Bisphenol A in our food: same toxicological studies but different risk assessment and risk management decisions around the world

Marie-Louise Scippo

Marie-Louise Scippo, Department of Food Sciences, Faculty of veterinary medicine, University of Liège, Belgium

Samenvatting

Bisphenol A (BPA) [2,2-bis-(4-hydroxyphenyl)propaan, CAS n° 80-05-7] is een industriële chemische stof, gesynthetiseerd uit de condensatie van twee fenolgroepen en één aceton molecule (de A in bisphenol A staat voor aceton). Andere synoniemen voor bisphenol A zijn 4,4'-dihydroxy-2,2-diphenylpropane (officieel IUPAC-nomenclatuur), 4,4'-(propan-2-ylidene) difenol, p, p'-isopropylidenebisphenol, of 4,4´-isopropylidenediphenol.

Het wordt gebruikt als een monomeer bij de productie van polymeren zoals polycarbonaat en de epoxyharsen, alsook als antioxidant en polymerisatie-inhibitor binnen polyvinylchloride (PVC). Het polycarbonaat wordt gebruikt in materialen die bedoeld zijn om in contact te komen met voeding, zoals bepaalde herbruikbare plastic flessen, zuigflessen, borden, drinkbekers, kopjes, enz. terwijl de epoxyharsen gebruikt worden als deklagen van voedsel- en drankblikjes. Niettemin wordt slechts 3 % van alle geproduceerde polycarbonaat en 10 % van de epoxyharsen gebruikt in materialen die bedoeld zijn om in contact te komen met levensmiddelen (Plastics Europe, 2007). Andere toepassingen zijn zonnebrillen, bouwmaterialen, cd's, medische hulpmiddelen, enz.

Résumé

Le bisphénol A (BPA) [2,2-bis-(4-hydroxyphényl)propane, CAS n° 80-05-7] est un composé chimique industriel issu de la condensation de deux groupes de phénol et une molécule d'acétone (le A de bisphénol A réfère à l'acétone). D'autres synonymes pour le bisphénol A sont 4,4'-dihydroxy-2,2-diphénylpropane (nomenclature officielle IUPAC), 4,4'-(propan-2-ylidène)diphénol, p, p'-isopropylidènebisphénol, ou 4,4'-isopropylidènediphénol.

Le bisphénol A est utilisé comme monomère pour la fabrication de polymères tels que le polycarbonate et les résines époxy, comme antioxydant et comme inhibiteur de polymérisation dans le polychlorure de vinyle (PVC). Le polycarbonate est utilisé dans les matériaux qui entrent en contact avec les denrées alimentaires, comme certaines bouteilles en plastique réutilisables, des biberons, des assiettes, des gobelets, des tasses etc., tandis que les résines époxy sont utilisées comme revêtement intérieur des boîtes de conserves.

Tout de même, ce n'est que 3 % de la production totale du polycarbonate et 10 % des résines époxy qui sont utilisés dans des matériaux destinés à entrer en contact avec les denrées alimentaires (Plastics Europe, 2007). D'autres applications sont les lunettes de soleil, les matériaux de construction, les CD, les moyens médicaux, etc.

INTRODUCTION

Bisphenol A (BPA) [2,2-bis-(4-hydroxyphenyl) propane, CAS n° 80-05-7] (figure 1) is an industrial chemical compound synthesized from the condensation of two phenol groups and one acetone molecule (the A in bisphenol A stands for acetone). Other synonyms for bisphenol A are 4,4'-dihydroxy-2,2-diphenylpropane (official IUPAC nomenclature), 4,4'-(propan-2-ylidene) diphenol, p, p'-isopropylidenebisphenol or 4,4´-isopropylidenediphenol.

It is used as a monomer in the manufacturing of polymers such as polycarbonate (figure 2) and the epoxy resins (figure 3), as well as antioxidant and inhibiter of end of polymerization in polyvinyl chloride plastics (PVC). The polycarbonate is used in materials intended to come into contact with food, like certain reusable plastic bottles, feeding bottles, plates, goblets, cups, etc., while the epoxy resins are used in the internal coating of cans. However, only 3 % of all the polycarbonate produced as well as 10 % of the epoxy resins are used in materials intended to come into contact with foodstuffs (Plastics Europe, 2007). The other uses are sun glasses, building materials, CD-ROM, medical devices, etc.

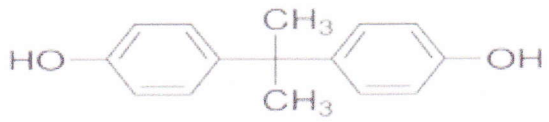

Figure 1: chemical structure of bisphenol A

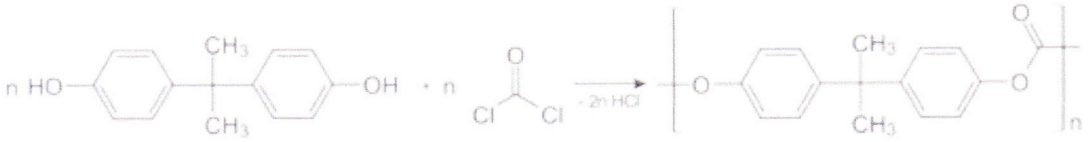

Figure 2: synthesis of polycarbonate from bisphenol A

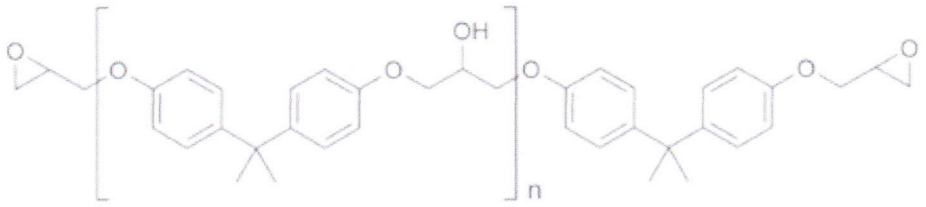

Figure 3: chemical structure of an epoxy resin

It is well known that chemical substances can be released from plastic materials and articles intended to come into contact with food, and limits of migration are mentioned in the European Legislation for all permitted substances in such plastic materials. At the moment, the legislation still in force is the Directive 2002/72/EC (EC, 2002), transposed in Belgium in the Royal Decree of 3 July 2005 which will be replaced, on 1st May 2011, by the Regulation (EU) N° 10/2011 (EU, 2011). For BPA, a specific limit of migration (SLM) is fixed since 2004 to 0.6 mg/kg food product, and is not changed in the new regulation.

BPA is described as an endocrine disruptor because many studies showed that it has estrogenic properties. It is in particular able to bind and activate the human estrogen receptor but, with a capacity 1,000 to 5,000 times less than the endogenous 17ß-oestradiol, the natural ligand of this receptor (FASFC, 2009).
BPA is classified as a substance reprotoxic poison of category 3 (alarming substance for the fertility of the mankind - INSERM, 2010).

Because of that characteristic, the BPA has a very bad reputation. BPA was very often cited in the media these last months, mainly about polycarbonate baby feeding bottles, which can release BPA when their content is heated (which correspond to a normal use of these bottles) however the amounts released are far lower than the SLM (De Coensel *et al.*, 2009). The consequence of this release is the exposure of the baby to an endocrine disrupting chemical, which is not very reassuring for the mother.

A kind of controversy exists since 2008 about the good decision to take about bisphenol A in baby feeding bottles. Canada and some states of the USA banish it since 2008, while in the European Union, the decision has just been taken (European Commision, 2011) and will enter in force on 1st March 2011, for the ban of manufacture of feeding bottles containing BPA, and on 1st June 2011, for the ban of placing on the market feeding bottles containing BPA.

This kind of decision is a part of the risk management process, which has to be conducted by public authorities.
The previous step before risk management is risk assessment, which is a scientific evaluation. Risk assessment is based on toxicological studies, as well as exposure studies, in the aim to assess the risk, for the consumer, linked to the ingestion of the substance of interest via food.

Here below are presented the risk assessment studies performed for BPA in various countries until now.
It will be shown that different risk assessment conclusions and different risk management decisions resulted from the evaluation of the same toxicological studies published in the literature.

Opinion on BPA of the Scientific committee on Food (SCF) and the European food safety authority (EFSA)

The toxic effects of BPA were evaluated for the first time in 1984 by the SCF (Scientific committee on food - SCF, 1986), which established a tolerable daily intake (TDI) of 0.05 mg/kg of body weight, on the basis of chronic oral exposure studies (90 days) carried out in rats and mice. A "no adverse effect level" (NOAEL) of 25 mg/kg body weight/day was found, related to a reduction in the body weight of the animals, to which a factor of uncertainty of 500 had been applied because of incomplete data.

The risks for health related to the BPA were then re-evaluated in 2002 by the SCF which established this time a provisional TDI of 0.01 mg/kg body weight, on the basis of studies carried out in rats (oral exposure during 90 days, study on 3 generations). The NOAEL, still related to the body weight, was of 5 mg/kg boy weight/day (CSAH, 2002).

In 2006, the EFSA established a TDI for BPA of 0.05 mg/kg body weight, on the basis of an unchanged NOAEL, compared to the preceding opinion, of 5 mg/kg body weight/day, but to which a factor of uncertainty of 100 instead of 500 was applied, because the databases were more complete than in 2002 (EFSA, 2006).

In 2008, the EFSA published an opinion on the toxicokinetics of BPA and confirmed the TDI of 0.05 mg/kg body weight. The opinion stated that the differences in toxicokinetics according to the age between animals and humans did not justify to increase the factor of uncertainty, on the basis that newborns would be able to metabolize BPA (this deduction came from structure – activity relationship studies) (EFSA, 2008).

Very recently, on September 30th, 2010, the EFSA published its most recent opinion based on an evaluation which had been carried with 3 distinct objectives:

1) to evaluate the study published by Stump and co-workers in 2009 concerning the developmental neurotoxicity of BPA in the rat;
2) to re-examine the recent scientific literature, in order to re-evaluate the risk related to BPA and the determination of its TDI;
3) to give an opinion on the risk evaluation realized by the national food institute, Technical University of Denmark (DTU, 2010) and to try to substantiate the subsequent banishment, in Denmark, of BPA in the feeding bottles.

With regard to item 1, following an elaborate statistical expertise (EFSA, 2010), the EFSA concluded that the study of Stump and co-workers (2009) does allow to draw conclusions.

With regard to item 2, the following conclusions were emitted:
- the studies of the toxicokinetics of BPA showed that BPA was eliminated more quickly in the primates than in the rodents. The premature children are able to metabolize and excrete BPA efficiently. The same conclusion is also emitted for the "slow metabolisers" (people among whom the isoenzymes of metabolisation are less active).
- the exposure of the fetus *in utero* and the infant nursed by his mother seems limited.
- recent epidemiological studies having shown a link between the exposure to the BPA (estimated on the basis of urinary concentration) and effects on the adult health (on the cardiovascular system and the reproductive apparatus) and on the behaviour of young girls, cannot be taken into account in the risk evaluation, because of weaknesses in these studies.
- the studies of the toxic effects of low doses of BPA (< NOAEL) on development and reproduction, carried out in rats, cannot be regarded as valid.
- according to a study on the sexual behaviour of females rats, the BPA *in vivo* does not seem to have an estrogenic effect (contrary to the rats treated with estrogens used as positive controls).
- two recent studies indicate that the BPA, following an exposure during lactation (Jenkins *et al.*, 2009) or *in utero* (Betancourt *et al.*, 2010), would increase the sensitivity of mammary gland to develop cancer, after exposure to carcinogenic substances. The two studies present limitations and cannot be taken into account but the EFSA indicates that the potential effects announced should be further studied.
- several studies showed effects of BPA on the immune system, but they cannot be validated because of experimental limitations.
- several *in vitro* and *in vivo* studies (but not corresponding to the criteria selected by the panel of experts of EFSA to be taken into account in the risk evaluation) showed modifications (including low doses) on the level of receptors, on the immune system, the cell proliferation, the apoptose, and at a genomic and epigenetic level. These modifications are in relation to the potential endocrine disturbing effect of BPA. These studies present limitations and it is difficult to deduce a clear mode of action at low doses as well as an effect on the human health.

With regard to the third point, the DTU in Denmark had advanced three arguments (DTU, 2010):
- the uncertainty related to the effect of BPA on the capacity of learning (study of Stump *et al.*, 2009);
- the existence of a doubt about the monotonous propriety of the dose-response curve of the BPA (which does not take into account the effects at low doses);
- certain effects were not studied: training and memory, anxious behaviour and gender-specific behaviour (sexual dimorphism).

For the reasons mentioned above (concerning the first 2 points), the EFSA did not regard the arguments advanced by the DTU as relevant.

This opinion of the EFSA (EFSA, 2010) also mentions a minority opinion of an expert from the CEF panel (panel on food contact materials, enzymes, flavourings and processing aids) who wished to mark its dissension with the conclusions of the majority of the other experts published in the opinion on BPA (EFSA, 2010) and to inform of its concern with respect to the possible effect of BPA on the human health, taking into account of some uncertainties in recently published toxicological studies.

Opinion on BPA of the ANSES, the former EFSA (French Agency for Food, Environmental and Occupational Health & Safety)

The ANSES published on opinion, on October 20th, 2009, in the aim to answer three questions:

1) Does the study of the toxicity of BPA on the nervous system development (American Chemistry Council, 2009), carried out according to guideline n° 426 of the Organization for Economic Co-operation and Development (OECD), show negative effects of BPA on the offspring consecutive to BPA exposure during gestation and breast-feeding?
The experts estimate that this study does not show any neurotoxic effect in the offspring of mothers treated with doses of BPA corresponding to the NOAEL. But at higher doses, the study does not allow to draw conclusions, taking into account the absence of investigation on the origin of the convulsions observed in some rats.

2) Does this study allow to assess the lack of toxicity of the BPA at low doses, on the neurological and behavioural development? Do the recent literature data confirm alarming effects in terms of public health, after exposure to very low doses of BPA? Do these data result in modifying the toxicological reference dose retained to establish the TDI?
In the studies of the literature, the effects observed with very low doses of BPA correspond to subtle functional modifications (neurological, hormonal or metabolic) and are to be interpreted as warning signal because their fatal consequences for the human health are not established. However, these studies display important methodological bias and do not allow to establish a dose-response relationship nor to define a toxicological dose of reference to establish a new TDI. In the current position of knowledge, it is not possible to correlate the data of exposure recorded in humans with the effects observed in vivo in animals, because of insufficient toxicokinetics data.

3) In a more general way, is the methodology of risk evaluation based on the concept of the TDI well adapted to endocrine disruptors, such as BPA?
The TDI corresponds to the maximum quantity of a contaminant which can be consumed daily during the whole life without harmful effects for the human health. In the case of endocrine disruptors compounds, being able to exert different effects according to the stage of development (critical windows of exposure during which harmful effects can appear, in particular the prenatal period), the TDI does not appear to be the best approach for risk evaluation. In addition, the guideline n° 426 of OECD does not appear entirely adapted to characterize subtle effects on the nervous system, such as they could be observed with endocrine disruptors and in particular with BPA.
In its opinion, the ANSES indicates the presence of warning signals observed in *in vitro* and *in vivo* studies, with amounts lower than the NOAEL (5 mg/kg PC/day), whose significance should be determined.

The ANSES recommends to use the principle of the MOE (Margin Of Exposure) to evaluate the risk related to the exposure to BPA, but for that, it would be necessary to determine the significance of the warning signals and to possibly re-examine the toxicological dose of reference (ANSES, 2010).

Opinion on BPA of the German federal institute for risk assessment: BfR (Bundesinstitut für Risikobewertung)

On July 29th, 2010, BfR published an opinion concerning the studies of Stump and collaborators (2009) and of Ryan *et al.* (2010). The purpose of the study of Stump *et al.* was to measure the neurotoxicity of the BPA and its effects on the behaviour in rats, after exposure to various amounts, including low doses. The study of Ryan and co-workers aimed to measure the oestrogenic effects in the offspring of female rats whose mothers had been treated with BPA during gestation and lactation.
According to BfR, none of the two studies brings substantial proof of a specific toxic effect of BPA (BfR, 2010).

The conclusion of the BfR is in agreement with that of EFSA, who also invalidated the study of Stump *et al.*, following a thorough statistical analysis which showed weaknesses in the experimental design (EFSA, 2010). With regard to the study of Ryan *et al.*, the EFSA concluded that the study was valid and that it did not show any effect of low doses of BPA on the development of an abnormal sexual behaviour in female rats.

Opinion on BPA of Health Canada

In 2008, Health Canada published a risk evaluation about the neurobehavioral toxicity of BPA. Health Canada concluded that evidences of the neurotoxicity of the BPA were limited. On the website of Health Canada it can be found that (*"Health Canada's Food Directorate has concluded that the current dietary exposure to BPA through food packaging uses is not expected to pose a health risk to the general population, including newborns and infants"*. However, by measure of precaution and to limit the exposure of the infants (application of the principle of exposure "ALARA" - As Low As Reasonably Achievable), the Canadian government prohibited the use of polycarbonate for the manufacturing of feeding bottles (coming into effect of this prohibition on March 11th, 2010).

Opinion on BPA of the National Japanese institute of Advanced Industrial Science and Technology (AIST)

In 2005, the AIST published a risk evaluation of the BPA on human health, on the basis of the toxicological profile of the BPA (effects on the body weight, the liver and reprotoxicity) and on estimates of the human exposure.
For the 3 types of effects observed, the NOAEL or BenchMark Dose Limit (BMDL) varied from 5 to 50 mg/kg PC/day, with a MOE from 85,000 to 1,800,000. In an extreme scenario (worst case), the MOE was > 1,000. The AIST thus concluded that the levels of exposure to BPA did not pose an unacceptable health risk for human health.

Opinion on BPA of the National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction (NTP - CERHR) (USA)

The NTP indicates that the possible effects of BPA on the brain, the behaviour and the prostate in the foetus, the young children and the children exposed to the BPA are worrying ("the NTP has some concern").
The effects on mammary gland and the development of an early puberty, in the fetus, infants and the children exposed to BPA, are slightly worrying ("minimal concern").
The consequences of the exposure of the pregnant woman to BPA on fetal mortality, the reduction of the weight to the birth, or the growth of the child are regarded as negligible ("negligible concern").
The effects of BPA on the reproduction are regarded as negligible ("negligible concern") for the non occupationally exposed adults and not very worrying ("minimal concern") for the professionally exposed adult (NTP-CERHR, 2008).

Opinion on BPA of the Food and Organization Agriculture (FAO) and the World Health Organization (WHO)

A joint FAO/WHO expert meeting was organized in Ottawa, Canada, from 1 to 5 November 2010, in order to review toxicological and health aspects of bisphenol A. Even if, at that time, we could read in the media (Le Soir, 12/11/2010) that following that meeting, the WHO considered that it was too early to ban bisphenol A from baby feeding bottles, the summary report of the meeting (WHO, 2010) clearly *"identified a number of gaps in knowledge and provided a range of recommendations for the generation of further information and the design of new studies to better understand the risk to human health posed by BPA"*.

Opinion on BPA of the Belgian Superior Health Council

Recently, to answer a question from the Minister of Public Health, the Belgian Superior Health Council recommended the decrease, to a level as low as possible of the exposure of young children to BPA (SHC, 2010), on the basis of uncertainties about toxic effects of BPA, in particular to low doses.

CONCLUSIONS

The questions here below seem to remain still without answers.

What about the effects of low doses of BPA?
Classically, the toxic effects related to a chemical substance follow to a linear dose-response curve.
It is not the same for substances acting on receptors (such as the endocrine disruptors) because the receptors can be activated with low doses and inhibited with stronger concentrations. In these cases, the dose-response curves appear "bell-shaped" instead of linear. Such effects with low doses were described for BPA, but in studies displaying certain weaknesses which do not allow to validate the results in order to re-examine downwards the TDI (EFSA, 2010).

Which alternatives to BPA in plastic material are intended to come in contact with food?
A lot "BPA free" baby feeding bottles are already found on the European market, even if the BPA banishment is not yet in application.
The question is: are these alternatives to BPA safe?
The polycarbonate bottles can be replaced by sulfonic polyether or polypropylene bottles. In its recent opinion (BfR, 2010), BfR pointed out that the polypropylene can release more substances in the food than polycarbonate, and that the toxicity of sulfonic polyether was less studied than that of BPA. The best alternative thus remains the glass baby feeding bottle.

What about the other ways of exposure to BPA than materials in contact with food?
Other ways of exposure (e.g. toys and other objects in polycarbonate or PVC) represent a considerable source of exposure to the BPA. This remark is also stressed in the study of Geens *et al.* (2010), who have shown that the urinary concentration of BPA in human is not completely explained by the exposure through BPA containing food consumption, suggesting that other way of exposure are not negligible. A recent study showed for example the possible absorption of BPA from a dermal exposure (Zalko *et al.*, 2010). This dermal exposure could occur through for example thermal paper coated with bisphenol A used for store receipts (Biederman *et al.*, 2010).

It is clear that further research is needed to clarify the effects on health of bisphenol A, as well as to asses the safety of alternatives of BPA in plastic materials intended to come in contact with food.
It is important, in particular, to clarify the effects of low doses of BPA and to determine the best approach for risk assessment (TDI or margin of exposure).
Finally, the other ways of exposure to BPA than food consumption should be investigated, knowing that only 3 % of the polycarbonate is used in plastic material intended to come in contact with food (Plastics Europe, 2007).

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