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- It is necessary to take into account confounding factors and biases:
  i) make the necessary adjustments based on age, body mass index, smoking, etc;
  ii) consider the potential effects of other interfering endocrine disruptors and contaminants (ideally, a wide range of chemicals should be monitored);
  iii) unmeasured factors may confound the interpretation of epidemiological studies.

To avoid some of these pitfalls, one should be careful about the quantity and quality of the information that could be obtained. For example, specific and detailed questionnaires could be used to record relevant information such as diet and cooking utensils used a few days prior to urine sampling, housing, occupational exposure, hobbies, etc. Importantly, the questionnaire has to be adapted taking into account the very short half-life of BPA. In addition, to refine and thus improve the assessment of the exposure to BPA and of the risk involved, the following should be taken into account:

- When considering all routes of exposure, more information is required on the bioavailability of BPA. Additional research is therefore needed about the absorption of BPA, predominantly through dermal contact or inhalation of dust but also through other exposure routes.
- As many different materials are liable to release BPA, it is also important to be able to rely on adequate testing procedures for measuring the migration of BPA. It is indeed known that the temperature, the nature of the simulant and material aging can affect the amount of BPA released. Standardized procedures adapted to contaminants and packaging materials of this type should be developed not only to control the market for kitchen utensils, but also to refine exposure prediction. It is also important to monitor the release of small BPA oligomers from various materials and not only the BPA monomer.

Several other highly relevant issues for future research were identified and should be devoted a greater deal of attention:

- Monitoring the concentrations of BPA in infant formula and foods for young children, especially if the food is packed in coated metal cans.
- Study the migration of BPA from food packaging paper, especially if recycled paper or coated paper is used.
- More data must be gathered about the concentrations of BPA in unpacked food, as well as data on consumption habits regarding products and materials containing BPA.
- Instead of just measuring BPA exposure, it would certainly be more helpful, to attempt to correlate epidemiological studies with “hormone-like” contamination of food and beverages, measured using *in vitro* methods, in order to assess the oral exposure to endocrine disruptors.
- Now that BPA has been banned in infant feeding bottles in the EU, other plastic materials are placed on the market that are indeed BPA free, but may contain other diphenyl alkanes, such as bisphenol F or S. Studies should be conducted on the toxicity of these compounds, which are similar to BPA, as well as on the consumers’ exposure to these chemicals.

2.2.2. Recommendations for BPA risk identification and characterization

Assessing the risk from exposure to BPA is seriously complicated by the fact that BPA is an endocrine disruptor. As a result, identifying and characterising the risk is by no means an easy task. Indeed, many molecular targets may be involved and determining a threshold for toxicity is not always possible. In addition, toxicological tests to study endocrine disruptors are not yet fully validated or internationally recognized for regulatory purposes, in contrast to *in vitro* and *in vivo* tests used to characterize mutagenic and carcinogenic substances. This critical point must be resolved in order to convince both the public authorities and the industry of the risks posed by endocrine disruptors to public health, the future of the human population and the environment.

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In particular, new toxicological approaches must be developed (for example based on biomarkers of exposure) that are suitable to study human exposure to multiple endocrine disrupting chemicals.

Indeed, it is important to be aware of the fact that BPA is not the only chemical of concern. There are many alternatives to BPA for which the toxicological properties have not been fully investigated yet, as well as many other contaminants (e.g. phthalates, ink curing agents, etc.), to which the consumer is also exposed. Therefore, it may be appropriate to recommend the use of multi-contaminant analytical methods on the one hand, so that a wide range of potential endocrine disruptors can be monitored simultaneously, as well as, on the other hand, the use of biological screening methods to be able to detect the presence of yet unknown chemicals with endocrine disrupting activity..

2.2.3. Recommendations for pregnant women and young children

Above the SHC concluded that the present knowledge about the toxicological properties and possible health effects is a reason to reduce the exposure the BPA and similar endocrine disrupting chemicals. This would hold in particular for pregnant women and young children. This recommendation is in line with recent conclusions of the Danish Environmental Protection Agency, which has recently published a survey which shows that everyday exposure to multiple endocrine disruptors from food, the indoor environment and consumer products may entail a risk for some pregnant women.

Recent biomonitoring studies have provided preliminary evidence of *in utero* exposure to BPA. The SHC therefore advises to reduce in particular the exposure of pregnant women to consumer products containing BPA.

In addition, as already mentioned above, foetal exposure to chemicals that disrupt the endocrine system is a serious cause of concern. Early exposure is more likely to disrupt homeostatic processes such as reproduction and energy balance control due to the vulnerability of mechanisms that are still in the process of being put in place. For these reasons, the SHC advises that early foetal exposure should be reduced to a minimum and carefully monitored.

Another area of concern regarding EDCs in general and BPA in particular is the fact that their effects may be felt over several generations as a result of alterations to the epigenome caused by exposure in early life. Such mechanisms pose a challenge to epidemiological studies and provide further justification for advising that the exposure in particular of pregnant women and young children should be reduced to a minimum.

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3. FURTHER DETAILS AND ARGUMENTATION

List of abreviations

ADI:	Acceptable daily intake
ANSES :	French Agency for Food, Environmental and Occupational Health and Safety - *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*
BPA:	Bisphenol A (2,2-bis(4-hydroxyphenyl)propane)
BPB	Bisphenol B (2,2-bis(4-hydroxyphenyl)butane)
BPE	Bisphenol E (1,1-bis(4-hydroxyphenyl)ethane)
BPF:	Bisphenol-F (bis(4-hydroxyphenyl)methane)
BPS:	Bisphenol-S (bis(4-hydroxyphenyl)sulfone)
bis-GMA:	Bisphenol-A glycidyl methacrylate
bis-DMA :	Bisphenol-A dimethacrylate
DEHP:	Di(2-ethylhexyl) phtalate
DEPA:	Danish Environmental Protection Agency's
DES:	Diethylstilbestrol
EPA :	US Environmental Protection Agency
EU:	European Union
EC :	European Commission
EDC:	Endocrine disrupting chemicals
EFSA:	European Food Safety Authority
FDA:	Food and Drug Administration
GerES:	German Environmental Survey
GM:	Geometric mMean
NHFS	Nutrition and Health, including Food Safety – Nutrition, Alimentation
NOAEL:	No-Observed-Adverse-Effect Level
PC:	Polycarbonate
PES:	Polypropylene (P polyethersulfone)
PET:	Polyethylene terephthalate
PP:	Polypropylene
PPAR γ:	Peroxysome proliferator-activated receptor gamma
PPSU:	Polyoxy-1,4-phenylene ether-ether-sulfone), known as polyphenylsulfone
PVC:	Polyvinyl chloride plastics
SHC:	Superior Health Council
TDI:	Tolerable daily intake
US:	United States
SML:	Specific migration limit
WHO:	World Health Organization

Keywords

Keywords	**Mesh terms***	**Sleutelwoorden**	**Mots clés**	**Stichwörter**
Bisphenol A	Bisphenol A	Bisfenol A	Bisphénol A	Bisphenol A
Endocrine disruptor	Endocrine disruptor	Hormoonontregelaar	Perturbateur endocrinien	endokriner Disruptor
	Environmental Exposure	Blootstelling van het milieu	Exposition environnementale	Umweltexposition
	Food contamination	Voedsel verontreiniging	Contamination des aliments	Kontamination von Lebensmitteln

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	Food Handling	Behandeling van voedsel	Manipulation des aliments	Umgang mit Lebensmitteln
	Food Packaging	Verpakking van levensmiddelen	Emballage alimentaire	Lebensmittelverpackungen
	Infant and Child, Preschool	Zuigeling en kind, voorschoolse	Nourrisson et enfant, préscolaire	Säuglinge und Kinder, Vorschule
	Pregnant women	Zwangere vrouwen	Femmes enceintes	Schwangere Frauen

** MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.*

3.1. METHODOLOGY

This advisory report is based on the literature on human exposure to BPA (until December 2011), which was reviewed by the experts of the NHFS working group, as well as on the ANSES opinion on the health risks of BPA (ANSES, 2011a) (for the toxicity of BPA), and on the opinion of the experts.

3.2. ELABORATION

3.2.1. Introduction

3.2.1.1. Properties and applications of bisphenol A

Bisphenol A (BPA) [4,4'-dihydroxy-2,2-diphenylpropane, CAS 80-05-7] (Figure 1A) is an industrial chemical compound synthesized by the condensation of two phenol equivalents with one acetone molecule. In 1936, Dodds and Lawson discovered the estrogenic effects of some diphenyl compounds containing two hydroxyl groups in para positions (Dodds & Lawson, 1936). Yet BPA was not used for estrogen replacement purposes for women following the discovery of diethylstilbestrol (DES) in the mid-1930s, which was found to be more active than BPA (Vogel, 2009). Since 1940, BPA has been used as a monomer in the manufacturing of polymers such as polycarbonate, PC (Figure 1B), epoxy resins (Figure 1C), polysulfone, or polyacrylate, as well as an antioxidant and inhibitor of end of polymerization in polyvinyl chloride plastics (PVC) (EFSA, 2002) and as precursor for the synthesis of the flame retardant tetrabromobisphenol-A (Geens et al., 2011). Polycarbonate is used in materials intended to come into contact with food, such as certain reusable plastic bottles, feeding bottles, plates, beakers, cups, microwave ovenware, storage containers, etc., while the epoxy resins are used in the internal coating of food and beverage cans (EFSA, 2006). However, only 3 % of all the polycarbonate produced as well as 10 % of the epoxy resins is used in materials intended to come into contact with foodstuffs (Plastics Europe, 2007). There are several other uses of polycarbonates, epoxy resins, polysulfone, and polyacrylates, such as sunglasses, building materials, CDs and DVDs, medical devices, dental materials, etc. In some cases, BPA can be used as such, as for example in thermal paper (Geens et al., 2011). For a review of all applications of polycarbonate and epoxy resins, see ANSES (2011b).

Besides BPA, many derivatives are obtained through condensation of a ketone or an aldehyde with bisphenols with variation in the carbonyl derivative or in the substituents on the aromatic ring. Although a large number of compounds can be obtained by this route, many are too expensive for an industrial application. The toxicity of most of these compounds is not known, especially when they have been synthesized in research laboratories. For instance, a systematic search in SciFinder yields 28746 compounds upon submitting the subunit OH-Ar-CH2-Ar-OH, (only) 1010 of which are commercially available. Among these bisphenols, bisphenol F (BPF) (bis(4-

hydroxyphenyl)-methane) (Figure 1E) is increasingly used because of its lower viscosity and better resistance against solvents compared to the BPA epoxy resin (Danzl et al., 2009). Bisphenol S (BPS) (4,4 dihydroxy-phenylsulfone) (Figure 1D) can also be used as a monomer in the plastic industry.

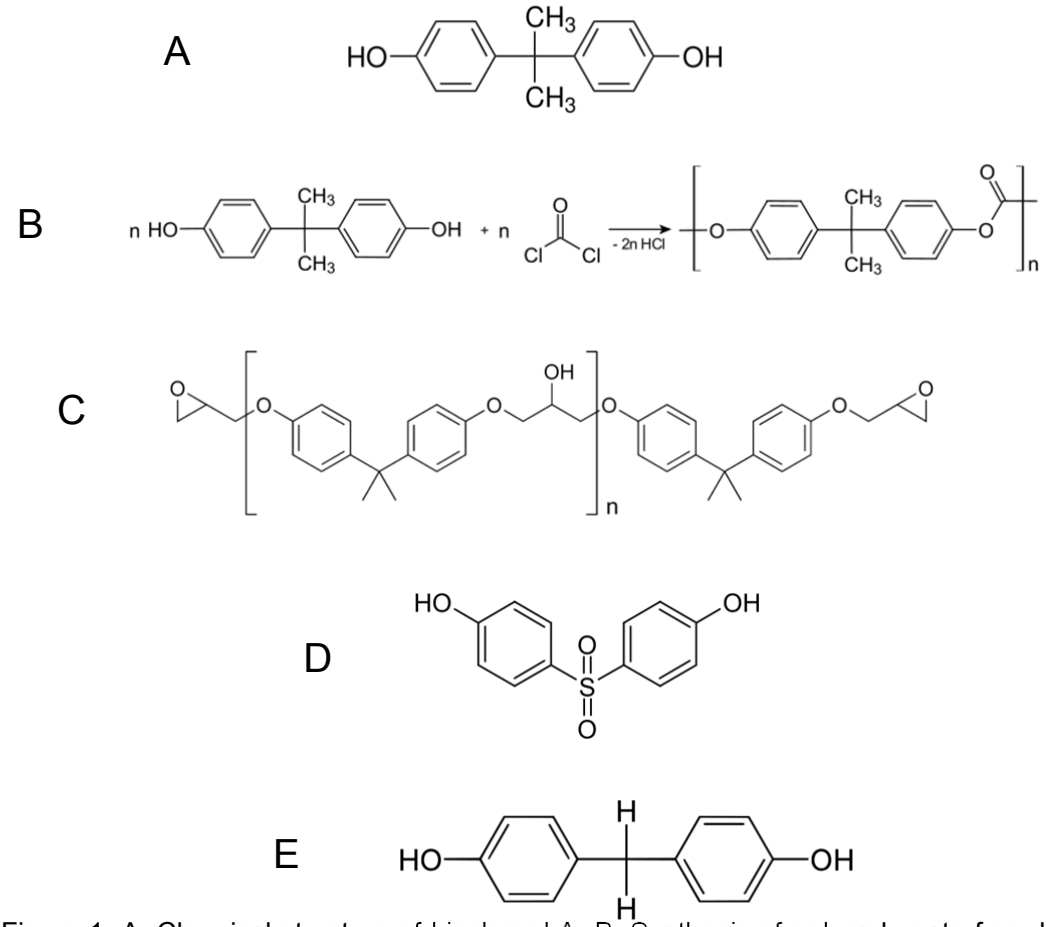

Figure 1: A. Chemical structure of bisphenol A; B. Synthesis of polycarbonate from bisphenol A; C. Chemical structure of an epoxy resin; D. Chemical structure of bisphenol S; and E. Chemical structure of bisphenol F.

3.2.1.2. Toxicity of bisphenol A

With BPA shown to have estrogenic properties in a large number of studies (reviewed by Chapin et al., 2008), it is described as an endocrine disruptor chemical (EDC). In particular, it is able to bind and activate the human estrogen receptors. The estrogenic properties of BPA had already been shown in 1936 by Dodds & Lawson, but with a capacity 1,000 to 100,000 times below that of endogenous 17ß-oestradiol (Dodds & Lawson, 1936; FASFC, 2009; Roy et al., 2009). BPF and BPS also display estrogenic properties (Chen et al., 2002). Moreover, BPA has been shown to interact with other endocrine receptors, such as thyroid hormone receptors, peroxysome proliferator-activated receptor gamma (PPRγ), G protein coupled receptor GPR30 (Diamanti-Kandarakis et al., 2009). BPA has been classified as a category 3 reproductive toxicant and thus as a cause for concern as regards human fertility (INSERM, 2010).

The EFSA published a first hazard assessment on BPA in 2006, . The EFSA-panel derived a tolerable daily intake (TDI) of 50 µg/kg body weight/day, and concluded that human dietary exposure is below the TDI, even for babies and young children (EFSA, 2006). In the light of new

published data, the EFSA concluded in 2008 and 2010 that there was no need to lower the TDI and also that exposure remained below the TDI (EFSA, 2008; 2010). However, only the dietary BPA exposure has been taken into account to date. Yet, as indicated above, BPA can be found in a large number of other (non-dietary) applications. A sound approach as a basis for risk assessment should include all exposure routes.

Several scientists, including the experts from the French Agency for Food, Environmental, and Occupational Health and Safety (ANSES), were opposed to using the TDI to assess the risks of EDCs (ANSES, 2010). There is scientific evidence that EDCs display low-dose effects (i.e. below the TDI derived by the EFSA), non-monotonic dose-response curves, as well as effects linked to very specific exposure windows (in particular, early in-utero exposure) (Vandenberg et al., 2012, Diamanti-Kandarakis et al., 2009).

A recent ANSES report once again reviewed the toxicity of BPA (ANSES, 2011b), with a special focus on the effects of BPA at low doses, viz. doses below the no-observed-adverse-effect level (NOAEL) of 5 mg/kg body weight/day from which the EFSA derived the current TDI of 50 µg/kg body weight/day (EFSA, 2006). The French experts have reviewed the state-of-the-art regarding the effects of BPA on the male and female reproductive system, on the brain and on behaviour, on metabolism and the cardiovascular system, on the thyroid, on the immune system, on the intestines, prostate and breasts (ANSES, 2011a). In general, it is not possible to draw a definitive conclusion on the effects of BPA on humans, due to heterogeneous and sometimes scarce epidemiological data. The “suspected” negative effects described in humans in the ANSES report concern oocyte maturation and reprotox-effects in males related to exposure during puberty, the cardiovascular system and the development of diabetes. The feasibility of human epidemiological studies, however, remains complex for several reasons. BPA cannot be isolated from the mixture of EDCs humans are exposed to. There is virtually no unexposed control population due to the ubiquity of BPA. There could be an interval of several decades between the foetal and early postnatal critical windows of exposure and delayed BPA effects such as metabolic syndrome in adulthood. Finally, BPA has such a short half-life that the assessment of urinary levels provides an estimate of the exposure during the few days prior to ingestion only (Rudel et al., 2011). In animals, the ANSES report indicates that BPA has an effect on different physiological systems following pre-natal or post-natal exposure at low doses. These systems are the male and female reproductive systems (increase in ovarian cysts, hyperplasia of the endometrium, precocious puberty, and, in exposed adults, a lower sperm production), the brain (neurogenesis and synaptogenesis), the lipid metabolism and insulin sensitivity, the immune system, and breast development (hyperplasia) (ANSES, 2011a).

3.2.1.3. European legislation regarding migration

Since chemical substances can be released from plastic materials and articles intended to come into contact with food (Barnes, 2006), the European Legislation has set migration limits for all substances authorised for use in plastic materials. For BPA, the specific migration limit (SML) was set at 0.6 mg/kg food in 2004 and has not been changed by the new regulation, except for infant feeding bottles, from which BPA has been banned in the EU since 2011. BPS has a SML of 0.05 mg/kg food (EC, 2011a), whilst BPF is not authorised for use in plastic materials intended to come into contact with food in Europe. For plastic materials in contact with food, the SMLs have been set assuming that a 60-kg individual consumes 1 kg of food per day.

In order to verify the extent to which these chemical substances migrate from the material into the food, it is necessary to distinguish between materials and articles that are already in contact with food and those which are not. For both groups, guidelines are provided in Regulation (EU) N°10/2011 (EC, 2011a).

Briefly, for materials in contact with food, the migration is measured in the food. The material can no longer be in contact with the food by the expiration date. The foodstuff has to be prepared in

accordance with the cooking instructions on the product label. The parts of food not intended for human consumption are then removed and discarded, and the remainder food is homogenized and analysed for the presence of the compound of interest in order to ascertain compliance with the SML.
As regards materials and articles not (yet) in contact with food, since food is a complex matrix, a series of test media are used to simulate the transfer of substances from the packaging material to the food. These media should represent the main physicochemical properties of food. When using these simulants, the standardized time and temperature of the assay must be as faithful a reflection as possible of the potential migration of the target substance into the food. These simulants are then analysed for the presence of the compound of interest in order to ascertain compliance with the SML (Grob et al, 2008, 2010).

3.2.2. Dietary exposure to bisphenol A

Food, especially food contained in cans coated with epoxy resins, is generally considered to be the predominant source of exposure to BPA. Food is usually contaminated with BPA through contact with food packaging materials that contain epoxy resins and PC. Epoxy resins, but also PVC organosols, are often used as internal can coatings to prevent direct contact between the metal wall of the can and the food or beverages, and to protect the cans from rusting and corrosion (Cao et al., 2011; Goodson et al., 2002). These protective coatings are also used on metal lids for foods in glass jars (Cao et al., 2011). Due to an incomplete polymerization process, residue BPA monomer in PC containers and coatings can migrate into food, especially during storage and processing at elevated temperatures (Cao et al., 2011; Geens et al., 2010; Noonan et al., 2011).

3.2.2.1. Epoxy resins

3.2.2.1.1. Migration

The influence of damage to the packaging material, storage conditions and heating on BPA migration was examined by Goodson et al. (2004). Empty epoxy phenolic coated cans were filled with four foods and 10 % ethanol as food simulant. Cans filled with each food type or simulant were sealed and processed under appropriate conditions. The cans were stored at 5 °C, 20 °C or 30 °C and analyzed at different time intervals (up to 9 months). Half of the cans were dented in order to evaluate the effect of damage on migration. As it turned out, between 80-100 % of free BPA already present as free monomer in the coating had migrated into the food during sterilization. Extended storage at various temperatures or damage to the can did not affect the levels of BPA migration (Goodson et al., 2004).

The effect of heat treatment on BPA migration was also observed by Munguia-Lopez et al. (2002, 2005) and Munguia-Lopez and Soto-Valdez (2001). Using an aqueous food simulant, a fatty food simulant, or tuna fish, most of the BPA was found to migrate during heat treatment (121 °C and 90 min) (Munguia-Lopez and Soto-Valdez, 2001; Munguai-Lopez et al., 2005). For jalapeño peppers, which are more acidic than tuna, sterilization for 9 min at 100 °C had a minimal effect on the migration of BPA, both for the aqueous food simulant and the acidic food simulant. Due to the milder heat processing conditions for jalapeño peppers compared to tuna, part of the residual BPA remained on the coating after processing. Consequently, BPA levels rose during storage time, especially during the first 40 days (Munguai-Lopez and Soto-Valdez, 2001; Munguia-Lopez et al., 2002). Kang and Kondo (2003) reported that the temperature has more influence than the heating time on the migration of BPA from an epoxy can coating into water.

3.2.2.1.2. Levels

That canned food contributes most to the overall exposure to BPA has been confirmed in several intervention studies. In a study conducted by Carwile et al. (2011), the urine of 75 volunteers who

consumed one serving of canned soup during five days showed a spectacular 1200 % increase in urinary BPA concentrations compared to those consuming fresh food during five days. Braun et al. (2011a) observed higher BPA concentrations in the urine of pregnant women who consumed canned vegetables at least once a day compared with those who did not. In a dietary intervention study where volunteers were subjected to a 3-day "fresh food" diet, i.e. food that was neither canned nor packaged in plastic, Rudel et al. (2011) observed a 66 % decrease in urinary BPA concentrations compared to the concentrations prior to the intervention.

Several studies worldwide determined BPA levels in canned food, including studies conducted in the US (Noonan et al., 2011; Schechter et al., 2010), Canada (Cao et al., 2010, 2011), Japan (Sajiki et al., 2007), Korea (Lim et al., 2009a), New Zealand (Thomson and Grounds, 2005), UK (Goodson et al., 2002) and Belgium (Geens et al., 2010). The sample size, detection frequency and concentration range can be found in Table 1.

In all studies, the BPA concentrations were not only found to vary significantly in different products of the same food type, but also in different lots of the same product. Noonan et al. (2011) observed a 10-fold difference (2.6 to 310 ng/g) between the minimal and maximal BPA values in peas, whilst different brands of green beans displayed a 30-fold difference (22 to 730 ng/g). Geens et al. (2010) also observed a significant amount of variation (1.2 to 82 ng/g) between five brands of corn. While some studies reported to have found the highest levels of BPA contamination in tuna (Cao et al., 2010; Lim et al., 2009a), others revealed that the tuna samples in fact showed the lowest BPA concentrations (Noonan et al., 2011). Such variation is probably due to the different proprietary coatings from can manufacturers and to the different can styles or coating choices for various products used by the food producers (Noonan et al., 2011). Unfortunately, these differences have received less attention. As a result, there are no regulations as regards this variability. In contrast, the lot-to-lot variability for samples of the same food type and brand was smaller than the variability between foods and within food types (Noonan et al., 2011). In food with both a solid portion and liquid supernatant, BPA tends to partition into the solid part (Geens et al., 2010; Noonan et al., 2011). Yet, the BPA concentration in the solid part seemed to be dependent on the type of food. While BPA was partitioned in the solid part of the food in corn (Yoshida et al., 2001), green beans and peas (Noonan et al., 2011), it remained in the aqueous solution in peeled oranges (Yoshida et al., 2001). It is not clear whether the migration of BPA into the solid portion could be accounted for by absorption by fibres, by the fat content of the food, or by other mechanisms (Yoshida et al., 2001).

As is the case with food cans, there can also be BPA migration in beverage cans. The most relevant studies are summarized in Table 1. Contrary to canned food samples, BPA concentrations in canned beverages showed a more narrow range. For the Canadian and the Belgian study, 85 % and 75 % of the samples, respectively, had concentrations below 1 ng/mL (Cao et al., 2009a; Geens et al., 2010). The lower concentrations found in beverages can possibly be accounted for by the differences in can type, can coating and sterilization conditions between canned food and beverages (Geens et al., 2010). Besides BPA, Cunha et al. (2011) detected BPB, another bisphenol compound, in 50 % of the canned beverages (range 0.07 - 0.16 ng/mL). Gallart-Ayala et al. (2011) could not detect BPB, Bisphenol E (BPE) or BPS in any soft drinks, but they did find BPF in two samples (0.14 and 0.22 ng/mL).

Table 1. Overview of BPA* in canned food samples and canned beverages.

Country	Sample size	Detection freq	Range	Reference
Canned food (ng/g)				
US	78	91 %	<2 – 730	Noonan et al. (2011)
US	97	59 %	<0.2 – 65	Schecter et al. (2010)
Canada	78	99 %	<0.6 – 534	Cao et al. (2010)
Japan	48	92 %	<1 – 842	Sajiki et al. (2007)
Korea	61	64 %	<3 – 136	Lim et al. (2009a)

Belgium	21	100 %	0.2 – 169	Geens et al. (2010)
Beverage cans (ng/mL)				
Spain	11	64 %	<0.05 – 0.61	Gallart-Ayala et al. (2011)
Canada	69	100 %	0.03 – 4.5	Cao et al. (2009a)
Belgium	45	91 %	<0.02 – 8.1	Geens et al. (2010)
Portugal	30	70 %	<0.01 – 4.7	Cunha et al. (2011)

* SML of BPA : 600 µg/kg (EC, 2011a).

Apart from being used as a protective layer in food and beverage cans, epoxy resins can also be used as an internal coating on metal lids for foods in glass jars, a source scarcely investigated until now. Whilst the food comes into contact with the lid more rarely than it does with the can, such contact may sometimes occur, e.g. during transportation due to shaking or as a result of accidental storage in a non-vertical position (Cao et al., 2009b). Therefore, Cao et al. (2009b) determined the BPA levels in 99 baby food products in glass jars with metal lids for seven Canadian brands . BPA was detected in 85 samples (86 %), 69 (70 %) of which displayed levels below 1 ng/g; the overall average concentration was 1.1 ng/g.

Cao et al. (2011) investigated 154 food composite samples from the 2008 total diet study in Quebec City, Canada. BPA was detected in 55 of the 154 food samples (36 %) tested. High concentrations of BPA were found mostly in the composite samples containing canned foods, with the highest BPA levels being observed in canned fish (106 ng/g). BPA was also detected in some foods that were neither canned, nor packaged in jars, such as yeast, baking powder, cheese, bread, cereals, and fast foods. The source of BPA in these food items was suggested to be the packaging paper, especially plastic packaging film made from PVC, or BPA could have been introduced during the production process if equipment or containers with epoxy coating or plastic parts were used. BPA contamination in fast-food could be due to the wrapping paper or BPA may already have been present in the ingredients used to prepare it. BPA intakes from 19 of the 55 samples in which BPA was detected, accounted for over 95 % of the total estimated dietary intake in Canada, and most of the 19 samples were either taken from canned food or food in jars. The remaining 36 samples in which BPA was detected, contributed only 5 % to the estimated dietary intake. Therefore, the intake of BPA from non-canned foods was estimated to be low (Cao et al., 2011).

3.2.2.2. Polycarbonate

3.2.2.2.1. Migration and hydrolysis

Despite the current ban on the production, importing and sale of PC infant feeding bottles in the European Union (EC, 2011b), Canada and several US states, exposure of infants through PC can still be relevant either as a result of the use of “old” PC feeding bottles or other PC food contact applications.

BPA can leach from PC into liquids as a result of two different processes: diffusion of residual BPA in PC after manufacturing and hydrolysis of the polymer (Aschberger et al., 2010). Experiments using official simulants usually report BPA migration levels which, even under rather drastic conditions (such as 1 h at 100 °C), are typically in the range of 0.1-1 µg/L (Biedermann-Brem and Grob, 2009). In the event of standard migration behaviour, the latter is found to decrease after continued use. Several recent studies have confirmed that the migration from PC feeding bottles into food simulants is low (Biedermann-Brem et al. 2008; Santillana et al. 2011; Simoneau et al. 2011). For most feeding bottles, the migration levels were below the detection limit of 0.1 µg/kg (Simoneau et al. 2011) or <0.4 µg/L from new infant feeding bottles and after 30 washing cycles (Biedermann-Brem et al. 2008).

Increased BPA migration from PC infant feeding bottles could be observed at higher temperatures and after longer testing periods (Biedermann-Brem and Grob, 2009; De Coensel et al., 2009; Kubwabo et al., 2009; Le et al., 2008; Lim et al., 2009b; Nam et al., 2010). An up to 55-fold rise in the rate of BPA migration was observed when the PC was exposed to boiling water (100 °C) compared to water at 20 °C (Le et al. 2008). Microwave heating did not seem to have a specific effect, and migration was mainly temperature dependent (Ehlert et al. 2008; De Coensel et al. 2009).

Contrary to standard migration behaviour, which was found to decrease or remain constant after repeated use of the PC bottles, several studies reported that BPA migration increased over time as a result of hydrolysis of the PC (Brede et al. 2003). Biedermann-Brem and Grob (2009) revealed that the higher concentrations could be accounted for by the observation that aging increases the wettability of the bottle wall, which promotes the adherence of water to the bottle surface. Drying in the dishwashing machine causes dissolved salts to reconcentrate on the bottle wall and to be baked onto the PC at elevated temperature. They may enhance polymer degradation and increase BPA release, especially when alkali material is deposited, such as washing solutions (Biedermann-Brem and Grob, 2009). Bottle rinsing prior to the drying step can overcome such “baking” and thus, prevent high BPA concentrations from being released. However, preparing a drink according to the usual recommendations generally results in < 0.5 µg/L BPA being released (Biedermann-Brem and Grob, 2009).

The highest levels of BPA migration or release from PC bottles were obtained under conditions which are generally unlikely to occur under normal use, i.e. at elevated temperatures or after extended contact (Table 2). De Coensel et al. (2009) reported only very low BPA migration levels (6–13 ng/L) when the bottles are used under normal conditions (20 s at 1000 W in the microwave oven at 37 °C). During normal use, the BPA quantities released are very small (at most 2 ng per feeding) .

3.2.2.2.2. Levels

The effect of BPA migration from PC drinking bottles was illustrated in an intervention study where volunteers were requested to consume all cold beverages from PC drinking bottles during one week. A 69 % increase in urinary BPA concentrations was observed after one week compared with urinary levels obtained after a wash-out period of one week, where no use of PC-bottles was allowed (Carwile et al., 2009).

In Canada, Cao and Corriveau (2008a) were unable to find any BPA in 51 non-PC bottled water products (detection limit 0.5 ng/mL). However, BPA was detected in 4 out of 5 water samples from PC bottles (<0.5 – 1.4 ng/mL). In a 5-week experiment, levels of 8.8 and 6.5 ng/mL were measured in two bottles. Therefore the authors warn that higher BPA levels could occur in some PC water bottles due to accidental or careless exposure to heat (e.g. sun) for extended periods of time during storage and transportation (Cao and Corriveau, 2008a). A Greek study determined the BPA levels in water from five PET-bottles, with a median concentration of 4.6 ng/L. Water from one PC bottle contained 112 ng/L, which rose to 170 ng/L after 30 days of sun exposure. The maximum daily intake through bottled water, assuming a daily intake of 2L water, was estimated to be 0.006 µg/kg bw/day (Amiridou and Voutsa, 2011).
PC is also used for water pipes and epoxy-phenolic resins are widely used as a surface-coating on residential drinking water storage tanks (Bae et al., 2002). Li et al. (2010) detected BPA in tap water from six different drinking water plants in Guangzhou, China in concentrations between 15 and 317 ng/L, but the potential source of contamination was not mentioned. The adult daily mean intake of BPA was estimated to be 148 ng/day from drinking 2 L of tap water. Still, more data would be needed to quantify the possible dietary exposure to BPA via drinking water (EFSA, 2006).

Table 2. Migration of BPA from polycarbonate infant feeding bottles.

Reference	Highest BPA concentration [µg/L]	Relevant conditions
De Coensel et al. (2009)	0.30	60 seconds and 1000 W (65 °C)
Ehlert et al. (2008)	0.73	3 cycles of 100°C in microwave oven (~ 3 min)
Le et al. (2008)	1.33 7.67	7 days at room temperature 24 h at 100 °C
Kubwabo et al. (2008)	6.5	Migration in water (24 h at 60 °C)
Maragou et al. (2008)	14.3	20 cycles of cleaning-sterilization-filling with boiling water and left at room temperature for 45 min
Nam et al. (2010)	18.5	100 times for 30 min in steam bath at 95 °C
Biedermann-Brem and Grob, (2009)	137	Previously boiled tap water (pH 9.5) in microwave for 10 min Release of BPA
Biedermann-Brem et al. (2008)	~ 500	A slanted position of the bottle in the dishwasher, hindering the detergent solution from running off and rinsing before drying
Cao and Corriveau (2008b)	521	Heating water at 70 °C for 6 days

3.2.2.3. Other food contact applications

BPA is sometimes detected in non-canned products, but generally the intake with such products is low (Cao et al., 2011). Geens et al. (2010) determined the BPA levels in 16 solid food samples packaged in glass, plastic, paper and Tetra Pak ™. BPA could be detected in all food samples in a concentration range of 0.1 – 1.28 ng/g, with an average concentration of 0.46 ng/g. This mean concentration is about 100 times lower than the average concentration in similar food types packaged in cans, which were examined in the same study.

BPA could not be detected above the quantification limit of 0.02 ng/mL in five beverages packaged in PET and laminated paperboard/polyethylene carton (e.g. Tetra Pak™)(Geens et al., 2010). Sajijki et al. (2007) too found considerably lower concentrations of BPA in 15 out of 23 samples (range <1 – 14 ng/g) of food packaged in plastic and in 4 out of 16 samples (< 0.2 – 1 ng/g) of food packaged in paper, compared with samples from canned food.

No BPA was found to migrate from EcoCare™ lined aluminium, stainless steel, or Tritan™ plastic water bottles during an incubation period of 120h (detection limit 0.05 ng/mL). In contrast, detectable amounts of BPA leached from PC bottles and epoxy-lined aluminium bottles (Cooper et al., 2011).

BPA was found in commercial PVC cling film and plastic sheeting bags available on the Spanish market and migration studies suggested it would migrate into food (Lopez-Cervantes and Paseiro-Losada, 2003). Some EU manufacturers formerly used BPA in the PVC polymerisation process, yet this practice appears to have ceased (EFSA, 2006). Therefore, based on this information, no BPA exposure from food contact uses of PVC should be expected in the EU today. Still, PVC materials which were produced before this measure was taken may still be in use.

3.2.2.4. Intake estimation from food exposure

The dietary intake of BPA as estimated by different national and international agencies can be found in Table 3. These estimations are sometimes based on the highest observed concentrations or migration values. Alternatively, they have been derived using 95th percentile

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consumption estimates. The highest estimated BPA dietary exposures (intake per unit body weight) were for infants aged 0–6 months who were exclusively fed with canned liquid infant formula using PC bottles. In this case, sources of BPA exposure include migration from both the formula packaging and the PC bottle (WHO, 2010). However, in all studies, even the worst cases estimated remained below the current TDI.

Mean exposures for infants fed with infant formula using PC bottles were 2.0–2.4 µg/kg bw per day, with 95th percentile exposures ranging from 2.7 to 4.5 µg/kg bw per day (WHO, 2010). Infants who were either fed with formula from non-PC bottles or exclusively breastfed had substantially lower estimated mean BPA exposures (0.01 µg/kg bw per day from powdered formula, 0.5 µg/kg bw per day from canned liquid formula and 0.3 µg/kg bw per day from breast milk), compared with those exclusively fed with infant formula using PC bottles.

Once solid foods are introduced (at 6–36 months), exposure to BPA decreases relative to body weight. For children aged 3 and older, the highest mean BPA exposure was estimated to be 0.7 µg/kg bw per day, with a maximum of up to 1.9 µg/kg bw per day (Table 3).

Depending on the amount of packaged food (canned) in the diet, adult BPA exposures were comparable to those for children aged 3 and older: a highest mean exposure of 1.4 µg/kg bw per day, with a maximum exposure up to 4.2 µg/kg bw per day (Table 3). It was assumed that all dietary exposure to BPA involved unconjugated BPA. These calculated international dietary exposure estimates (WHO, 2010) are consistent, but slightly higher than those obtained using data reported from comparable national surveys.

In Canada, dietary intake estimates of BPA by different age-sex groups were made based on the concentrations found in the food composites combined with data of the 24-h diet recall from the Nutrition Canada Survey (Cao et al., 2011). Dietary intakes of BPA were low for all age–sex groups, viz. 0.17–0.33 µg/kg bw/day for infants, 0.082–0.23 µg/kg bw/day for children aged 1 to 19, and 0.052–0.081 µg/kg bw/day for adults. Whilst Cao et al. (2011) included both canned and non-canned food in their estimation, other studies made intake estimations that were exclusively based on canned food and only considered adults. For example, Thomson and Grounds (2005) estimated that the dietary intake of BPA in New Zealand is 0.008 µg/kg bw/day, Geens et al. (2010) concluded that it is 0.015 µg/kg bw/day in Belgium, whilst Lim et al. (2009a) estimated that it is 0.030 µg/kg bw/day in Korea. Besides canned food, Mariscal-Arcas et al. (2009) included migration from polycarbonate tableware in their analysis and estimated that the BPA intake amounted to 0.030 µg/kg bw/day.

Overall, the dietary BPA intake is less than 5 µg/kg bw/day and according to most data less to than 1 µg/kg bw/per day (table 3). However, more knowledge is necessary on the effect of food processing, preparation and cooking procedures on BPA levels in the final cooked foods in order to validate these estimates based on BPA concentrations in uncooked foods. Since PC utensils and containers with epoxy coatings may be used during food preparation, BPA could ultimately end up in the cooked food after having migrated into it from PC and coatings (Cao et al., 2011).

Table 3. Estimated BPA intake in children and adults.

	Age category	**Estimation through dietary exposure (µg/kg bw/day)**
Children		
EFSA (2006)	Infants (3-12 m) Children	0.2 - 13 5.3
Health Canada (2008)	1-4 y 5-11 y	0.26 - 1.98 0.15 - 1.28
Chapin et al. (2008)	Infants-bottle fed Infants-breast fed	1 - 11 0.2 - 1

	Children (6-12 m) Children (2-6 y)	1.7 - 13 0.04 - 14.7
FDA (2009)	0-12 m 12-24 m >2 y	0.3 - 0.6 0.5 - 1.1 0.1 - 0.3
ANSES (2010)	Infants (<36 m) Children (3-17 y)	0.1 - 0.5 0.2 - 0.6
WHO (2011)	Infants 0-6 m Infants 6-36 m Children >3 y	0.01 - 4.5 0.01 - 3.0 0.2 - 1.9
Adults		
EFSA (2006)	Adults	1.5
Health Canada (2008)	12-19 y >20 y	0.09 - 0.73 0.07 - 0.60
Chapin et al. (2008)	Adults	0.008 - 1.5
FDA (2009)	>2 y	0.1 - 0.3
ANSES (2010)	Adults	0.1 - 0.3
WHO (2010)	Adults	0.4 - 4.2

3.2.3. Non-dietary bisphenol A sources

3.2.3.1. Dust

Because of the low vapour pressure of BPA [1] and, therefore, its low concentration in the air, inhaling BPA-contaminated air is unlikely to be a significant source of exposure (Dekant and Völkel, 2008).

Ingesting household dust has been demonstrated to be an important route of exposure to several contaminants in young children due to their more frequent hand-to-mouth contact and more significant intake of dust compared to adults (Jones-Otazo et al., 2005). The widespread use of BPA in a variety of indoor applications and consumer products (such as epoxy-based floorings, adhesives, paints, electronic equipments, and printed circuit boards) means that household dust is liable to be contaminated as a result of volatilization and/or leaching of BPA from these products (Loganathan and Kannan, 2011). Consequently, BPA has been found in household dust with a high detection frequency. Also, the degree of contamination shows a wide range of variation that reaches ~10,000 ng/g dust (Geens et al., 2009). Median concentrations of BPA reported in various studies were 422 ng/g (Loganathan and Kannan, 2011), 555 ng/g (Völkel et al., 2008 and 1460 ng/g (Geens et al., 2009).

Higher concentrations were observed in laboratories (Loganathan and Kannan, 2011) and offices (Geens et al., 2009), most probably due to the greater use of electric and electronic equipment and furniture than in homes. Conversely, lower concentrations were found in dust samples from daycare centers in the US (Rudel et al., 2003; Wilson et al., 2007). Although there is no certainty over the daily amount of dust ingested, the intake of BPA from dust ingestion is low and was estimated to be less than 0.006 µg/kg bw/day for toddlers and less than 0.0005 µg/kg bw/day for adults (Geens et al., 2009; Loganathan and Kannan, 2011). The contribution of dust to the overall BPA intake is therefore probably less than 5 %.

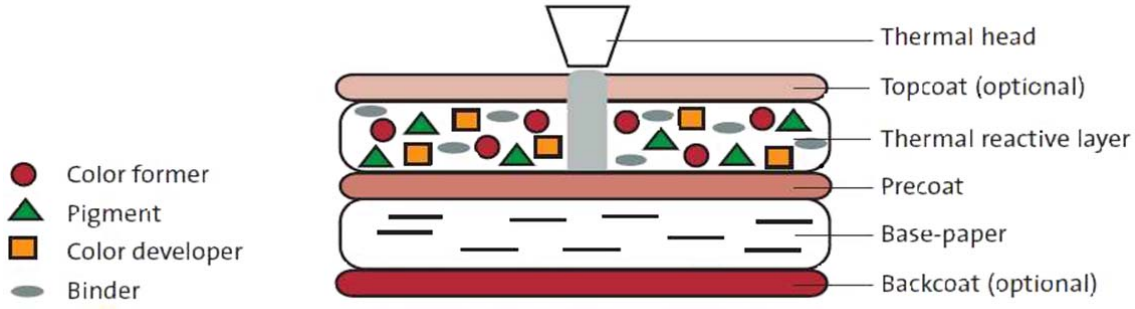
3.2.3.2. Thermal paper

BPA is used as an additive in thermal paper made for printers relying on thermal transfer technology, in which BPA is used as a colour developer. One side of the paper is coated with a powdery layer of BPA (Lassen et al., 2011), which reacts with the thermal paper dye to produce a

[1] $5.3\ 10^{-9}$ kPa or $4\ 10^{-8}$ mm Hg (25°C)

colour-developing complex when heat or pressure is applied (Figure 2). This technique is mainly used in lightweight printing devices (cash registers, credit card terminals).

Figure 2. Structure of thermal paper (from Lassen et al., 2011).



Many people come in contact with thermal paper on a daily basis. The presence of BPA in thermal paper may contribute to the overall exposure as a result of oral intake (direct contact of unwashed hands with food or the mouth) or dermal exposure. Moreover, thermal paper is also a major source of contamination of recycled paper with BPA (Takahashi et al., 2002; Zalko et al., 2011). Braun et al. (2011a) already reported the higher levels of urinary BPA in cashiers, whose skin contact with BPA-containing thermal paper might be more significant than that of the general population. Worldwide, BPA has been found in thermal paper (Denmark, Sweden, Switzerland, US) with a detection frequency between 44 and 100 %. BPA concentrations in thermal paper were up to 2.3 % (Biedermann et al. 2010; EWG, 2010; Lassen et al., 2011; Liao and Kannan, 2011a; Mendum et al., 2011; Östberg and Noaksson, 2010) (Table 4). Remarkably, Liao and Kannan (2011a) could not detect any BPA in all seven thermal papers from Japan, most probably because this country phased out BPA in thermal paper in 2001.

Table 4. Overview of BPA in thermal paper.

Country	Sample size	Detection freq.	% (g BPA/100 g paper)	Reference
Denmark	12	65 %	n.d – 1.7	Lassen et al. (2011)
Sweden	16	100 %	0.6 – 2.3	Ostberg and Noaksson (2010)
Switzerland	13	85 %	$< 5.10^{-5}$ – 1.7	Biedermann et al. (2010)
US	36	44 %	0.8 – 2.8	EWG (2010)
US, Boston	10	80 %	< 0.09 – 1.7	Mendum et al. (2010)
US, Japan, Korea, Vietnam	103	94 %	$< 1.10^{-7}$ – 1.4	Liao and Kannan (2011a)

The amount of BPA transferred to the skin after holding such paper for 5 s was between 0.2 and 6 µg BPA, with an average of 1.1 µg per finger (Biedermann et al., 2010). If the fingers were wet or very greasy, the transferred amount was about ten times higher. Repeated contact with fresh recorder paper did not result in a significant increase in BPA on the skin, indicating an equilibrium between the BPA concentration in the paper and on the surface layer of the skin. Biedermann et al. (2010) could not conclude whether or not BPA passed through the skin, but found that BPA can enter the skin deeply enough to prevent it from being washed off. Vectors, such as ethanol or hand cream, can increase the permeability of the skin and enhance the uptake of BPA by the skin. For normal skin, the potential exposure from frequently touching the most contaminated paper during a 10-hour working day was estimated to reach 71 µg/day (Biedermann et al., 2010).

Mielke et al. (2011) predicted that dermal exposure can contribute to the overall BPA exposure in a way that is indeed relevant.
Based on the maximal dermal exposure of 71 µg/day (0.97 µg/kg bw/day) determined by Biedermann et al. (2010), and on the extent of dermal absorption according to recent publications (10 % (EU 2008), 13 % (Mørck et al., 2010), 46 % (Zalko et al., 2011) and 60 % (Biedermann et al., 2010)), the SHC calculated that the dermal exposure can result in an uptake between 7.1 µg/day (0.1 µg/kg bw/day) and 42.6 µg/day (0.58 µg/kg bw/day). Similarly, a Danish study reported a realistic worst-case scenario in which the daily uptake reached 240 µg BPA (Lassen et al., 2011). In this scenario it is assumed that the receipts are touched with wet fingers and that 50 % of the quantity left on the skin is absorbed (Lassen et al., 2011). However, in most cases, the actual exposure of general consumers will be considerably lower.

3.2.3.3. Other types of papers

Thermal paper can also be the primary cause of contamination for paper currencies. Paper currencies from 21 countries were analyzed for BPA (Liao and Kannan, 2011b). BPA was found in all paper currencies at concentrations ranging up to 82.7 µg/g. The contamination of the paper currencies can probably be accounted for by the frequent contact with thermal paper in wallets. Because the BPA used in thermal paper is not chemically bound, it can be easily transferred from thermal receipt papers to other objects, including paper currencies. The estimated daily BPA intake through dermal absorption from handling paper currencies was a few ng per day (Liao and Kannan, 2011b).

It has been estimated that approximately 30 % of thermal papers enter the municipal wastepaper recycling streams. Recycling thermal paper can lead to BPA being introduced into the paper production cycle (Liao and Kannan, 2011a). Vingaard et al. (2000) showed that, whilst virgin paper contained no or negligible amounts of BPA, the levels in recycled kitchen-roll paper ranged from 0.6 to 24 µg BPA/g. Similarly, a Japanese study examined cardboard and papers used for food packaging. The concentrations found in virgin paper and cardboard were between (0.034-0.36 µg/g), whereas those in recycled paper and cardboard were > 10 times higher (range 0.19 – 26 µg/g) (Ozaki et al. 2004). Over 80 % of other types of paper, including flyers, tickets, newspapers, toilet paper, contained BPA, with BPA concentrations reaching 14.4 µg/g. Thus, the concentrations in “other” papers were 3 to 4 orders of magnitude lower than in thermal paper, and were most probably due to the recycling of thermal paper (Liao and Kannan, 2011a). The contribution of these other papers to the overall BPA exposure is therefore believed by the SHC to be insignificant. Liao and Kannan (2011a) carried out an assessment of the dermal exposure to BPA via thermal and “other” types of paper. The median dermal exposure to BPA of the general population was 17.4 ng/day, whilst this was 1303 ng/day for the occupationally-exposed population. Thermal paper was responsible for over 98 % of this exposure. Liao and Kannan (2011a) calculated that for an overall BPA exposure of 1 µg/kg bw/day, the contribution from paper could be 1.6-51 % in an occupationally-exposed population.

3.2.3.4. Dental materials

Dental composite resins consist of a mixture of monomers and are most commonly based on bisphenol-A glycidyl methacrylate (bis-GMA). In addition to bis-GMA, these resins contain other monomers to modify its properties, e.g. bisphenol-A dimethacrylate (bis-DMA). Although BPA is not used itself in composite resins, it might be present as an impurity from the synthesis process (Fleisch et al., 2010; Fung et al., 2000; Nathanson et al., 1997; Van Landuyt et al., 2011). BPA might also leach into the saliva as a result of bis-DMA hydrolysis by salivary esterases.

Several *in vivo* studies measured BPA in saliva after sealant placement. Salivary BPA levels decreased over time; the highest exposures were measured immediately after sealant placement. BPA exposure after sealant placement is most likely to be an acute event, yet none of the studies were able to find any BPA 3 h after sealant placement. It is possible that the analytical methods

used in these studies were not sensitive enough to detect very low levels of BPA that could chronically leach from the resin over longer periods of time. Thus, chronic low-dose BPA exposure after dental sealant placement cannot be ruled out (Fleish et al., 2010).

The relevance of the amounts of BPA released from dental materials is debatable. Based on the meta-analysis carried out by Van Landuyt et al. (2011), it was computed that, in the worst-case scenario, one full crown restoration of a molar may result in 30 mg BPA being released after 24 h, which is higher than the TDI of 0.05 mg/kg body weight/day (or 3 mg/day for a 60-kg individual). This indicates that the amount of BPA released from dental materials after 24 hours may be relevant in patients with multiple large restorations and that resin-based dental materials may represent a relevant source of BPA in such patients. This worst-case calculation was based on the maximum value measured for a dental adhesive that is never used in large quantities. A more common situation resulted in 13 µg being released after 24 hours (Van Landuyt et al., 2011). Sealants produced by different manufacturers released markedly different amounts of BPA (Vandenberg et al., 2007).

Von Goetz et al. (2010) estimated that the chronic exposure after dental surgery amounts to 215 ng BPA/day. This estimation was based on the results from one out of 21 individuals whose BPA was measured in the saliva 120 h after surgery: in this case, the BPA levels were 0.3 ng/mL . This probably represents a worst-case scenario for chronic exposure, since BPA concentrations in the saliva will continue to decrease over time and only one individual still had measurable concentrations after 120 h.

3.2.3.5. Medical devices and healthcare applications

A small fraction of the BPA-based polymers polycarbonate and polysulfone are used in medical and healthcare applications such as eye lenses, tube connections, blood oxygenators, inhaler housing, newborn incubators (PC), and surgical trays, nebulizers, humidifiers (polysulfone) (Geens et al., 2011). BPA can also leach into drug formulations: this is most likely to occur with liquid and suspension formulations that are packaged in PC container-closures or metal canisters with epoxy lining (FDA, 2009).

Flexible PVC, which may also contain BPA, is used in the manufacturing of medical products, such as those found in the neonatal intensive care units, including bags containing intravenous fluids and total parenteral nutrition and tubing associated with their administration; nasogastric and enteral feeding tubes; and umbilical catheters. In a study conducted by Calafat et al. (2009), BPA was analysed in the urine of 42 low-birth-weight infants in neonatal intensive care units using a large number of PVC-containing devices, such as mechanical and high-frequency ventilation, surgery, and cardiac catherization equipment. Median BPA concentrations in these premature infants were one order of magnitude higher than the median concentration and almost twice the 95th percentile of the general population (children aged 6-11y who were examined as part of the NHANES 2003-2004 study) (Calafat et al., 2009).

Hemodialysis patients can be exposed to substantial amounts of BPA due to the use of PC as casing and the fact that the hollow-fibers' hemodialysis membrane is often made of polysulfone. Moreover, the released BPA is directly introduced into the blood circulation. Though not an exposure source for the general population, hemodialysis may be an important contributor for this specific group (Geens et al., 2011; Haishima et al., 2001). Almost no data exist to quantify the dose of BPA that patients undergoing medical procedures receive(FDA, 2009).. The SHC concludes that further research is therefore necessary

3.2.3.6. Other non-dietary sources

A Danish study looked at migration from the shield and ring of baby pacifiers. These parts can be made of PC, though these materials have been largely replaced by polypropylene and co-

polyester. Even when the shield and ring contained PC, migration of BPA into sweat and saliva was low and the calculated exposure to BPA through pacifiers was far below the BPA exposure from infant feeding bottles (Lassen et al., 2011).

3.2.4. Toxicokinetics and metabolism of bisphenol A

The toxicokinetics of BPA have been studied in rodents, non-human primates and humans (Doerge et al. 2010a, b; Völkel et al. 2002, 2005). After oral administration, BPA undergoes a rapid first-pass metabolism in the intestine and liver, being completely absorbed by the gastrointestinal tract. BPA is not extensively metabolized via Phase I reactions, but is rapidly conjugated with glucuronic acid (Phase II metabolism) to the non-active BPA-glucuronide in the gut wall and liver. Minor amounts of BPA might also react with sulfate to form BPA-sulfate. The formation of BPA conjugates is considered a detoxification process (Matthews et al., 2001; Snyder et al., 2000) and only the free BPA forms display estrogenic activity (Matthews et al., 2001). The BPA conjugates formed in the human liver enter the bloodstream and reach the kidneys before being excreted through the urine, with terminal half-lives of less than 6h (Völkel et al., 2002; 2005). The applied doses were completely recovered in the urine, which means that BPA exposure can be estimated from its urinary levels (Völkel et al., 2002). BPA reaching the body through inhalation or dermal contact does not undergo a first-pass effect and will therefore be eliminated at a slower rate.

In adult rhesus monkeys, the concentration-time profile after oral BPA administration was remarkably similar to humans, given a similar dose (Doerge et al., 2010b). Minimal pharmacokinetic differences were observed between neonatal and adult monkeys for the free form of BPA, which amounted to less than 1 % of the total circulating BPA concentrations (Doerge et al., 2010b). In rodents, BPA-glucuronide is subject to enterohepatic recirculation, which prolongs elimination processes, thereby increasing internal exposures to BPA, and leads to extensive fecal excretion (Pottenger et al., 2000). The absence of enterohepatic circulation of BPA-glucuronide in humans is most likely due to a higher threshold for biliary elimination than in rats.

β-glucuronidase is present in the lysosomal membranes and endoplasmic reticulum of several organs, including the human liver and kidney (Sperker et al., 1997). It has been suggested that β-glucuronidase activity in tissues, especially the placenta, could reverse the detoxification of BPA at the tissue level (Ginsberg and Rice, 2009). The experimental evidence to support this hypothesis is largely indirect and not consistent with the rapid elimination of aglycone BPA from the circulation in adult non-human primates and humans (Völkel et al., 2002). Also viable human skin explants efficiently absorb and metabolize BPA. About 46 % of the applied dose of BPA was absorbed and largely converted into BPA-glucuronide and BPA-sulfate (Zalko et al., 2011).

3.2.5. Human biomonitoring

As a non-persistent chemical with an elimination half-life of a few hours, the BPA concentrations in blood are lower than those in urine and fall rapidly after the ingestion (Needham and Sexton, 2000). As a result, current analytical technology will be unable to detect BPA in blood in many subjects given the low levels present (WHO, 2010). Moreover, it is difficult to rule out contamination with trace levels of free BPA during sample collection, storage and analysis because of the ubiquitous presence of BPA in the environment (WHO, 2010; Markham et al., 2010; Völkel et al., 2008).

Since BPA is rapidly and almost completely excreted as BPA-conjugates, urine is the matrix of choice for biomonitoring. Long-term daily intake of BPA leads to steady-state BPA concentrations in the ng/mL range in human samples (Welshons, 2006). Urinary concentrations of total (free plus conjugated) BPA have often been used to evaluate exposure to BPA from all sources

(Vandenberg et al., 2010). Several urine-based biomonitoring studies have been conducted in North America, Europe and Asia, revealing the worldwide exposure to BPA. The most important studies are summarized in Table 5.

Table 5. Overview of the most recent worldwide urine-based biomonitoring studies of BPA.

Country	Population	Concentrations	Exposure	Det. Freq.	References
US	2514 (≥6-≥60 y)	GM 2.6 ng/mL (2.6 µg/g cr)	GM 0.047 µg/kg bw/day	93 %	Calafat et al., 2008 – Lakind and Naiman, 2008
	314 (6-11 y)	GM 3.6 ng/mL (4.3 µg/g cr)	GM 0.065 µg/kg bw/day		
	713 (12-19 y)	GM 3.7 ng/mL (2.8 µg/g cr)	GM 0.071 µg/kg bw/day		
	950 (20-59 y)	GM 2.6 ng/mL (2.4 µg/g cr)	GM 0.053 µg/kg bw/day (20-39 y) GM 0.038 µg/kg bw/day (40-59 y)		
	537 (≥ 60 y)	GM 1.9 ng/mL (2.3 µg/g cr)	GM 0.034 µg/kg bw/day		
US	394 adults	GM 1.33 ng/mL (1.36 µg/g cr)	GM 0.023 µg/kg bw/day[1]	95 %	Calafat et al., 2005
Canada	5476 6-79 y	GM 1.16 ng/mL (1.40 µg/g cr)		91 %	Bushnik et al., 2010
	6-11 y	GM 1.30 ng/mL (2.00 µg/g cr)	GM 0.025 µg/kg bw/day	93 %	
	12-19 y	GM 1.50 ng/mL (1.31 µg/g cr)	GM 0.031 µg/kg bw/day	94 %	
	20-39 y	GM 1.33 ng/mL (1.49 µg/g cr)	GM 0.026 µg/kg bw/day	91 %	
	40-59 y	GM 1.04 ng/mL (1.33 µg/g cr)	GM 0.020 µg/kg bw/day	88 %	
	60-79 y	GM 0.90 ng/mL (1.26 µg/g cr)	GM 0.017 µg/kg bw/day	88 %	
Germany	599 (3-14 y)	GM 2.66 ng/mL median 2.74 ng/mL	GM 0.060 µg/kg bw/day	99 %	Becker et al., 2009
	137 (3-5 y)	GM 3.55 ng/mL median 3.53 ng/mL		99 %	
	145 (6-8 y)	GM 2.72 ng/mL median 2.81 ng/mL		99 %	
	149 (9-11 y)	GM 2.22 ng/mL median 2.13 ng/mL		99 %	
	168 (12-14 y)	GM 2.42 ng/mL median 2.60 ng/mL		98 %	
Germany	147	<0.3 ng/mL – 9.3 ng/mL	median 0.030 µg/kg bw/day		Völkel et al., 2008
Belgium	193	0.1-53.4 ng/mL (0.18-32.4 µg/g cr)	GM 0.040 µg/kg bw/day	99 %	Milieu en Gezondheid, 2010
	14-16 y	GM 2.22 ng/mL (1.66 µg/g cr)			
Italy	715 (20-74 y)	GM 3.59 ng/mL	GM 0.063 µg/kg bw/day[1]		Galloway et al., 2010
	111 (20-40 y)	GM 4.31 ng/mL median 4.4 ng/mL	GM 0.075 µg/kg bw/day[1]		
	157 (41-65 y)	GM 3.95 ng/mL median 3.7 ng/mL	GM 0.069 µg/kg bw/day[1]		
	452 (66-74 y)	GM 3.32 ng/mL median 3.2 ng/mL	GM 0.058 µg/kg bw/day[1]		
Korea	516	mean 2.74 ng/mL, median 0.64 ng/mL	mean 0.055 µg/kg bw/day[2]	76 %	Hong et al., 2009
China	419 males	GM 1.41 ng/mL (0.72 µg/g cr)	GM 0.032 µg/kg bw/day[3]	58 %	He et al., 2009
	503 females	GM 0.58 ng/mL (0.23 µg/g cr)	GM 0.010 µg/kg bw/day[4]	44 %	
China	287	GM 3.0 ng/mL (2.75 µg/g cr)	GM 0.060 µg/kg bw/day[1]	100 %	Li et al., *in press*
	3-24 y	0.41-198.05 µg/g cr			
China	116	GM 1.10 ng/mL (1.03 µg/g cr)		90 %	Zhang et al., 2011
Vietnam	30	GM 1.42 ng/mL (1.27 µg/g cr)		100 %	Zhang et al., 2011
Malaysia	29	GM 1.00 ng/mL (1.93 µg/g cr)		97 %	Zhang et al., 2011
India	21	GM 1.59 ng/mL (2.51 µg/g cr)		100 %	Zhang et al., 2011

Kuwait	32	GM 1.24 ng/mL (1.09 µg/g cr)		81 %	Zhang et al., 2011
Japan	36	GM 0.84 ng/mL (0.67 µg/g cr)		100 %	Zhang et al., 2011
Korea	32	GM 2.00 ng/mL (2.53 µg/g cr)		97 %	Zhang et al., 2011
All Asian countries	Children Adults		median 0.039 µg/kg bw/day median 0.037 µg/kg bw/day		Zhang et al., 2011
US	404 pregnant women	median 1.3 ng/mL <0.36-35.2 ng/mL	median 0.027 µg/kg bw/day[5]	91 %	Wolff et al., 2008
The Netherlands	100 pregnant women	GM 1.5 ng/mL (1.7 µg/g cr), median 1.2 ng/mL (1.6 µg/g cr), range <0.26-46 ng/mL (0.1-22.7 µg/g cr)	GM 0.024 µg/kg bw/day[5] median 0.019 µg/kg bw/day[5]	82 %	Ye et al., 2008
Spain	120 pregnant women	median 2.2 ng/mL	median 0.035 µg/kg bw/day[5]	91 %	Casas et al., 2011
Mexico	60 pregnant women	GM 1.95 ng/mL, 0.41 – 7.47 ng/mL	GM 0.034 µg/kg bw/day[1]	80 %	Cantonwine et al., 2010
Germany	91 samples from 47 infants (1-5 months)	<0.45-17.85 ng/mL		42 %	Völkel et al., 2011
US	81 (23-64 months)	GM 4.8 ng/mL (6.6 µg/g cr) 0.4-211 ng/mL (0.5-334 µg/g cr)	median 0.114 µg/kg bw/day	100 %	Morgan et al., 2011
Spain	30 (boys 4 y)	median 4.2 ng/mL		97 %	Casas et al., 2011
US	90 (girls 6-8 y)	GM 2.0 ng/mL (3.0 µg/g cr) median 1.8 ng/mL <0.3-54.3 ng/mL	GM 0.033 µg/kg bw/day[6] median 0.030 µg/kg bw/day[6]	94.4 %	Wolff et al., 2007
US	195 samples from 35 children (6-10 y)	GM 3.4 ng/mL (3.4 µg/g cr) median 3.6 ng/mL (3.5 µg/g cr) <0.36-40 ng/mL (0.2-36.3 µg/g cr)	GM 0.057 µg/kg bw/day median 0.060 µg/kg bw/day	95 %	Teitelbaum et al., 2008

[1] assuming 1.4 L urine (Lakind and Naiman, 2008) and 80 kg bw (EPA Exposure Factors Handbook 2011)
[2] assuming 1.4 L urine (Lakind and Naiman, 2008) and 70 kg bw (Hong et al., 2009)
[3] assuming 1.6 L urine (Lakind and Naiman, 2008) and 70 kg bw (Hong et al., 2009)
[4] assuming 1.6 L urine (Lakind and Naiman, 2008) and 70 kg bw (Hong et al., 2009)
[5] assuming 1.2 L urine (Lakind and Naiman, 2008) and 75 kg bw (EPA Exposure Factors Handbook 2011)
[6] assuming 0.6 L urine and 36 kg bw (Lakind and Naiman, 2008)

A study documenting measurable urinary BPA levels in Mexican women provides preliminary evidence that pregnant women who delivered prematurely (< 37 weeks gestation) had higher urinary concentrations of BPA compared to women delivering after 37 weeks (Cantonwine et al., 2010). The impact of gestational versus childhood BPA exposure is unclear. In a recent US study, gestational BPA exposure affected behavioural and emotional regulation domains at age 3, especially among girls. These results suggested that gestational BPA exposure might be associated with anxious, depressive, and hyperactive behaviours related to impaired behavioural regulation at the age of 3 (Braun et al., 2011b).

Two recent large-scale studies which included 2514 and 5476 participants were performed in the USA and Canada, respectively. Exposure to BPA was ubiquitous, with a detection frequency of more than 90 % in both studies (Calafat et al., 2008, Bushnik et al., 2010). Also in seven Asian countries, BPA was found in 94 % of the samples (Zhang et al., 2011). In the US study, the highest urinary concentrations were detected in adolescents (12–19 years), followed by children (6–11 years) and adults (>19 years). After adjusting BPA levels for creatinine, children had the highest BPA concentrations, followed by adolescents and adults (Calafat et al., 2008). Also in the Canadian study (Bushnik et al., 2010), creatinine-adjusted BPA levels were higher in the youngest age category (6-11y) than in the other age categories. In the GerES IV study, which was conducted in Germany, children aged 3-5y had higher concentrations than those aged 6-8y, 9-11y, and 12-14y (Becker et al., 2009). Vandenberg et al. (2010) also concluded that there are indications that young children face the highest exposure risk.

For practical reasons, urine-based biomonitoring studies generally collect single spot urine samples instead of 24h urine samples. Because of BPA's short elimination half-life, spot urine samples primarily reflect the exposure that occurred within a relatively short period prior to urine collection (Koch and Calafat, 2009). However, when the population investigated is sufficiently large, the spot sampling approach may provide enough statistical power to categorize the average population exposure to BPA (WHO, 2010). Recently, BPA and DEHP exposures were shown to be substantially reduced when participants' diets were restricted to food with limited packaging for 3 days (Rudel et al, 2011), indicating that urinary levels provide an estimate of very short term exposure.

Assuming steady-state excretion, the daily intake of BPA can be derived from the excretion of BPA within 24 h (Lakind and Naiman 2008). In order to assess the daily BPA intake, the urinary concentrations of total BPA (free and conjugated after the hydrolysis of the conjugates) (ng/mL) in the urine samples are multiplied with the 24 h urinary output (mL) to obtain the daily excretion of BPA in ng/day. Since the urinary excretion of ingested BPA is essentially complete within 24 h (Völkel et al., 2002; Völkel et al., 2005), this was assumed to be equal to the daily intake. This estimated intake can be adjusted for body weight to yield an exposure expressed in ng/kg bw/day (Lakind and Naiman, 2008).

Intake ng BPA/kg/day = Urinary BPA (ng/mL) x urinary output (mL/day) / body weight (kg)

Instead of adjusting for urinary output, BPA concentrations can also be adjusted for daily creatinine excretion. However many factors contribute to the daily variability in creatinine output such as diurnal variation, changes in the rate of glomerular filtration, body mass, age, gender, health status, and external factors such as diet, exercise, and drug use. Since the variation in the range of urinary creatinine concentrations may be over 1000 %, whilst the variation in daily urinary volume reaches 300 % (Boeniger et al., 1993), correction for urinary output is generally preferred over creatinine excretion (Lakind and Naiman, 2008). However, the urine volume is also related to several factors such as liquid intake, physical exercise, and individual health and lifestyle factors (WHO, 2010). Next to generic values to describe typical urinary output specified for age and gender, generic values for body weight have to be used as well when individual values are not available.

Daily intake calculations based on biomonitoring data make it possible to compare individual (or group) exposures with doses that toxicological studies have determined to be harmful. Although these dose calculations are performed using certain assumptions (e.g. daily urine volume or creatinine excretion, uniform metabolism), they reflect real exposures, where all possible exposure sources are included (Needham et al., 2007). These urinary data (Table 5) show that estimated median exposures are in the range of 0.01– 0.05 µg/kg body weight (bw) per day for adults and somewhat higher (0.02–0.12 µg/kg bw per day) for children. The 95th percentile exposure estimates are 0.27 µg/kg bw per day for the general population and higher for infants (0.45–1.61 µg/kg bw per day) and 3- to 5-year-old children (0.78 µg/kg bw per day) (WHO, 2010).

3.2.6. Overall estimation of exposure to bisphenol A

Based on the data from reviewed in the previous sections, it becomes clear that the exposure to BPA from non-dietary sources is generally lower than that from dietary sources by at least one order of magnitude for most subgroups investigated. The SHC calculated estimated intakes through different routes of exposure based on a median and worst-case intake scenario using data from different studies (Table 6). In a median exposure scenario, food was estimated to contribute over 90 % to the overall BPA-exposure for all age groups of non-occupationally exposed individuals. This assessment took into account BPA concentrations in food (based on food surveys) and BPA migration from food contact materials. Exposure through dust ingestion, dental surgery and dermal absorption from thermal paper remained below 5 % in normal situations for toddlers and children and adults alike (Table 6). Some additional potential sources of exposure (unpackaged food and medical devices) have been identified, but in general, the non-dietary exposure to BPA is less studied.

A comparison between the dietary and non-dietary intake assessments and biomonitoring values indicates that in general it is possible to rely on biomonitoring data to assess overall human exposure to BPA. Figure 3 shows the overall exposure to BPA that was calculated for canned food/drinks, based on the mean/median/GM values taken from WHO (2010), references from that document as well as from the specific national studies (see Chapter 2 in WHO, 2010). Non-dietary sources include exposure from dust, thermal paper, medical devices and dental materials (see Chapter 3 in WHO, 2010). The cumulative exposure to BPA was calculated on the basis of biomonitoring data (see Chapter 6 in WHO, 2010).

Table 6. Overview of the estimated intake of BPA through multiple exposure routes based on a median intake scenario.

Source	Country	Population	Daily intake of BPA	Contribution to median exposure scenario	Reference
Children					
Total Food		Toddlers	1088-4992 ng/day	> 90 %	Von Goetz et al. (2010)
Total Food	USA	Children 18 m – 5 y	1700-2700 ng/day (median)	99 %	Wilson et al. (2007)
Dust	Eastern US	Toddlers	42.2-435 ng/day (median – 95th percentile)	< 1 %	Loganathan and Kannan (2011)
Dust	Belgium	Toddlers	73-975 ng/day (median – 95th percentile)	< 5 %	Geens et al. (2009)
Inhalation (dust-air)	USA	Children (18 m – 5 y)	7.8 – 14 ng/day	< 1 %	Wilson et al. (2007)
Dental Surgery		Children (> 6 y)	215 ng/day	< 5 %	Von Goetz et al. (2010)
Adults					
Total Food		Adults	1560-10453 ng/day	> 90 %	von Goetz et al. (2010)
Canned food	New-Zealand	Adults	570 ng/day (average) – 6900 (99th perc)		Thomson and Ground (2005)
Canned food and beverages	Belgium	Adults	1050 ng/day (average) – 6050 ng/day (95th perc)	> 90 %	Geens et al. (2010)
Dust	Eastern USA	Adults	8.44-109 ng/day (median – 95th perc)	< 1 %	Loganathan and Kannan (2011)
Dust	Belgium	Adults	29-244 ng/day (median – 95th perc)	< 5 %	Geens et al. (2009)
Thermal paper	USA-Japan-Korea-Vietnam	General population Occupationally exposed	17.4 – 541 ng/day (median – 95th perc) 1303 – 40590 ng/day (median – 95th perc)	< 5 %	Liao and Kannan (2011a)
Paper Currencies	Worldwide	General population Occupationally exposed	0.0001-1.41 ng/day (median) 0.0007-14.1 ng/day (median)	< 1 %	Liao and Kannan (2011b)
Paper other than thermal paper	USA	General population	0.1 ng/day	< 1 %	Liao and Kannan (2011a)
Dental Surgery		Adults	215 ng/day	< 5 %	Von Goetz et al. (2010)

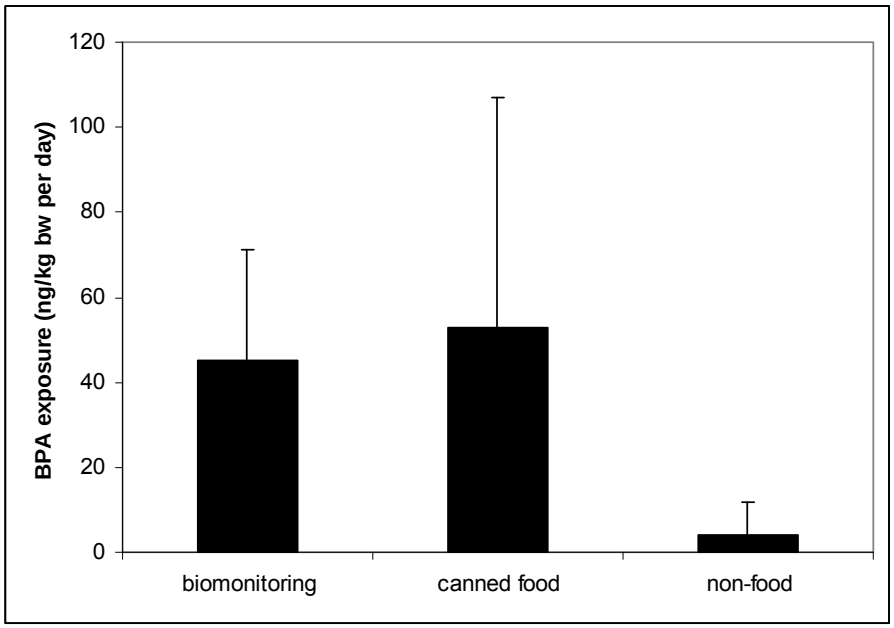


Figure 3. Comparison between BPA exposure calculated on the basis of biomonitoring data and BPA exposure from canned food and non-dietary sources. Error bars represent standard deviations.

3.2.8. Alternatives to polycarbonates in infant feeding bottles

On January 28, 2011 the European Commission (EC) published a Directive that holds that PC shall no longer be used in infant feeding bottles (EC, 2011b). Additionally the EC issued regulation Nr. 321/2011 (EC, 2011c), indicating that feeding bottles made of PC shall no longer be produced from May 1st, 2011 and shall not be put on the market from June 1st, 2011. This recent European regulation has compelled producers of plastic feeding bottles to search for alternatives to PC in infant feeding bottles.

But alternatives to PC are not very well known (may be they also have possible toxic effects ?) and have not been the subject of extensive research. The SHC provides here below a brief overview of these alternatives.

Polyethylene terephthalate plastics (PET) are commonly used in water and soft drink bottles. PET bottles are less suitable for re-utilization, but can be recycled (Welle, 2011). Some recent papers suggest that phthalates may leach into the contents of bottles made from PET (Sax, 2010). Wagner and Oehlmann (2009) have found indications that substances leaching from PET bottles act as functional estrogens *in vivo*. Several authors demonstrated that heating PET bottles could lead to significant antimony leaching (Cheng et al., 2010; Welle and Franz, 2011). Antimony is used as a catalyst during the production of PET, but is a toxic metal (Stemmer, 1976).

Polypropylene (PP) is also used as an alternative material for infant feeding bottles. Some recent papers have suggested that chemicals could migrate out of PP. Alin and Hakkarainen (2011) have found that microwave heating of PP in contact with fatty food simulants caused antioxidant degradation. McDonald et al. (2008) have reported that bioactive compounds leach from polypropylene material.

2,2,4,4-tetramethylcyclobutane-1,3-diol is an aliphatic diol (Hoppens et al., 2004). It is used as a monomer for the synthesis of Tritan copolymer. This copolyester is often used in high-end re-usable water bottles and also for infant feeding bottles. The EFSA and FDA have included the monomer on the positive list of food contact materials (EFSA, 2009; FDA, FCN No. 1041). Its SLM is 5 mg/kg (EC, 2011a).

Poly(oxy-1,4-phenylenesulfonyl-1,4-phenylene), known as polyethersulfone (PES), and Poly(oxy-1,4-phenylene ether-ether-sulfone), known as polyphenylsulfone (PPSU), are thermoplastic polymers that are increasingly used as alternatives to polycarbonate plastics. The monomers are 4,4'-dichloro-diphenylsulphone and 4,4'-dihydroxydiphenol sulphone (bisphenol S), respectively, and are approved for use in food contact materials by the FDA (21CFR177.2440) and EU (CE, 2011a). Simoneau et al. (2011) have investigated the migration of monomers from these bottles and concluded that very low amounts of diphenyl sulphone did migrate into the food simulant, but far below the limits.

Silicones are also an alternative to polycarbonate infant feeding bottles. They form a flexible material that usually requires an exoskeleton made from a more rigid plastic. Silicones are heat-resistant and rubber-like. They are well known for their medical applications (e.g., breast implants). Siloxanes have been reported to migrate from silicones (Helling et al., 2009; 2010).

It is important to note that any of these new or existing alternative materials would need to be assessed for appropriate functionality and safety using state of the art methodology and scientific knowledge.

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5. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity.*** The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts took part in drawing up the advisory report :

BOURGUIGNON Jean-Pierre	Pediatrics – neurology	Ulg
COVACI Adrian	Toxicology	UA – toxicology center
GOEYENS Leo	Analytical and environmental chemistry	VUB - KUL
LECOMTE Philippe	Polymers	ULg – Center for Education and Research on Macromolecules (CERM)
MAGHUIN-ROGISTER Guy	Food sciences	Ulg
PUSSEMIER Luc*	Residues and contaminants, chemical risks	CODA-CERVA
SCIPPO Marie-Louise*	Residues and contaminants, stability of fatty acids	ULg
VAN LOCO Joris*	Chemistry, contaminants	IHP

The administration was represented by:

AERTS Dominique	Multilateral and strategic affairs	DG5- Federal Public Service Health, Food chain safety and Environment
BERTHOT Carl*	Food sciences, feed and other consumer products	DG4- Federal Public Service Health, Food chain safety and Environment

The following individuals were heard:

GEENS Tinne	Toxicology	UA

The working group was chaired by Marie-Louise SCIPPO, the scientific secretary was Anne-Madeleine PIRONNET.

The following experts of the standing NHFS working group read and approved the advisory report:

DE BACKER Guy*	Preventive medicine, public health, epidemiology	UGent
DE HENAUW Stefaan*	Public health nutrition	UGent
FONDU Michel	Chemistry, additives, contaminants	ULB
KOLANOWSKI Jaroslaw	Food physiology and physiopathology ; physiopathology of obesity, metabolic syndrome and type 2 diabetes	UCL

LARONDELLE Yvan	Biochemistry of nutrition	UCL
MAGHUIN-ROGISTER Guy *	Food analysis	ULg
NEVE Jean*	Medicinal chemistry and nutritional sciences	ULB
PAQUOT Michel*	Chemistry, technology	FUSAGx
PAQUOT Nicolas*	Medicine - academic and scientific relationships	ULg
VANSANT Greet*	Food and health	KULeuven

The administration was represented by:

HORION Benoît	Service Food, Feed and Other Consumption products	Federal Public Service Health, Food Chain Safety and Environment DG 4- Animals, Plants and Food

The working group was chaired by Guy MAGHUIN-ROGISTER, the scientific secretary was Anne-Madeleine PIRONNET.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send an e-mail to info.hgr-css@health.belgium.be .

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