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Health Risk Assessment of Bisphenol A from Food Packaging Applications

Bureau of Chemical Safety
Food Directorate
Health Products and Food Branch

A WHO Collaborating Centre for Food Contamination Monitoring

August, 2008

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Veiller à ce que les produits chimiques ne soient pas présents dans les aliments à des niveaux pouvant entraîner des effets néfastes sur la santé des canadiennes et des canadiens.

Our Mission
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BACKGROUND

Bisphenol A (BPA) is a chemical monomer used in the production of polycarbonate and epoxy-phenolic resins. Polycarbonate (PC) is widely used in the manufacture of food containers (e.g., milk, water and infant bottles) and epoxy resins are used as an interior protective lining for food and beverage cans. As a result of these food contact uses, minute quantities of BPA can potentially leach out into the water or food and consumers may be exposed to BPA through the diet.

BPA was included in Batch 2 of the Challenge under the Chemicals Management Plan carried out by Health Canada and Environment Canada. To assist the review of BPA under this process, the Bureau of Chemical Safety (BCS) in the Food Directorate of the Health Products and Food Branch (HPFB) has summarized recent data gathered by the Bureau for purposes of conducting a health risk assessment of BPA from dietary sources. While all age groups were considered as part of the assessment, particular attention was given to potential risks posed to infants by BPA exposure from epoxy-based cans which are used to package infant formulas. As canned infant formula can be the sole source of nutrition for certain age categories, it was anticipated that overall BPA exposure, and therefore risk, would be highest for newborns/infants consuming this product. Additional sources of potential BPA exposure for this segment of the population would be from the use of various consumer products such as polycarbonate (PC) baby bottles and tableware. However, they were not considered in this assessment of prepackaged foods.

EXPOSURE ASSESSMENT

The main potential exposure to BPA for infants from food packaging uses is from epoxy-based lined cans that are used in packaging infant formulas. Another minor source is the BPA in liners of metal closures for jars or bottles that may be used to package solid foods or beverages for infants. Additional sources of BPA exposure for this segment of the population would be from the use of various consumer products such as polycarbonate (PC) baby bottles and tableware. However, they were not considered in this assessment of prepackaged foods.

HPFB has previously estimated the probable daily intake (PDI) of BPA for the general population from food packaging uses to be 0.18 μg/kg b.w from tested food cans in 1995, based on the results of food simulant extraction studies conducted on epoxy-lined cans. For infants, the PDI of BPA from infant formula packaged in the epoxy-based cans was estimated at 2.63 μg/kg b.w. (Pelletier, 1995).

In October 2007, HPFB performed studies to measure the levels of BPA in canned liquid infant formulas from the Canadian market. Samples of 21 canned liquid infant formula products of various brands were analysed for BPA using a GC-MS method with quantification limit as low as 0.5 ppb, and the results were used to estimate dietary intakes of BPA for infants in different age groups (Cao et al, 2008). BPA was detected in all 21 products. The concentrations of BPA in formulas as sold ranged from 2.27 to 10.2 ppb (average of 5.2 ppb). However, as most of formulas are diluted 1:1 before feeding, only half of the average and maximum levels were used to estimate the BPA exposure to infants. These results are consistent with those reported by the FDA (Biles et al., 1997).

Table 1 presents the estimated average and maximum PDIs of BPA for infants at different developmental stages for the average and maximum formula intakes as recommended by the Institute national de santé publique du Québec (2001).
Table 1: The average and maximum PDIs of BPA for infants of different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Overall Average (2.6 ppb)</th>
<th>Maximum (5.1 ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average Formula Intake</td>
<td>Maximum Formula Intake</td>
</tr>
<tr>
<td></td>
<td>Average Formula Intake</td>
<td>Maximum Formula Intake</td>
</tr>
<tr>
<td>0 to 1 month</td>
<td>0.45</td>
<td>0.75</td>
</tr>
<tr>
<td>2 to 3 months</td>
<td>0.50</td>
<td>0.69</td>
</tr>
<tr>
<td>4 to 7 months</td>
<td>0.38</td>
<td>0.52</td>
</tr>
<tr>
<td>8 to 12 months</td>
<td>0.21</td>
<td>0.28</td>
</tr>
<tr>
<td>12 to 18 months</td>
<td>0.23</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*For PDI calculations, a dilution factor was applied to those infant formula products sold in concentrate form (1:1 water:formula).

The PDIs of BPA varied from as low as 0.21 for infants 8-12 months of age to as high as 1.35 µg/kg b.w. for 0-1 month old infants with the maximum formula intake and the maximum concentration of BPA migrating from epoxy lined infant formula cans.

HAZARD CHARACTERIZATION

Human exposure to low doses of BPA occurs mostly through food contact uses such as leaching from plastic bottles and from the coating of food and beverage cans. Whether these low doses of BPA are capable of causing adverse health effects in humans has been debated for many years. Prompted by this concern, the Society of the Plastic Industry (SPI) in 1995 submitted several reports to Health Canada for review: 1) a carcinogenesis bioassay in rats and mice conducted by National Toxicology Program (NTP); and 2) summary reports on estrogenic activity, reproductive and developmental toxicity, and subchronic and chronic toxicity (all prepared by SPI). These reports, along with additional toxicology studies received and reviewed prior to 1979, were evaluated.

According to the original evaluation of BPA in food packaging applications by BCS, BPA appeared to have estrogen-like activity and might be regarded as a potential endocrine-disrupting agent, although no maternal or developmental effects were noted at doses up to 160 mg/kg bw/day in standard reproductive assays in rodents. In the U.S. National Toxicology Program (NTP) carcinogenesis bioassay, BPA was shown not to be tumorigenic in rats or mice, and had no effect on general toxicity parameters at the lowest dose tested of 25 mg/kg bw/day in the 90-day preliminary study. In additional 13-week oral dosing studies in rats and dogs, no effects were observed at 50 mg/kg bw/day and 78 mg/kg bw/day, respectively. Based on the lowest NOEL of 25 mg/kg bw/day observed in the 90-day study in rats, a provisional tolerable daily intake (pTDI) of 25 µg/kg bw/day was established in 1996 by the Food Directorate of Health Canada.

Since this pTDI of 25 µg/kg bw/day was higher than the probable daily intake (PDI) for BPA of 0.18 µg/kg bw/day for the general population and 2.63 µg/kg bw/day for infants, based on the migration data provided by SPI (see above in the Exposure Assessment Section), the use of BPA in can coating resins and lacquers for packaging foods was considered to represent no health concern for the general population. However, based on concerns about potential estrogen-like activity of BPA, it was recommended at the time that the use of BPA in can-coating resins for packaging infant formulas should be limited.
Subsequent evaluations by the Food Directorate have focused on reproductive/developmental effects of BPA from available published and non-published studies. In rats and mice, NOAELs of 5 mg/kg bw/day and 50 mg/kg bw/day for systemic effects and developmental toxicity, respectively, were observed in multigeneration studies conducted by Tyl et al. (2002, 2007) and were considered valid (i.e., appropriate study protocols, adequate dose groups and animal numbers, conducted under GLP). The lower NOAEL of 5 mg/kg bw/day would still provide a margin of safety of 200 in comparison with the 1996 pTDI of 25µg/kg bw/day.

In addition to the traditional toxicological endpoints evaluated, the possible effects of BPA based on endocrine-disrupting activities have also been considered by the Food Directorate since 1996. In 1999, it was concluded that there appeared to be sufficient evidence to describe BPA as an endocrine disrupter, but it was noted that some of the estrogenic effects were not repeatable under similar conditions in different laboratories. Certain experimental studies with rats and mice published up to 2006 on the other hand revealed that BPA at dose levels lower than the NOAELs identified through classical/traditional toxicological endpoints might still have an impact on the neuroendocrine feedback system. These effects also might not necessarily be exerted in a straight threshold type dose-response manner and, in several instances, have been found to follow an inverted U-shaped dose-response (Akingbemi et al., 2004; Nishizawa et al., 2003; Nishizawa et al., 2005b; Negishi et al., 2004).

Although the significance of these observations was unclear, it was considered appropriate at this point to continue to monitor new findings related to the endocrine-disrupting potential of BPA. As the Food Directorate’s pTDI of 25 µg/kg bw/day fell within the range of similarly derived values (TDI of 16µg/kg bw/day by Willhite (2007) for NSF International, TDI of 50 µg/kg bw/day by the European Food Safety Authority (EFSA, 2006), oral reference dose (RfD) of 50 µg/kg bw/day set by US EPA (EPA, 1988), and maximum exposures from food packaging applications were approximately an order of magnitude lower, at the time, it was not considered necessary to revise this TDI.

In November 2007, the draft report of an expert panel evaluation convened by the NTP Center for the Evaluation of Risk to Human Reproduction (CERHR) was published. The expert panel consisted of 12 independent scientists and considered more than 500 studies. For assessing the potential reproductive and developmental hazard of BPA, a large literature database of studies in rodents and other species were evaluated, according to the NTP/NIEHS guidelines, with the format including synopses and assessments (under Strengths/Weaknesses and Utility headings) of studies reviewed. Because of pharmacokinetic issues related to how BPA is metabolized in experimental animals (mainly rodents) compared to humans and that oral exposure is considered more relevant to the human situation, greater weight was given to studies using the oral route of exposure for formulating levels of concern. Based on consideration of the potential for various health hazards relative to current estimates of general population exposure to BPA in the U.S., the expert panel expressed “negligible” concern for birth defects, malformations in fetuses and adverse reproductive effects in adults, and “minimal” concern for effects on prostate and accelerated puberty in infants and children. In addition, the expert panel identified having “some” concern with neural and behavioral effects for pregnant women and fetuses, as these effects may be associated with neural changes in the brain and sexually dimorphic alterations in rodents. It should be noted that the actual conclusions and recommendations of the NTP report are not expected to be finalized until mid-2008.
In response to this report, 8 studies in rodents considered pivotal for assessing neural and behavioural effects of BPA, as identified in the CERHR evaluation, were selected for further review. The findings of these 8 studies can be summarized in the table below:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal</th>
<th>Endpoints/Effects</th>
<th>Dose (ug/kg bw/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishizawa et al., 2005a</td>
<td>mice</td>
<td>Increased expression levels of AhR, AhRR and Arnt mRNAs (cerebra and cerebella; embryos).</td>
<td>NOEL 2, LOEL 0.02</td>
<td>Effects also observed at 200 and 20000 ug/kg bw/day.</td>
</tr>
<tr>
<td>Nishizawa et al., 2005b</td>
<td>mice</td>
<td>Increased expression levels of AhR, RARα and RXRα mRNAs (cerebra and cerebella; embryos).</td>
<td>NOEL 2, LOEL 0.02</td>
<td>No positive controls. Effects also observed at 200 and 20000 ug/kg bw/day.</td>
</tr>
<tr>
<td>Nishizawa et al., 2003</td>
<td>mice</td>
<td>Increased expression levels of RARα mRNA and decreased expression levels of RXRα mRNA (cerebra, cerebella, gonads; embryos).</td>
<td>NOEL 2, LOEL ND</td>
<td>One dose group only. Effects were not consistently found (observed at 14 but not at 16-18 days post-coitum)</td>
</tr>
<tr>
<td>Negishi et al, 2004</td>
<td>rats</td>
<td>Behavioral alterations (failure to avoid electrical stimuli and to show increment in locomotion in response to tranylcypromine; offspring).</td>
<td>NOEL ND, LOEL 100</td>
<td>One dose group only.</td>
</tr>
<tr>
<td>Laviola et al., 2005</td>
<td>mice</td>
<td>D-amphetamine-related reinforcing effects reduced (affect organization of the brain dopaminergic systems; female offspring).</td>
<td>NOEL ND, LOEL 10</td>
<td>Effects were observed in females only and involved only a single dose with no positive control. A pharmacological challenge (D-amphetamine) is not a usual part of conventional neurotoxicity testing methods as recommended by OECD.</td>
</tr>
<tr>
<td>Ryan and Vandenberg, 2006</td>
<td>mice</td>
<td>Increased anxious behavior (elevated-plus maze and a light/dark preference chamber); only female offspring tested.</td>
<td>NOEL 2, LOEL 200</td>
<td>no effects on short-term spatial memory (radial-arm maze and Barnes maze)</td>
</tr>
<tr>
<td>Ceccarelli et al., 2007</td>
<td>rats</td>
<td>Increased ER-labelled neurons (ARC and MPA of hypothalamus) and testosterone (males) and estradiol (females) levels during early puberty.</td>
<td>NOEL ND, LOEL 40</td>
<td>One dose group only.</td>
</tr>
<tr>
<td>Funabashi et al., 2004</td>
<td>rats</td>
<td>Affected the sex difference in CRH neurons (BST of brain) in offspring, probably due to an increase in CRH neurons in males and a decrease in CRH neurons in females.</td>
<td>NOEL ND, LOEL 2500</td>
<td>One dose group only and with no positive control.</td>
</tr>
</tbody>
</table>

AhR: aryl hydrocarbon receptor; AhRR: aryl hydrocarbon receptor repressor; Arnt: AhR nuclear translocator; ARC: arcuate nucleus; BST: bed nucleus of stria terminalis; CRH: corticotropin-releasing hormone; MPA: medial preoptic area; ND: no data; RARα: retinoic acid receptor α; RXR α: retinoid X receptor α
These eight studies all showed that in utero, perinatal or postnatal exposure to BPA may produce some effects on the neurobehavioral development of rodents during fetal or early postnatal life at levels below the NOAELs of 50 mg/kg bw/day for developmental/reproductive effects and 5 mg/kg bw/day for systemic toxicity in rats and mice reported by Tyl et al. (2002; 2007). The observed NOEL for effects on mRNA expression of various brain receptors (retinoic acid, aryl hydrocarbon; Nishizawa et al., 2003; 2005a; 2005b) and for increased anxious behaviour in female mice relative to controls (Ryan and Vandenbergh, 2006) was 2 µg/kg bw/day. The effects on receptor mRNA expression were characterized by an inverted U-shaped dose response phenomenon, such that effects were observed at the lowest dose tested (0.02 µg/kg bw/day) but not at the next highest dose (2.0 ug/kg bw/day).

This biphasic dose-response curve is presumed to be mediated by both positive and negative feedback effects on estrogenic receptors (Welshons et al., 2003; 2006) or related to physiological responses to estrogenic activity of BPA via the feedback mechanism of the endocrine system. The significance of the LOEL of 0.02 µg/kg bw/day however is difficult to interpret or extrapolate to human circumstances, particularly in light of the fact that it was the only dose level tested below the NOEL of 2 µg/kg bw/day and some of the effects were not consistently observed throughout the study periods. In addition, since the studies (exposure period and endpoints measured) were carried out only up to certain embryo development stages, they may or may not be necessarily applicable to the postnatal developmental period for newborns and infants. Therefore, further investigation of the toxicological and clinical significance of the dose representing the LOEL for effects on behaviour and estrogen receptors was undertaken.

General concerns were also noted in terms of the study design and conduct for several of the neurobehavioural studies. It was recognized that certain neurobehavioural effects are known to show distinct response variability depending on the species and strain of experimental animal. For example, in Sprague Dawley rats exposed to BPA perinatally, no affects on behaviour, including open field testing, were noted at doses up to 0.2mg/kg bw/day (Ema et al., 2001). In a comparison of the responses of 8 different mouse strains in six different behaviours, despite standardizing testing equipment and environments, considerable variability was noted in the responses of the different strains, including with the elevated plus maze (Crabbe et al., 1999).

While it is unclear whether the endpoints for the LOEL of 0.02 µg/kg bw/day may be associated with effects other than those mediated via the estrogen receptor, from the standpoint of endocrine disruption potential of BPA, it is noteworthy that at both the NOEL of 2 µg/kg bw/day and the LOEL of 0.02 µg/kg bw/day, BPA can be estimated to contribute only a minimal quantity of estrogenic activity, in terms of comparison to background 17β-estradiol (E2 levels in humans). In human (adult) dosing studies with BPA (Volkel et al., 2002, 2005), a Cmax BPA blood level (glucuronide conjugate) of 800 nM (182 ug/L) was reached after 80 minutes following an oral dose of 5 mg BPA (average volunteer body weight 67 kg). Assuming an equal volume of distribution on a body weight basis for infants, an oral dose of 0.02 ug/kg bw/day would therefore theoretically result in an infant blood BPA concentration of approximately 50 pg/mL. This dose level, after dividing by a BPA/E2 estrogenic equivalency ratio, of 1000, would yield an estrogenic activity equivalent to that of 0.05 pg/ml E2 if it were totally in the unconjugated form (free BPA). While a number of factors can influence the ability of BPA to induce “oestrogen-like” effects in experimental animals, such as the species and strain, the route of administration and the timing of exposure, an estrogen equivalency factor of 0.001 is thought to conservatively represent the range of in vivo responses, especially for those studies where a concurrent positive control was included (Markey et al., 2001; Milligan et al., 1998; Papaconstantinou et al., 2000; Steinmetz et al., 1997,1998; Tyl et al.,
2007). This value of 0.05 pg/mL would be 280 and 140 times lower, respectively, than reference serum estradiol levels of up to 14 pg/ml for children 0-8 years old (Carey and Knafla, 2007) and 0-7 pg/ml for infants of 0-2 years of age (American Association for Clinical Chemistry, 1977).

For rodents, the estrogenic activity in the blood following an oral dose at the LOEL of 0.02 µg/kg bw/day expressed in terms of E2 would be even lower and can be predicated by the application of similar pharmacokinetic comparisons to calculate the equivalent doses as follows:

a) According to the metabolic study in rats by Domoradzki et al. (2004), the BPA Cmax in plasma within 24 hours following a single oral administration of 1 mg/kg bw/day at postnatal day (PND) 4, 7 and 21 are approximately 0.04 µg/g plasma, 0.06 µg/g plasma and 0.005 µg/g plasma, respectively. By comparison, this suggests that at the oral intake of 0.02 µg/kg bw/day (LOEL) at PND 7, the BPA Cmax level would be approximately 1.2 x 10^-6 µg/g plasma or 1.2 pg/g plasma. With the application of the same BPA/E2 estrogenic equivalency ratio of 1000 the estrogenic activity of BPA at this LOEL of 0.02 µg/kg bw/day would be equivalent to that of 1.2 x 10^-3 pg/ml E2.

b) Using a similar metabolic study approach with findings from infant mice (Taylor et al., 2008) in which the BPA Cmax in plasma within 24 hours following a single oral dose of 35 µg/kg bw/day at postnatal day (PND) 2 was determined to be 1.78 ng/ml, the oral intake of 0.02 µg/kg bw/day (LOEL) at PND 2 would result in a BPA Cmax level of approximately 1.02 pg/ml plasma. With the application of the BPA/E2 estrogenic equivalency ratio of 1000, the estrogenic activity of BPA at this LOEL of 0.02 µg/kg bw/day would be equivalent to that of 1.02 x 10^-3 pg/ml E2. This is also low (about 196-fold less) when compared with the background reference free serum E2 concentration of approximately 0.2 pg/ml in mice (Judy et al., 1999).

Based on these estimates, it seems likely that the intake of BPA at the LOEL of 0.02 µg/kg bw/day probably will add only a minimal amount of estrogenic activity in blood of both humans and rodents (based on BPA/E2 estrogenic equivalency ratio of 1000), in comparison to their respective reference estradiol levels in serum. With these limited increases in estrogenic activity anticipated at a BPA intake of 0.02 µg/kg bw/day and considering that no adverse effects of BPA (on brain nuclear receptors) had been found at the second lowest dose level of 2 µg/kg bw/day in these studies (Nishizawa et al.2005a; 2005b), the toxicological significance of this LOEL (0.02 µg/kg bw/day), in our opinion, is questionable and should not be accepted as a LOEL for a hazard characterization of BPA.

However, since this dose (0.02 µg/kgbw/day) is likely to be below the threshold for any adverse effects of BPA in rodents, it may be considered relevant for the purpose of the safety evaluation of BPA residues in relation to the current canned infant formula petition. In view of the fact that there were no effects on behavior or specific nuclear receptors at an intake of 2.0 µg/kg bw/day in mice over the exposure period from gestation day 3 through postnatal day 21 (Ryan and Vandenbergh, 2006), and that the low estrogenic potency of a dose of 0.02 µg/kg bw/day was based on a very conservative calculation using the Cmax instead of an average BPA concentration in serum, a BPA intake of 1-2 orders of magnitude higher than the 0.02 µg/kg bw/day level may be considered to pose a minimal health risk to infants and children.
CONCLUSION AND RECOMMENDATIONS

Probable Daily Intakes (PDIs) of BPA resulting from its use in epoxy linings from cans used to package infant formula were estimated using data from analyses of 21 types of infant formula available on the Canadian retail market. Estimates suggested that average BPA intakes from canned infant formula were 0.2 to 0.5 ug/kg bw/day in newborns to infants up to 18 months of age. Maximum intakes (highest BPA concentration in canned formula, maximum formula intake) ranged up to 1.35 ug/kg bw/day for the same age groups.

New toxicology data published since the pTDI of 25 µg/kg bw was allocated in 1996 were reviewed. Results of the NTP CERHR Expert Panel Report on BPA (2007) confirmed that the NOAELs from standard toxicity assays published since our initial evaluation were similar to those used to establish the pTDI in 1996. However, the NTP Expert Panel in its review did identify as having “some concern” with various experimental studies investigating neurobehavioural endpoints which reported NOAELs/LOAELs several orders of magnitude lower. A subsequent review of these studies questioned the potential clinical and toxicological significance and/or relevance of the findings to human health risk assessment, while recognizing they did identify the need for further research in this area.

Based on the overall weight of evidence, 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 young children. This conclusion has been re-affirmed by health agencies in other countries, including notably the United States, the European Union and Japan.

However, the neurodevelopmental and behavioural dataset in experimental animals, suggest a heightened sensitivity during stages of development in rodents. These studies present several uncertainties related to methodological concerns raising questions as to the actual significance these findings may have on the potential risk to human health. In particular, certain studies involve only single doses of BPA, behavioural assessments done at a single time point, lack of a dose response, limited numbers of animals per test group or a lack of consistency in the findings.

Although highly uncertain, these data sets suggest the need for more focussed attention on products consumed by newborns and infants. It is therefore recommended that general principle of ALARA (as low as reasonably achievable) be applied to continue efforts on limiting BPA exposure from food packaging applications for this segment of the population.
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gestation and lactation causes loss of sex difference in corticotropin-releasing hormone-immunoreactive 

reduced in mice exposed prenatally to estrogenic endocrine disruptors. Brain Research Bulletin 65:235-
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