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Establishment of the Korean Tolerable Daily Intake of Bisphenol A Based on Risk Assessments by an Expert Committee

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Recently, reproductive and neurobehavioral effects of bisphenol A (BPA) have been documented, and thus a review was requested for BPA management direction by the government. Therefore, this study was performed to establish a Korean tolerable daily intake (TDI) for BPA. An expert committee, consisting of specialists in fields such as toxicology, medicine, pharmacology, and statistics, was asked to evaluate BPA health based guidance values (HbGVs). Although many toxicological studies were reviewed to select a point of departure (POD) for TDI, rat and mouse reproductive studies by Tyl *et al*. (2002, 2006), which were performed according to GLP standards and OECD guidelines, were selected. This POD was the lowest value determined from the most sensitive toxicological test. The POD, a NOAEL of 5 mg/kg bw/day, was selected based on its systemic toxicity as critical effects. An uncertainty factor of 100 including interspecies and intraspecies differences was applied to calculate the TDI. According to the evaluation results, a TDI of BPA for Korean was suggested at 0.05 mg/kg bw/day. In addition, the BPA exposure level based on food consumption by the Korean population was estimated as 1.509 μg/kg bw/day, and the HI was evaluated at 0.03 when the TDI of 0.05 mg/kg bw/day was applied. This HI value of 0.03 indicated that hazardous effects would not be expected from BPA oral exposures. Although highly uncertain, further studies on low dose neurobehavioral effects of BPA should be performed. In addition, it is recommended that the 'as low as reasonably achievable' (ALARA) principle be applied for BPA exposure from food packaging materials in newborn infants and children.

Key words: BPA, TDI, Risk assessment, Expert committee

INTRODUCTION

The establishment of health based guidance values (HbGVs) provides quantitative information from risk assessments for risk managers, enabling them to make decisions concerning the protection of human health. The HbGVs developed for substances found in food and drinking-water are the quantitative expression of a range of oral exposure that would be expected to be without appreciable health risk (WHO, 2010). For food contaminants that are generally unavoidable, The World Health Organization (WHO) has used the term acceptable daily intake (ADI), tolerable daily intake (TDI), and provisional tolerable weekly intake (PTWI); the United States Environmental Protection Agency (U.S.EPA)

has used the term reference dose (RfD); and the Agency for Toxic Substances and Disease Registry (ATSDR) has used the term minimal risk level (MRL) for their unique HbGVs (WHO, 2010; U.S.EPA, 2002; ATSDR, 2008). However, until now, only four Korean HbGVs have been suggested; therefore, when a hazardous case requiring risk assessment has occurred, we have used other country's HbGVs. Regarding the HbGVs of other countries, often each domestic department and division has used different values for risk assessment because each organization has established different values for the same compound.

The substance 2,2-bis(4-hydroxyphenyl)propane, more commonly known as bisphenol A (BPA), is used as a monomer in the manufacture of polycarbonates and epoxy resins (Yuji *et al*., 2002). Polycarbonates are used in food contact materials such as returnable beverage bottles, infant feeding bottles, tableware, and storage containers (Nam *et al*., 2010). Epoxy resins are used in protective linings for food and beverage cans and vats (Brotonx *et al*., 1995). Ever since BPA's weak estrogen-like activity was identified by *in vivo*

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testing in 1936 (Dodds and Lawson, 1936), many studies have been conducted to identify whether BPA works as an endocrine disrupter. Recently, new reproductive toxicity studies on BPA have been presented, and the neurobehavioral effects of low doses have raised some concerns. Several countries carried out policies to reinforce BPA management based on such toxicological data. According to this, infant feeding bottle manufacturers have stopped using BPA, and some states in the U.S.A prohibit using BPA. In addition, the Canadian government created legislation on the prohibition of imports, sales, and advertisements of BPA-containing infant feeding bottles (Canada, 2009). Moreover in Korea, concerns are rising relating to BPA exposure in pregnant women and infants. For this reason, the Korean government chose to consider a management direction for BPA.

Therefore, in this study, we reviewed toxicological studies, human exposure levels, and BPA strategies of other countries using an expert committee to establish Korean BPA HbGVs.

MATERIALS AND METHODS

Risk identification. Carcinogenic and non-carcinogenic toxicological data were collected from internal and external databases for hazard identification of BPA.

Risk characterization. Expert committees operate at foreign institutes to perform risk assessments, such as the CONTAM panel of the European Food Safety Authority (EFSA) and the science advisory board panel of the U.S.EPA. The expert committee is responsible for providing scientific judgments and other recommendations after reviewing toxicological data, and then an appropriate uncertainty factor (UF) is determined. Several years ago, a National Institute of Food and Drug Safety Evaluation (NIFDS) has organized an expert committee, consisting of experts in fields of toxicology, medicine, pharmacology, and statistics etc., to establish Korean HbGVs. This expert committee reviewed toxicological data and risk assessment documents to select an optimal study and determined a point of departure (POD). In addition, they concluded on the level of UF to apply for TDI establishment. The TDI was calculated as

Tolerable daily intake (mg/kg bw/day)

$$= \frac{\text{Point of departure (NOAEL etc.)}}{\text{Uncertainty factor}}$$

Exposure assessment and hazard characterization. Data describing bio-monitoring and daily intake levels from foods were collected from Science Citation Index (SCI) level papers. The hazard index (HI), representing the degree of risk associated with BPA in food, was also calculated as

$$\text{Hazard index} = \frac{\text{Human daily exposure (mg/kg bw/day)}}{\text{TDI (mg/kg bw/day)}}$$

HI ≤ 1: Hazardous effect would not be expected
HI > 1: Hazardous effect would be expected

where an HI ≤ 1 indicated that hazardous effects were not expected.

RESULTS

Risk identification.
Absorption, distribution, metabolism and excretion: BPA is rapidly absorbed from the gastrointestinal tract and forms BPA-glucuronide as a major pathway of biotransformation in primates and rodents. The formation of BPA conjugates is considered a deactivation reaction since BPA-glucuronide has a much lower hormonal activity compared to the activity of BPA (Shimizu *et al.*, 2002; Stowell *et al.*, 2006). However, there are major differences in the dispositions of BPA-glucuronide in rodents and primates, due to different pathways of elimination from the liver. In primates, including humans, orally administered BPA is rapidly absorbed from the gastrointestinal tract and undergoes first-pass metabolism to BPA-glucuronide in the intestinal wall and the liver. Rapid elimination of BPA-glucuronide from the blood, and rapid urinary excretion of BPA-glucuronide, were confirmed in human subjects given oral doses of BPA (Völkel *et al.*, 2002, 2005). In contrast to primates, several studies that gave oral doses of BPA ranging from 20~100 µg/kg bw/day to rats confirmed that BPA-glucuronide formed in the intestinal wall and the liver after oral administration underwent enterohepatic circulation after cleavage of glucuronide back to BPA, and most of the dose was slowly excreted with the feces (Kurebayashi *et al.*, 2005; Sakamoto *et al.*, 2002). It was also confirmed that BPA in rats is mainly metabolized to BPA-glucuronide and excreted from the liver with the bile (Kurebayashi *et al.*, 2003). This is in contrast to humans where BPA-glucuronide is excreted through the urine (Kurebayashi *et al.*, 2003, 2005).

Short-term and long-term toxicity: In an acute toxicity study, rats were dosed orally with BPA at 2000 mg/kg bw and clinical signs including lethargy, prostration, hunched posture, and piloerection were observed (NTP, 2008). The National Toxicology Program (NTP) conducted acute, subacute, and subchronic BPA toxicity studies in F344 rats and B6C3F1 mice. When BPA was administered through the diet, the non-observed adverse effect level (NOAEL) for reduced weight gain in rats was 25 mg/kg bw/day (NTP, 1982). In mice, the critical effect was the induction of multinucleated giant cells in the liver at doses of 143 mg/kg bw day and above in a chronic study, but no NOAEL was established (NTP, 1982).

Carcinogenicity and genotoxicity: Genotoxicity has been tested in bacteria or mammalian cells, and the results are

clearly negative (EFSA, 2006). In addition, the NTP conducted a 2-year rat and mouse carcinogenicity study where no increase in tumor incidence was found in test groups as compared to a control group (NTP, 1982). Based on these results, the expert committee concluded that BPA is non-genotoxic and non-carcinogenic.

Reproductive and developmental toxicity: Several reproductive and developmental toxicity studies conducted in the 1970s and 1980s indicated that BPA is not a selective reproductive and developmental toxicant at high dietary

Table 1. Reproductive and developmental toxicity of BPA

Reference	Species, strain, number and sex of animals	Route, dose, duration	Results/Comments
Cagen *et al.* (1999)	Rats, Han-Wistar albino, 28 F/dose group	Oral (Drinking), 0, 0.01, 0.1, 1.0, 10 ppm BPA and 0.1 ppm DES, 10 weeks	No treatment-related effects on growth or reproductive endpoints in adult females exposed to any concentration of BPA. No treatment-related effects were observed on the growth, survival, or reproductive parameters of male offspring from dams exposed to BPA.
Ema *et al.* (2001)	Rats, Crj:CD(SD)IGS, 25 M and F/dose group	Oral(gavage), 0.2, 2, 20, 200 µg/kg bw/day, two-generation	No significant changes in reproductive or developmental parameters between 0.2 and 200 µg/kg bw/day group.
Kim *et al.* (2001)	Rats, Sprague Dawley, 20 F/dose group	Oral(gavage), 0, 100, 300, 1,000 mg/kg bw/day, GD 1-20	No adverse signs of either maternal toxicity or developmental toxicity in the 100 mg/kg bw/day group. Pregnancy failure, pre- and post-implantation loss, fetal developmental delay and severe maternal toxicity in 300 and 1,000 mg/kg bw/day group. No embryofetal dysmorphogenesis in the 1,000 mg/kg bw/day group.
Kim *et al.* (2002)	Rats, Sprague Dawley, castrated, M	Oral (gavage), 7 days	BPA did not exhibit any androgenic or anti-androgenic activities in Hershberger assay.
Tyl *et al.* (2002)	Rats, Sprague Dawley, 30 M and F/dose group	Oral (diet), 0, 0.001, 0.02, 0.3, 5, 50, 500 mg/kg bw/day, three-generation	Adult systemic NOAEL was 5 mg/kg/day. Reproductive and postnatal NOAEL was 50 mg/kg bw/day. No treatment-related effects in the low-dose region (0.001-5 mg/kg bw/day) on any parameters and no evidence of nonmonotonic dose-response curves across generations for either sex.
Nagao *et al.* (2002)	Mice, C57BL/6N, M	Oral (gavage), 0, 2, 20, 200 µg/kg	No body weight changes, weights of reproductive organs (testes, epididymides, seminal vesicles), cauda epididymal sperm density, and histology of reproductive organs at any dose.
Tinwell *et al.* (2002)	Rats, Sprague Dawley and Alderley Park, M and F	Oral (gavage), 20, 100 µg/kg, 50 mg/kg, GD 6-21	Decrease in daily sperm production and increase in the age of vaginal opening for AP rats at 50 mg/kg.
Schönfelder *et al.* (2004)	Rats, Sprague Dawley, F	Oral (gavage), 0.1, 50 mg/kg bw/day BPA, 0.2 mg/kg bw/day EE2, GD 6-21	Morphological changes were observed in the uterine epithelium of offspring.
Timms *et al.* (2005)	Mouse, CD-1, F	Oral (diet), 10 µg/kg bw/day BPA, 0.1 µg/kg bw/day DES, GD 14-18	Increase in the number and size of dorsolateral prostate ducts and an overall increase in prostate duct volume for BPA.
Tyl *et al.* (2006)	Mouse, CD-1, M and F	Oral(diets), 0, 0.003, 0.03, 0.3, 5, 50, 600 mg/kg bw/day, two-generation	The systemic NOAEL was 5 mg/kg bw/day. The reproductive/developmental NOAEL was 50 mg/kg bw/day. At lower doses (0.003-5 mg/kg bw/day), there were no treatment-related effects and no evidence of nonmonotonic dose-response curves for any parameter.

concentrations (Morrissey *et al.*, 1987, 1989; Wazeter *et al.*, 1984a, b). On the other hand, some studies conducted in the 1990s reported that low-dose BPA exposure of below 5 mg/kg bw/day resulted in certain reproductive and developmental changes in experimental animals (Nagel *et al.*, 1997; vom Saal *et al.*, 1998). However, these results have not been repeatable in reproductive or developmental toxicity studies using more test animals or broader dose ranges (Cagen *et al.*, 1999; Ema *et al.*, 2001; Tinwell *et al.*, 2002). During this research, several reproductive and developmental BPA toxicity studies were fully reviewed and are summarized in Table 1 (Kim *et al.*, 2001, 2002; Nagao *et al.*, 2002; Schönfelder *et al.*, 2004; Timms *et al.*, 2005).

Neurobehavioural effects of BPA: In addition to reproductive and developmental toxicity, some studies report that low dose exposure of BPA in pregnant rats and mice might have neurobehavioral effects (Nishizawa *et al.*, 2003; Ryan and Vandenbergh, 2006; Laviola *et al.*, 2005). Based on these results, the NTP expert panel recognized that BPA presents "some" concern of neural and behavioral effects in pregnant women and fetuses, as these effects may be associated with neural changes in the brain and sexually dimorphic alterations in rodents (NTP, 2008). In addition, Health Canada considered 8 studies in rodents to be pivotal for assessing neural and behavioral low dose effects of BPA (Health Canada, 2008). While such studies have indicated low dose effects of BPA, no effects were reported when pregnant rats and mice were given doses of 0.2~200 μg/kg bw/day during the perinatal period (Ema *et al.*, 2001). Moreover, the suggestion of low dose effects has limitations because neurobehavioral effects have only been shown below a no observed effect level (NOEL) of 2 μg/kg bw/day, and it is difficult to find relevance to human health risk assessments. In addition, since studies have been conducted only up to specific embryonal development stages, their results are not applicable to the postnatal developmental period of infants. Thus, it is predominately thought that further studies should focus on low dose effects of BPA (Health Canada, 2008).

Risk Characterization. As can be seen from the above summary of toxicity data, more recent studies indicate that reproductive and endocrine-related endpoints are important in BPA risk assessment. For studies to be used for risk assessment purposes, it is important that adequate numbers of animals are tested to control for individual variability of responses and that an adequate dosing range is tested to show a dose-response relationship. The most appropriate toxicological studies to evaluate human health risk have been 3 generation rat and 2 generation mouse reproductive toxicity studies conducted by Tyl *et al.* In a 2002 study, the systemic NOAEL was 5 mg/kg bw/day based on reduced body weight and the reproductive NOAEL was 50 mg/kg bw/day based on reduced ovary weight and decreases in live pups/litter (Tyl *et al.*, 2002). In a 2006 study, the sys-

temic NOAEL was 5 mg/kg bw/day based on liver toxicity and centrilobular hepatocyte hypertrophy, and the reproductive NOAEL was 50 mg/kg bw/day based on reduced organ weight in offspring (Tyl *et al.*, 2006). Thus, the expert committee concluded that the systemic NOAEL of 5 mg/kg bw/day, based on the results of comprehensive three-generation and two-generation reproductive toxicity studies conducted by Tyl *et al.*, is appropriate as the point of departure for TDI establishment. If toxicological data from well-conducted animal studies are the basis for evaluating human health effects, a UF of 100 that consists of interspecies and intraspecies differences can be considered an appropriate default value. However in 1993, Renwick proposed the subdivision of each uncertainty factor of 10 to consider toxicodynamics and toxicokinetics. According to this study, the UF for interspecies differences was divided to 2.5 for toxicodynamics and to 4 for toxicokinetics, and for intraspecies differences the UF of 10 was divided to 3.2 for toxicodynamics and to 3.2 for toxicokinetics. The size of UF is usually determined by the estimations of an expert committee (IPCS, 1994). Some studies on BPA toxicokinetics reported that the excretion rate of BPA in rodents was slow because orally administered BPA experienced enterohepatic recirculation. On the other hand, BPA-glucuronide metabolized in the liver is excreted rapidly via urine. This is just one of several differences that potentially exist between humans and other species, so the committee decided to apply a UF of 10 for interspecies differences. In addition, a UF of 10 was applied for intraspecies differences considering there might be polymorphisms between humans. Low dose effects on specific endpoints have been reported in some studies, but the evidence is too limited to consider it in human health evaluations. The Korean government has carried out continuous management strategies to reduce BPA exposure levels. Considering these situations, the committee decided not to apply additional modifying factors. As a result, the committee established a Korean BPA TDI of 0.05 mg/kg bw/day, derived by applying a UF of 100 to a NOAEL of 5 mg/kg bw/day cited from Tyl *et al.*

Exposure assessment and hazard characterization. Yang *et al* conducted biological monitoring of environmental BPA using urinary BPA as an exposure biomarker of BPA in 73 (Yang *et al.*, 2003) and 172 (Yang *et al.*, 2006) Korean individuals. The 2003 study yielded a geometric mean of urinary BPA of 9.54 μg/*l* with a geometric standard deviation of 8.32 μg/*l*, and the 2006 study yielded urinary levels of conjugated BPA in a range of 0.03~62.4 μg/*l* (median 7.86 μg/*l*). These studies provided valuable information for monitoring situations in Korea; however, no external dose could be calculated. In one study of Korean adults, sixty-one canned food items were analyzed for BPA concentrations (Lim *et al.*, 2009), and BPA was detected in 7 food items such as tuna, fish, fruits, vegetables, meats,

coffee, and tea, and mean concentrations of BPA were 3.1 μg/kg (vegetables) ~45.51 μg/kg (coffee). Based on this study, the total human BPA exposure level was presented as 1.509 μg/kg bw/day and the HI was 0.03 when a TDI of 0.05 mg/kg bw/day was applied. Thus, this HI value of 0.03 indicated that hazardous effects would not be expected from oral BPA exposure.

DISCUSSION

The expert committee's conclusion on BPA was based on toxicological data in rodents and toxicokinetic differences between primates and rodents. In this study, a NOAEL was selected as 5 mg/kg bw/day from 3 generation rat and 2 generation mouse reproductive studies, and a UF of 100, considering interspecies and intraspecies differences, was applied to establish a BPA TDI of 0.05 mg/kg bw/day. To protect human health, various HbGVs of BPA were suggested and are summarized in Table 2 (Calvin *et al*., 2008; EFSA, 2006; Health Canada, 2008; U.S.EPA, 2002). The TDI offered in this study is similar to TDIs of the European Food Safety Authority (EFSA) and U.S. EPA, but it is 2~3 times higher than those of Health Canada and the National Sanitation Foundation (NSF) International. Some government departments such as the Ministry of Environment, Ministry of Knowledge Economy, and Korea Food & Drug Administration (KFDA) handle BPA exposure, and these departments have carried out strong policies to reduce human exposure (Table 3). Hence, the current level of BPA

exposure used in these strict management plans is expected to be reduced. In 2010, EFSA called European expert to reconsider the BPA toxicity, and more than 800 studies on BPA has been retrieved. On this evaluation, EFSA has indicated that the expert committee would maintain the TDI for BPA at 0.05 mg/kg bw/day for no evidence of neurobehavioural effect and low dose effect on learning ability (EFSA, 2010). This opinion supports our study results, the TDI of 0.05 mg/kg bw/day. With the consent of other departments, the TDI suggested in this study will be used as a representative value for risk assessments in Korea. Although highly uncertain, further studies on the low dose effects of BPA on neurobehavioral functions should be performed. In addition, it is recommended that the 'as low as reasonably achievable' (ALARA) principle be applied for BPA exposure from food packaging materials in newborn infants and children.

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Table 2. BPA health-based guidance values of international organizations

Organization	Endpoint	POD	UFs	HbGV
EFSA	Reduced body weight and liver toxicity	NOAEL 5 mg/kg bw/day	100	TDI 0.05 mg/kg bw/day
Health Canada	Reduced body weight	LOAEL 25 mg/kg bw/day	1,000	pTDI 0.025 mg/kg bw/day
U.S.EPA	Reduced body weight	LOAEL 50 mg/kg bw/day	1,000	RfD 0.05 mg/kg bw/day
NSF International	Reduced body weight and liver toxicity	NOAEL 5 mg/kg bw/day	300	RfD 0.016 mg/kg bw/day

Table 3. Government policies for BPA exposure reduction

Government	Policies on BPA
Ministry of Environment	BPA is included in the "TOXIC CHEMICALS CONTROL ACT" in accordance with standards prescribed by a Presidential Decree, announced by the Minister of Environment. In addition, standards of BPA in drinking water were planned.
Ministry of Knowledge Economy	The elution standard of BPA in infant feeding bottles is set as 3 mg/kg, and a continuous monitoring and regulation plan is expected.
KDFA	The existing standard for BPA, phenol, and tertiary-butylphenol was a total of 2.5 ppm, however, in December 2008 it was reduced to below 0.6 ppm for BPA alone.

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