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## International Food Safety Authorities Network (INFOSAN)

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INFOSAN Information Note No. 5/2009 - Bisphenol A

# BISPHENOL A (BPA) - Current state of knowledge and future actions by WHO and FAO

### SUMMARY NOTES

- Bisphenol A (BPA) is a widely used chemical in polycarbonate plastic and epoxy resins
- Consumer exposure via food can occur through migration of BPA from food contact materials
- Concern has been raised because of potential toxic and hormonal properties of BPA
- Hazard assessments by major regulatory and advisory bodies are in agreement that the overall no-observed-adverse-effect level (NOAEL) for BPA from robust data is 5 mg/kg body weight/day. This is minimally five hundred-fold above conservative estimates of human exposure, including in bottle-fed infants.
- Several areas of uncertainty remain in the risk assessment of BPA:
  - effects have been reported from animal experiments on neurobehaviour following exposure to BPA during the developmental period at doses below the overall NOAEL;
  - kinetics of absorption, metabolism and excretion of BPA show important differences between primates, including humans (lower internal dose), and rodents, and between routes of exposure, so care is needed in extrapolation of animal studies to humans;
  - animal studies have not provided convincing evidence of risk of cancer from BPA exposure

### Introduction

Bisphenol A (2,2-bis(4-hydroxyphenyl) propane, CAS No. 80-05-7) is a chemical used primarily as a monomer in the production of polycarbonate plastic (PC), and epoxy resins. It also has uses in polyester, polysulfone and polyacrylate resins, and flame retardants. Polycarbonate (PC) is widely used in food contact materials such as infant feeding bottles, tableware, microwave ovenware, food containers, water bottles, milk and beverage bottles, processing equipment and water pipes. Epoxy resins are used as protective linings for a variety of canned foods and beverages and as a coating on metal lids for glass jars and bottles, including containers used for infant formula. These uses result in consumer exposure to BPA via the diet.

Daily dietary intakes, based on concentrations measured in food, vary widely, but have been estimated in Europe to be about 0.2µg/kg body weight in breast-fed babies, 2.3µg/kg body weight in formula-fed babies using non-PC bottles, 11µg/kg body weight in formula-fed babies using PC bottles, and 1.5µg/kg body weight in adults. Assessment of daily human exposure to BPA in the general population by biomonitoring of urinary excretion of BPA metabolites also varies widely, but has been estimated to be up to 0.16µg/kg body weight in the USA, and 0.04-0.08µg/kg body weight in Japan. The urine values may more accurately reflect the actual exposures since estimates based on dietary exposures assume 100% absorption and 'high consumer' exposure scenarios.

### **The scientific problem**

A very large number of publications on the toxicity and endocrine activity of BPA in animals have been published. Some of these studies have been performed in compliance with regulatory/OECD guidelines, using oral administration, large groups of animals and several dose groups. Many others have been research studies, often using smaller numbers of animals, fewer or single dose groups, and including non-oral routes of administration. There have been considerable discrepancies in outcomes among these studies, both with respect to the nature of the effects observed and, where reported, the levels at which they occur. It is notable that effects have been described in some of the research studies at dose levels several orders of magnitude below those at which effects were reported in the guideline (regulatory) studies. This has led to controversy about the safety of BPA, not only among scientists, but also in the media, in national and state legislatures and in the general public.

### **The key findings**

A number of effects of BPA in animals have been extensively investigated and target organs identified in repeat-dose animal studies include intestine, liver and kidney. However, the effects of most concern have been those related to the hormonal activity of BPA and potentially related effects on physical, neurological and behavioural development. BPA acts as a weak oestrogen. It has a much lower affinity for the oestrogen receptors (ER $\alpha$  and ER $\beta$ ) than endogenous oestrogen and it is rapidly metabolized to BPA-glucuronide which is not hormonally active. More recently, BPA has been shown to bind with high affinity to estrogen-related receptor (ERR- $\gamma$ ), which may be related to its ability to function as a reported endocrine disruptor. In vivo studies have not consistently demonstrated either androgenic or anti-androgenic activity of BPA.

Effects on the prostate/male reproductive tract have been reported following in utero exposure to oral doses as low as 2  $\mu$ g/kg bw/day; however, these findings have not been confirmed in studies conducted to OECD guidelines also including in utero exposure at similar low doses.

Developmental toxicity studies have reported delays in onset of puberty at high dose levels (475mg/kg bw/day) in male and female rodents but no effect on subsequent fertility. Numerous studies have shown that BPA up to very high oral dose levels of 640 or 1000mg/kg body weight, in rats and mice respectively, do not cause birth defects. Little information on the effects of BPA on development in humans is available.

Several research studies in rodents of variable quality have suggested that BPA treatment during development can cause alterations in brain development and behaviour. The endpoints examined in these studies (behavioural changes related to stress, pharmacological challenges and sexual dimorphism) represent an emerging area in developmental neurotoxicity for which validated protocols are currently unavailable. These data suggest findings at doses that are relevant to human exposures; however, limitations of the studies for regulatory decision-making have been extensively discussed in the national and international risk assessment reports (see references). The data, collectively, suggest that more research, using validated study methods and the oral exposure route may be necessary for conclusive risk assessment. OECD guidelines for animal testing have only recently included detailed guidance on behavioural and neurodevelopmental testing, and this is an expanding area of research.

Although BPA does not demonstrate genotoxic potential in in vivo studies, concern has been expressed about possible carcinogenicity. Carcinogenicity studies conducted under the US National Toxicology Program, using F344 rats and B6C3F1 mice showed small increases in leukaemia and testicular interstitial cell tumours in male rats. However these studies have not been considered as convincing evidence of a potential cancer risk because of the doubtful statistical significance of the small differences in incidences from controls. An in utero exposure phase was not included in these studies, and there has been some limited evidence suggesting that there may be a risk of increase in susceptibility to precancerous changes in the prostate following neonatal exposure in rats.

### **Importance of comparative toxicokinetics**

In humans and other primates, orally administered BPA is rapidly absorbed and transformed to BPA-glucuronide during first pass metabolism in the gut wall and the liver and a small amount of BPA is converted to a sulphate conjugate. More than 80% of orally administered BPA is cleared from the body in 5 hours. The conjugated forms of BPA are devoid of endocrine activity.

In rodents, orally administered BPA is also very rapidly glucuronidated, but is highly bound to plasma protein, excreted in the bile, cleaved again to free BPA and reabsorbed from the intestine into the blood stream. This enterohepatic recirculation may occur several times before BPA is finally excreted, mainly in the faeces, several days later. This results in slow elimination of BPA so that, for the same oral dose, rodents will have a prolonged higher exposure to free, oestrogenically active BPA, compared to primates. In mice oxidation products of BPA have been identified after low-dose administration, suggesting possible formation of metabolites with higher oestrogenic potency. Due to the importance of first-pass metabolism of BPA, the value for human risk assessment of animal studies that have used non-oral routes of administration has been questioned. Kinetics also varies markedly with route of administration, dose, age and even gender. These differences have to be taken into account, especially with regard to interpretation of the significance for human health of low-dose effects observed in rodents.

The presence of BPA in human fetal tissues at around the same concentrations as in maternal blood, demonstrates that BPA passes through the placenta. BPA also passes into maternal milk, resulting in concentrations of about 1-3µg/L, which are comparable with, or slightly higher than, those reported for maternal blood. Thus, there is very low oral bioavailability of the parent substance, BPA, in humans, including the fetus.

Toxicokinetic data suggest that embryonic/neonatal humans and animals lack the adult capacity to conjugate BPA, but neonates have capacity to metabolise BPA via sulphation. Maternal exposure to BPA results in embryos and newborns receiving BPA via placental transfer and milk. Exposure of human infants to BPA directly, in the absence of maternal transfer or excretion, also occurs through PC bottle feeding and/or infant formula feeding. The fetus and neonate may therefore be a sensitive and more highly exposed subpopulation deserving special attention.

### **Risk assessments to date**

The key area in the risk assessment of BPA is the interpretation of a number of research studies reporting effects at very low dose levels in rodents. Some have posed difficulties in interpretation of the significance of their results for human health due to use of non-oral routes of administration, small numbers of animals, single dose levels, or, where more than one dose level had been used, absence of dose-response relationships. The published literature is also inconsistent with regard to strain and species sensitivity to low-dose effects of BPA and failure to confirm effects in repeat studies. Thus, it is difficult for experts involved in risk assessment to know how much weight should be given to such studies, especially when they report effects at variance with the results obtained from well-conducted studies performed in accordance with accepted guidelines. To date, regulatory authorities have generally considered that low-dose effects of BPA in rodents have not been demonstrated in a robust and reproducible way, such that they could be used as pivotal studies for risk assessment. Some recent food-related risk assessments are summarized below.

**In Europe**, the European Food Safety Authority (EFSA, 2006) concluded that the overall NOAEL<sup>1</sup> of 5 mg BPA/kg bw/day from a comprehensive three-generation study in the rat, identified as the pivotal study in the earlier European evaluation of 2002 (SCF, 2002), was still valid. It was further supported by the NOAEL of 5 mg/kg bw/day from a more recent two-generation reproductive toxicity study in mice. The available studies covered the majority of endpoints considered relevant for assessment of reproductive effects and other toxicities and did not indicate the presence of

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<sup>1</sup> No-observed-adverse-effect level (NOAEL): The greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure.

effects on reproduction or development at doses lower than 50 mg/kg bw/day. The lowest NOAEL of 5 mg/kg bw/day derived from the newer two-generation reproductive toxicity study in mice was based on liver effects. Toxic effects of repeated administration of BPA on the liver in mice have also been observed in previous studies with a lowest-observed-adverse-effect level (LOAEL) of 120 mg/kg bw/day, suggesting that liver toxicity is at least as sensitive an endpoint for BPA as reproductive and developmental effects. EFSA's conclusions were based on the extensive database on repeated-dose toxicity, reproductive and developmental toxicity of BPA in rodents and on the comparative toxicokinetics in primates, including humans, and rodents. EFSA further concluded that the new studies provided a basis for revising the uncertainty factors that were used in the earlier 2002 evaluation to derive the temporary Tolerable Daily Intake (TDI)<sup>2</sup> of 0.01 mg/kg bw. In particular, EFSA considered that the database concerning reproduction and development had been considerably strengthened and that the additional factor of 5, introduced in 2002 because of uncertainties in the database, was no longer required. A default uncertainty factor of 100 was applied to the overall NOAEL from the rodent studies and was considered to be conservative in view of the well-described species differences in toxicokinetics, showing a low systemic concentration of free BPA in humans compared with rats. EFSA therefore established in 2006 a full TDI of 0.05 mg BPA/kg bw, derived by applying a 100-fold uncertainty factor to the overall NOAEL of 5 mg/kg bw/day. EFSA noted that the conservative estimates of exposure were less than 30% of this TDI in all population groups considered, including infants fed using PC bottles.

**In the USA**, the Food and Drug Administration (USFDA) issued a draft assessment in 2008 which is not an official statement of the FDA. It considered recent reports on BPA made by expert panels of the National Toxicology Program and the Center for the Evaluation of Risks to Human Reproduction. The draft assessment estimates that BPA exposure from use in food contact materials in infants and adults is 2.42 µg/kg bw/day and 0.185 µg/kg bw/day, respectively. It considered that the appropriate NOAEL for assessment of BPA was the NOAEL for systemic toxicity of 5 mg/kg bw/day derived from two multigenerational rodent studies. This NOAEL was considered to provide adequate margins of safety of approximately 2,000 and 27,000 for infants and adults, respectively, at current levels of exposure from uses of BPA in food contact materials. The data reviewed on endpoints such as the prostate gland and developmental, neural and behavioural toxicity, were considered insufficient as a basis to alter the NOAEL used to calculate the margins of safety. At a later date, FDA intends to publish a separate document that provides a safety assessment of BPA exposure from other FDA-regulated products.

**In Japan**, Under the current Food Sanitation Act, BPA in polycarbonate food containers, etc. is specified to be not more than 2.5 ppm in migration test standard<sup>3</sup>. The adequacy of this standard value had been confirmed by the TDI of 0.05 mg/kg bw/day based on the results of standard toxicity tests in 1993. In recent years, BPA has been reported to affect fetal and newborn animals at much lower doses compared to those causing adverse effects in the previous standard toxicity studies. Several studies monitoring low dose effects on developing animals were funded by and reported to the Ministry of Health, Labour and Welfare (MHLW) as Scientific Research Reports (<http://www.nihs.go.jp/edc/english/edc.html>). In order to examine the need for new measures for BPA in light of international concerns and the new research reports, the MHLW has asked the Food Safety Commission (FSC) of the Cabinet Office in 2008 for an opinion on the low dose effects of BPA. A draft risk assessment report on BPA, especially focusing on reproductive and developmental toxicity, is under discussion and information is available from the FSC web site (<http://www.fsc.go.jp/>).

At present, almost all domestic industries related to food containers have voluntarily taken measures to prevent BPA exposure since the 1990's, when the issue of low dose effects of BPA became public. Since then, high levels of exposure have not been reported from the containers in Japan. However, from the standpoint of public health, MHLW stated that it would be appropriate to

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<sup>2</sup> Tolerable daily intake (TDI): estimate of the amount of a contaminant in food or drinking-water, expressed on a body-weight basis that can be ingested daily over a lifetime without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation. It is expressed in milligrams of the chemical per kilogram of body weight.

<sup>3</sup> The Notice No. 370 of the Ministry of Health and Welfare, 1959.

reduce BPA exposure as much as possible, and therefore urged related industries to promote further voluntary efforts. For consumers, MHLW created a FAQ document, including advice for pregnant women and infant care-takers, about diet and breast-feeding, in order to deepen their understanding of BPA (in Japanese: <http://www.mhlw.go.jp/topics/bukyoku/iyaku/kigu/index.html>).

**In Canada**, BPA was assessed under the federal government's Chemical Management Plan (CMP) in 2008 and was considered to meet the criteria of a substance capable of having harmful effects on the environment and human health. As a result, in 2009 the government has announced that it is moving forward with proposed regulations to ban the importation, sale and advertising of polycarbonate baby bottles made with the BPA monomer. The Food Directorate of Health Canada also issued a statement in 2009 concluding that the current dietary exposure to BPA through food packaging uses was not expected to pose a health risk to the general population, including newborns and infants. The statement was based on the overall weight of evidence, including reaffirmation by other international regulatory agencies (notably the United States of America, Europe and Japan), and was in keeping with the conclusions re-confirmed in the most recent assessment of BPA from food packaging applications in August 2008. However, the statement went on to say that, due to the uncertainty raised in some animal studies relating to the potential effects of low levels of BPA, the Government of Canada is taking action to enhance the protection of infants and young children. It is therefore recommended that the general principle of ALARA (as low as reasonably achievable) be applied to continue efforts on limiting BPA exposure from food packaging applications to infants and newborns, specifically from pre-packaged infant formula products as a sole source food, for this sensitive segment of the population.

#### **Future WHO/FAO expert consultation**

In light of the uncertainties about possible adverse health effects at low doses of BPA, especially on the nervous system and on behaviour, and also the relatively higher exposure of very young children compared with adults, the WHO and FAO will jointly organize an ad hoc expert consultation in 2010 to assess the safety of BPA. The consultation will be supported by Health Canada and is tentatively planned for October 2010. Calls for experts and for data will be published in due course on the respective websites of WHO and FAO.

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The information summarized in this document was prepared by consulting the key information and conclusions in the published national and international assessments on the safety of BPA as listed below.

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USFDA: Draft assessment of bisphenol A for use in food contact applications: draft version 08/14/2008. Available from: [http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1\\_01\\_02\\_FDA%20BPA%20Draft%20Assessment.pdf](http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf)

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