Environ Sci Pollut Res
DOI 10.1007/s11356-016-7207-y

RESEARCH ARTICLE

Probabilistic integrated risk assessment of human exposure risk to environmental bisphenol A pollution sources

Keng-Yen Fu[1] · **Yi-Hsien Cheng**[2] · **Chia-Pin Chio**[3] · **Chung-Min Liao**[2]

Received: 14 March 2016 / Accepted: 8 July 2016

Abstract Environmental bisphenol A (BPA) exposure has been linked to a variety of adverse health effects such as developmental and reproductive issues. However, establishing a clear association between BPA and the likelihood of human health is complex yet fundamentally uncertain. The purpose of this study was to assess the potential exposure risks from environmental BPA among Chinese population based on five human health outcomes, namely immune response, uterotrophic assay, cardiovascular disease (CVD), diabetes, and behavior change. We addressed these health concerns by using a stochastic integrated risk assessment approach. The BPA dose-dependent likelihood of effects was reconstructed by a series of Hill models based on animal models or epidemiological data. We developed a physiologically based pharmacokinetic (PBPK) model that allows estimation of urinary BPA concentration from external exposures. Here we showed that the daily average exposure concentrations of BPA and urinary BPA estimates were consistent with the published data. We found that BPA exposures were less likely to pose significant risks for infants (0–1 year) and adults (male and female >20 years) with $<10^{-6}$-fold increase in uterus weight and immune response outcomes, respectively. Moreover, our results indicated that there was 50 % risk probability that the response outcomes of CVD, diabetes, and behavior change with or without skin absorption would increase 10^{-4}–10^{-2}-fold. We conclude that our approach provides a powerful tool for tracking and managing human long-term BPA susceptibility in relation to multiple exposure pathways, and for informing the public of the negligible magnitude of environmental BPA pollution impacts on human health.

Keywords Environmental bisphenol A (BPA) · Endocrine disrupters · PBPK modeling · Human health · Risk assessment

Responsible editor: Philippe Garrigues

Electronic supplementary material The online version of this article (doi:10.1007/s11356-016-7207-y) contains supplementary material, which is available to authorized users.

✉ Chung-Min Liao
cmliao@ntu.edu.tw

[1] Division of Plastic and Reconstructive Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan 11490, Republic of China

[2] Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan 10617, Republic of China

[3] Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, Taipei, Taiwan 10055, Republic of China

Introduction

Bisphenol A (BPA) is categorized as one of the endocrine disrupters by the United States Environmental Protection Agency (USEPA) and has one of the highest volumes of produced chemicals of 5–6 billion pounds each year (CDC 2013). BPA, known as a plastic monomer and plasticizer, is mainly used in manufacturing polycarbonate plastic and epoxy resins and plastic consumer products including toys, drinking containers, tubing, consumer electronics, etc (Vandenberg et al. 2007). BPA is also used in the production of dental sealant and medical materials (Kubwabo et al. 2009; Zimmerman-Downs et al. 2010). The up-to-date tolerable daily intake (TDI) set by the European Food Safety Authority (EFSA) has been lowered from 50 to 4 μg kg^{-1} day^{-1} based on newly incorporated investigation and experimental data with potential uncertainties considered (European Food Safety Authority (EFSA)).

Published online: 16 July 2016

Moreover, the molecular mechanism for BPA revealed a variety of pathways that induced cell responses at very low concentrations (Michałowicz et al. 2015; Naciff et al. 2010; Welshons et al. 2006). Several researches hypothesized that exposure during the early life period to BPA may increase the risk of infertility, weight loss, or behavior change (Braun et al. 2009, 2014; Li et al. 2011; Miao et al. 2011). On the other hand, a previous study indicated the association between urinary BPA excretion and the incidence of heart disease, diabetes, or abnormal expression of liver enzymes (Melzer et al. 2010).

BPA exposure through daily meal was considered an important part of the total body burden. Most of the BPA was leached from epoxy-coated canned foods or polycarbonate baby bottles (Brenn-Struckhofova and Cichna-Markl 2006; Maragou et al. 2007; Noonan et al. 2011). Meanwhile, high levels of BPA were detected from migration via the food package wrap or thermal paper (Biedermann et al. 2010; Duffy et al. 2006). In addition to food or drink ingestion, other exposure pathways of environmental BPA should not be neglected. Stahlhut et al. (2009) found that a higher urinary BPA concentration was detected while investigating the BPA elimination rate of the participant. Therefore, the nonfood route may also be taken into consideration in the exposure pathway.

In general, inhalation was minor in total exposure due in part that airborne BPA was relatively low compared to that of food intake. On the other hand, skin absorption of BPA was likely to be an important route because BPA-containing thermal paper was often used in stores (Biedermann et al. 2010; Kaddar et al. 2008; Marquet et al. 2011; Rocha et al. 2015). Biedermann et al. (2010) indicated that when holding thermal printing paper for 5 s, nearly 1 μg of BPA (0.2–6 μg) could migrate into the forefinger and the middle finger if skin was rather dry, whereas 10-fold of BPA transfer was measured if skin was wet or greasy. To date, however, until recently, investigations of skin absorption and metabolic mechanisms of BPA have been incorporated in risk assessment protocols (EFSA 2015).

The physiologically based pharmacokinetic (PBPK) model was developed to provide insights into the tissue distribution of BPA in humans. Moreover, the daily intake of BPA into the human body via different routes can be calculated through the PBPK model. The PBPK model was originally established based on the data from rats and could be extrapolated to predict steady-state concentrations of BPA in human tissues after multiple intravenous instillations (Cho et al. 2002). To date, other chemicals like acetone, isopropanol, hydroquinone, etc. with skin absorption were applied in the PBPK model (Bois et al. 2010; Gajewska et al. 2014); however, there were only scarce studies considering BPA skin absorption in the PBPK model (Mielke et al. 2011; Mielke and Gundert-Remy 2012; Shin et al. 2010, 2004).

Although studies related to consumer exposure have raised concerns about the health effects of BPA sources, there has been no systematic attempt to examine and assess under what exposure pathways would various effects be expected to arise. Therefore, this study aimed to quantify the urinary BPA concentration distributions from various exposure pathways in Chinese residents through a PBPK model. Different health outcomes have been examined by the constructed Hill models. Monte Carlo simulation was also performed to estimate the BPA concentration distributions within the human body for a better understanding of the potential BPA exposure-associated impacts on age- and gender-specific human health risks with or without skin absorption.

Materials and methods

General framework

Based on the USEPA risk assessment protocol (USEPA 1998), the proposed approach for estimating risk of BPA through different pathways is depicted in Fig. 1. In brief, we categorized people potentially being exposed to BPA into four subgroups based on their life stages and corresponding different dietary habits. Exposure pathways including food, drink, and inhalation were integrated to estimate the total external exposure. On the other hand, dose-response profiles of five health outcomes of animal models or human epidemiological data were constructed.

Specifically, the risks of immune response and uterine weight increase derived from animal experiments were evaluated. Internal urinary concentration of BPA estimated by applying the PBPK model either with skin absorption considered was further implemented to assess other health outcomes including human behavior change and increased odds ratio in cardiovascular disease (CVD) and diabetes derived from epidemiological analyses. Combining exposure and dose-response profiles, the probabilistic risks with respect to each outcome were estimated.

Exposure analysis

Populations with potentials of BPA exposure were categorized into four subgroups based on different age groups as infants I and II as well as adult male and female due to variety in dietary habits which would impact much on determining external BPA exposures (Miyamoto and Kotake 2006; von Goetz et al. 2010) (Fig. 2). Specifically, the crucial exposure routes for infant I aged 0–6 months may include baby bottle, toy, and milk simulant. The BPA concentration in breast milk that ranged 0.28–0.97 ng mL^{-1} with a mean of 0.61 ng mL^{-1} is much lower than that in infant simulant from the report of Sun et al. (2004). For infant II subgroup aged 7–12 months, baby

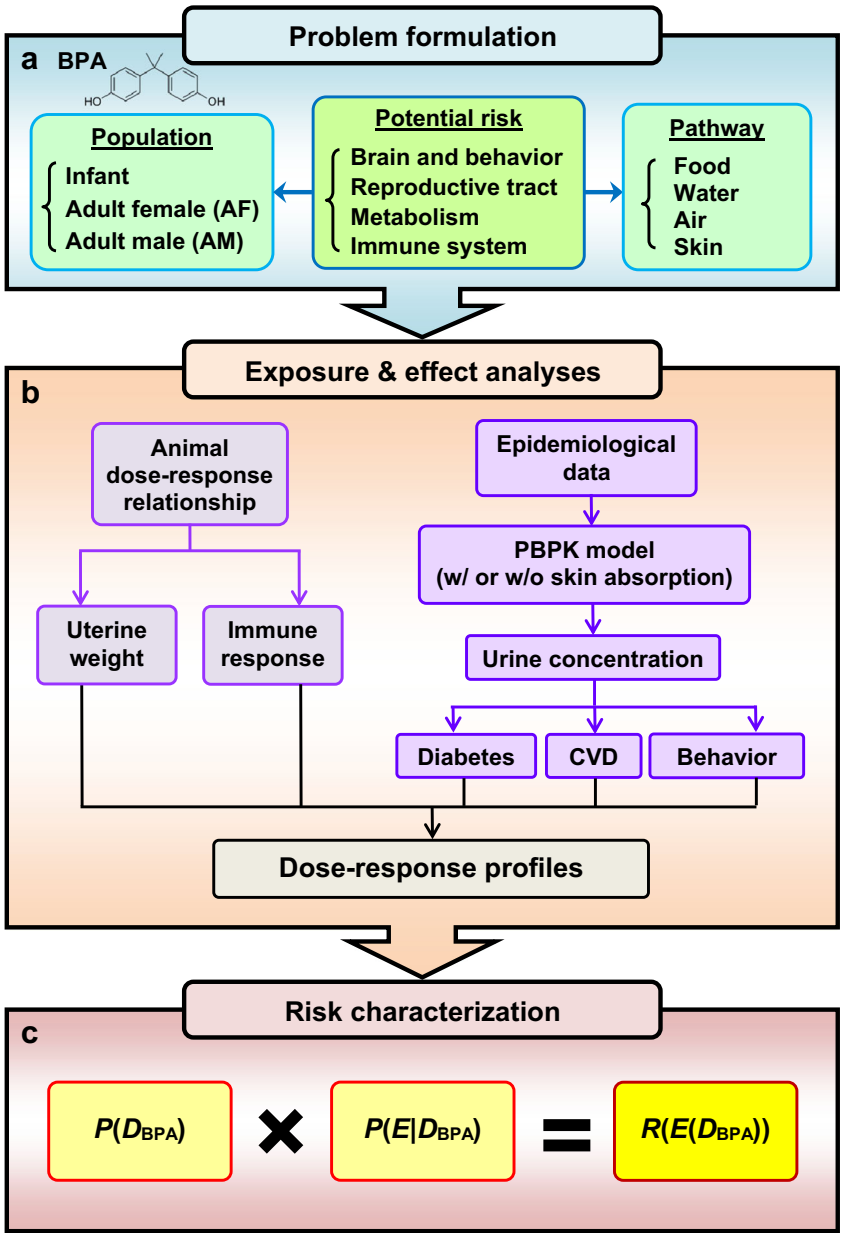

Fig. 1 Probabilistic BPA health risk assessment framework

food needs to be supplied as an additional food supplement. People older than 20 years were further divided into adult male and female according to significant differences in food intake and breathing rate.

In practice, the intake from air, water, and food media can be calculated as follows:

$$I_i = G_i \times C_i, \tag{1}$$

where I_i is the BPA intake rate (μg kg^{-1} day^{-1}), G_i is the ingestion rate (m^3 day^{-1} or L day^{-1} or kg day^{-1}), and C_i is the BPA concentration (μg m^{-3} or μg L^{-1} or μg kg^{-1}) where the subscript "i" denotes the exposure media such as air, water, or food items.

The BPA migration from consumer articles including infant feeding bottles, toys, and microwave food was calculated as follows:

$$I_j = D_j \times T_j, \tag{2}$$

where I_j is the BPA intake rate from the consumer product (μg kg^{-1} day^{-1}), D_j is the migration rate (μg cm^{-2} min^{-1} or μg L^{-1} or μg kg^{-1}) from the consumer product, and T_j is the contact time (min cm^2 day^{-1}) or frequency (L day^{-1} or kg day^{-1}) to the consumer product where "j" denotes the consumer product such as infant feeding bottles, toys, or microwave food. Eventually, both BPA intake rates, I_i and I_j, shown in

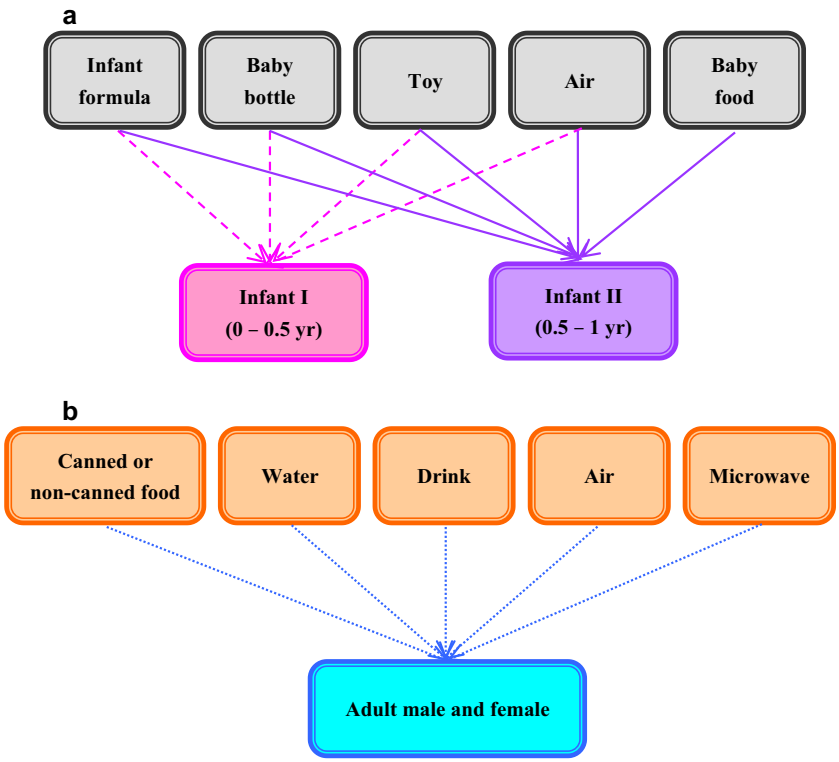

Fig. 2 Schematic for the important exposure pathways to age-specific population of **a** infant I and infant II, and **b** adult male and female

Eqs. (1) and (2) were integrated as inputs to the PBPK model to estimate internal BPA exposure based on various exposure routes and sources.

Human BPA-PBPK modeling

The PBPK model adopted from Shin et al. (2004) was originally implemented to illustrate the dynamic transport of BPA from intravenous instillation or oral administration that could reflect the mechanisms including glucuronidation, biliary excretion, and enterohepatic recirculation (Fig. 3). The equations and associated model parameters used in the present study are shown in Tables S1 and S2 (see Supplementary materials). In this study, 20 compartments (organs and tissues) were included in our proposed PBPK model. On the other hand, scenarios (70 kg male or female) with or without 1 h skin absorption of BPA from sources such as thermal papers were taken into account. The external dose of BPA from oral administration or skin absorption was converted into urinary BPA concentration through the human BPA-PBPK model.

Because we adopted the study by Shin et al. (2010, 2004) to model the urinary BPA levels after several scenarios being considered, we proposed that the urinary BPA is determined as the free BPA concentration. In brief, the input BPA dose is metabolized by several glucuronides, whereas the free BPA concentration in urine and other tissues can be estimated by our PBPK model. However, our selected endpoints were adopted from published epidemiological studies in which their data might only be performed as total BPA concentration in urine.

Therefore, we transferred the free BPA concentration into the corresponding total BPA concentration in urine (in kidney compartment) as follows (Zhang et al. 2011):

$$\mathrm{DI} = \frac{C_u \times Q_u}{(1-\alpha)}, \tag{3}$$

where DI is the daily intake rate (μg day^{-1}), C_u is the urinary BPA concentration (μg L^{-1}), Q_u is the urinary excretion rate (L day^{-1}), and α is the meta ratio (dimensionless, i.e., BPAG/(free BPA + BPAG). The adopted value of Q_u is 1.7 L day^{-1} (Zhang et al. 2011) and α is fitted as 0.9995. It was evidenced that the free BPA in urine is likely to be less than 0.01 % (Krishnan et al. 2010; Lacroix et al. 2011).

Dose-response analysis

A three-parameter Hill equation was used to optimally fit the data adopted from animal or epidemiological studies to obtain dose-response relationships. The Hill model captures the relationship between external or urinary BPA concentration and health outcome as follows:

$$E = \frac{E_{max} C^n}{EC_{50}{}^n + C^n}, \tag{4}$$

where C is the external or urinary concentration of BPA (μg

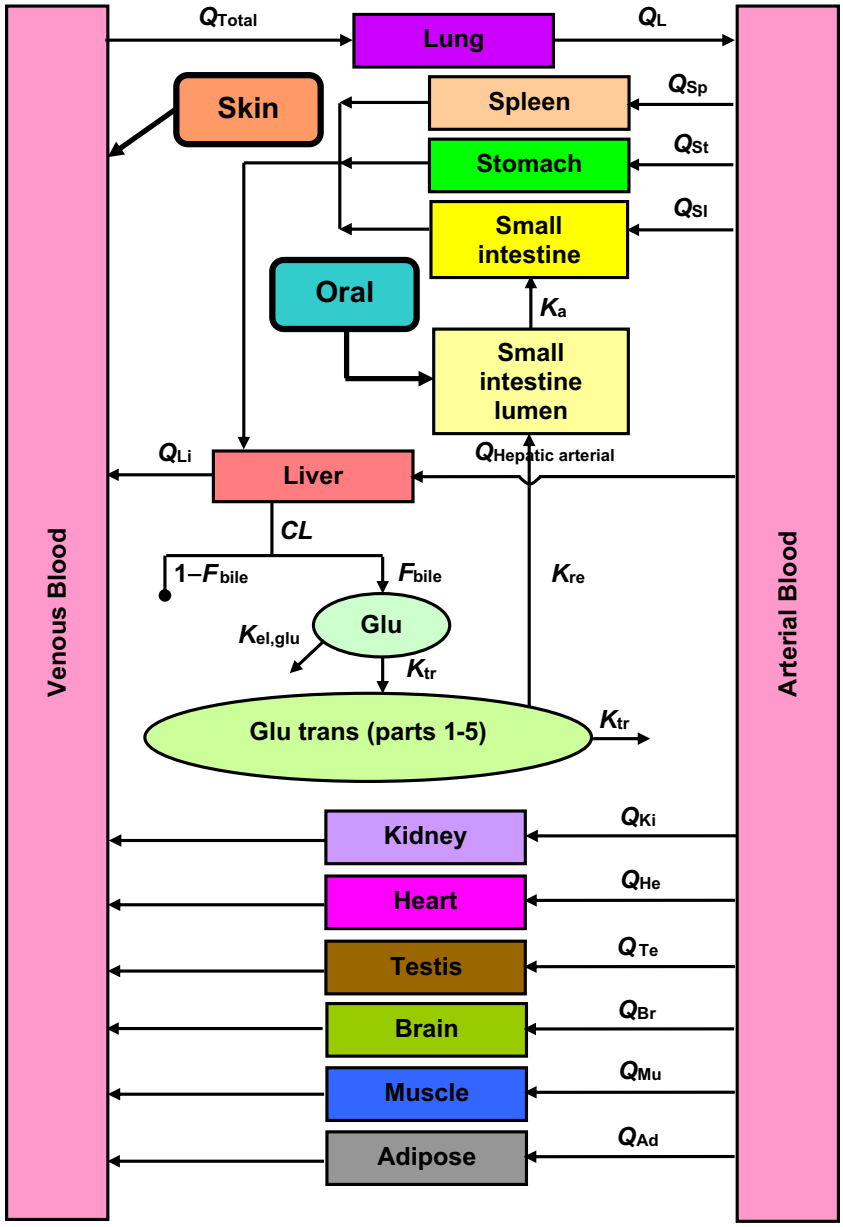

Fig. 3 Schematic of the physiologically based pharmacokinetic (PBPK) model for BPA (revised from Shin et al. 2004). Compartments with *shadow area* represent the exposure pathways for the PBPK model

kg^{-1} or $mg\ kg^{-1}$ or $\mu g\ L^{-1}$), E_{max} is the maximum effect, EC_{50} is the concentration that caused an equal effect to half of E_{max} ($\mu g\ kg^{-1}$ or $mg\ kg^{-1}$ or $\mu g\ L^{-1}$), and n is a slope factor referred to as the Hill coefficient representing the overall shape of the dose-response curve.

Among various health outcomes associated with BPA exposure, we selected five representative ones: immune response, reproduction, cardiovascular disease, diabetes, and behavior change (Kundakovic and Champagne 2011; Mileva et al. 2014). Specifically, Yamasaki et al. (2000) and Yoshino et al. (2003) performed in vivo experiments with a wide concentration range of BPA being considered. On the other hand, a strong association was shown between maternal urinary BPA concentration and child externalizing behaviors in 2-year-old female children determined by the Behavioral Assessment System for Children (BASC-2) score (Braun et al. 2009). An epidemiological study of cross-sectional analysis based on the National Health and Nutrition Examination Survey (NHANES) during the period 2003–2006 found that the increase of urinary BPA concentration also caused the elevation of the odds ratio in CVD and diabetes (Lang et al. 2008). Health outcomes were selected whenever the values of the fitted Hill coefficient were larger than 1.

Risk characterization

Exceedance risk could be calculated as the external or urinary BPA concentration distributions ($P(D_{BPA})$)

multiplied by the conditional probability of the effect for health outcomes given a certain BPA concentration $P(E|D_{BPA})$ as,

$$R(E(D_{BPA})) = P(D_{BPA}) \times P\left(E\middle|D_{BPA}\right), \quad (5)$$

where $R(E(D_{BPA}))$ is the probabilistic risk of the adverse health outcome at a specific BPA concentration D_{BPA}. Notably, the adjusted factor was set as 1000 when animal data was used to evaluate long-term human health risk by linear extrapolation.

To quantify the variability of BPA exposure from a variety of routes, the lognormal distribution model was used to estimate the total exposure of BPA from food and nonfood sources including water, air, toy, or thermal paper from data mostly adopted from investigations in Chinese. The Monte Carlo simulation was used to quantify the uncertainty and variability of the data by performing 10,000 iterations to obtain the 95 % confidence interval (CI) using the Crystal Ball software (Version 2000.2, Decisioneering Inc., Denver, CO, USA). The three-parameter Hill model was applied to construct the dose-response profile by using TableCurve 2D (Version 5.0, AISN Software Inc., Mapleton, OR, USA).

Results

Environmental BPA exposure

The total external and urinary concentrations of BPA from different subgroups in China were calculated by accounting the entire intake from different routes. Through multiplication of each media concentration distribution represented by lognormal distribution (Table 1) and the age-specific daily intake for each food category (Table 2), the total concentration distributions of exposure on each age-specific subgroup in China could be determined (Fig. 4).

Integrating all possible exposure routes, the distribution of daily intake for adult male had a geometric mean (gm) of 2.50 μg day^{-1} with a geometric standard deviation (gsd) of 1.87, whereas for infant II, the highest concentration distribution among all subgroups was obtained with a gm of 4.75 μg day^{-1} and a gsd of 1.74. On the other hand, the urinary concentration distribution of BPA was obtained from external concentration distribution via the PBPK model. The estimated urinary concentration distribution of BPA for the male adult was 1.03 μg L^{-1} with a gsd of 1.48, whereas for the female adult, a gm of 1.21 μg L^{-1} with a gsd of 1.59 was obtained.

Table 1 Investigation of BPA concentrations from various sources

Source	BPA concentration				Reference
	Min	Max	Median	90th-tile	
Infant					
PC baby bottle (ng L^{-1})	38	4112	395.29	1436.29	Li et al. (2010)
Infant formula (μg L^{-1})	0.1	13.2	1.15	4.41	Biles et al. (1997)
Baby food (μg kg^{-1})	0	5	0.22	1.24	Miyamoto and Kotake (2006)
Toy (ng cm^{-2} min^{-1})	0	20.4	1.43	6.18	Sun et al. (2006)
Adult					
Bottled water (ng L^{-1})	17.6	285	70.8	152.5	Li et al. (2010)
Soft drinks (μg kg^{-1})			0.5	2.3	von Goetz et al. (2010)
Canned food (μg kg^{-1})	0.21	1.04	0.47	0.73	Xiao et al. (2007)
Meat (μg kg^{-1})	0.33	7.08	1.53	3.56	Shao et al. (2007a)
Fish (μg kg^{-1})	0.27	1.01	0.52	0.75	Shao et al. (2007a)
Vegetable (μg kg^{-1})	0.43	6.37	1.66	3.48	Ren and Jiang (2010)
Eggs (μg kg^{-1})	0.35	10.45	1.91	4.87	Shao et al. (2007b)
Cereals (μg kg^{-1})			3.5	11.0	von Goetz et al. (2010)
Microwave (μg kg^{-1})	5	19	9.75	14.08	Lim et al. (2009)
Air (ng m^{-3})	0	2.34	0.15	0.69	Fu and Kawamura (2010)

Table 2 Age- and body weight-specific daily intakes of infants and adults selected consumers

Consumer	Infant I	Infant II	Adult		Reference
			Male	Female	
Age (years)	0–0.5	0.5–1	>20	>20	Wang et al. (2010)
Body weight (kg)	6	9	66	58	
Formula amount per feeding (mL)	180–200	180–220			Meiji Dairies Corporation (2002)
Number of formula feeding (times day^{-1})	5	5			Meiji Dairies Corporation (2002)
Baby food (g day^{-1})		300			Assumed
Toy (mouthing time)[a]	41.7	73.9			Miyamoto and Kotake (2006)
Bottled water (L day^{-1})			2	2	Li et al. (2010)
Soft drinks (mL day^{-1})			29	29	Zhang et al. (2005)
Canned food (g day^{-1})[b]			5.5	5.5	Market investigation
Meat (g day^{-1})			54	59	Villegas et al. (2007) Zhang and Ho (2009)
Fish (g day^{-1})			39	45	Villegas et al. (2007) Zhang and Ho (2009)
Vegetable (g day^{-1})			342	348	Villegas et al. (2007) Zhang and Ho (2009)
Eggs (g day^{-1})			25	24	Villegas et al. (2007) Zhang and Ho (2009)
Cereals (g day^{-1})			361	269	Villegas et al. (2007) Zhang and Ho (2009)
Microwave (g day^{-1})			12.6	12.6	von Goetz et al. (2010)
Air (m^3 day^{-1})[c]	3.2	4.3	19.1	17.4	Travis (1987)

[a] The surface area of the toy is set as 10 cm^2

[b] From http://www.highbeam.com/doc/1G1-66101015.html

[c] Breath rate (m^3 day^{-1}) = 20 × (body weight (kg) / 70)$^{3/4}$

Dose-response assessment

The Hill model was used to optimally fit to the dose-response data of BPA (Table 3 and Fig. 5). The five health outcomes, namely immune response and uterotrophic assay from animal experiments as well as CVD, diabetes, and behavior change from epidemiological investigation were selected in dose-response profiles.

The median effective BPA concentration estimates (EC_{50}) were 811 (95 % CI 693–933) μg kg^{-1}, 408 (388–426) mg kg^{-1}, 15.00 (11.86–18.13) μg L^{-1}, 10.83 (10.51–11.16) μg L^{-1}, and 1.59 (1.21–1.97) μg L^{-1} for immune response, uterine increased weight, CVD, diabetes, and behavior change, respectively. The values of the Hill coefficient that ranged from 1.06 to 3.10 were chosen for positive cooperativity. In this study, the larger values of the Hill coefficient were found for the outcomes from epidemiological investigation (n = 2.29–3.10) than those for the outcomes from animal data (n = 1.06–1.43).

Risk estimates

The exceedance risk was calculated separately with or without skin absorption (Figs. 6 and 7, Table 4). Figure 6 shows the curves on exceedance risks that were depicted only from animal data without skin absorption, whereas Fig. 7 reveals the curves of exceedance risks that were drawn from epidemiological data with or without skin absorption. Table 4 lists the risk values of five health outcomes at exceedance probabilities of 0.2, 0.5, and 0.8, respectively, in Chinese population. Our findings suggested that BPA exposures were unlikely to pose significant risks for infants (0–1 year) and adults (male and female >20 years) with less than 10^{-6}-fold increase for uterus weight gain and immune response outcomes, respectively.

Moreover, results showed that approximate 10^{-4}–10^{-2}-fold increase was estimated for CVD, diabetes, and behavior change outcomes with and without skin absorptions at the exceedance risk probability of 0.5. On the other hand, no significant difference between the urinary concentration of

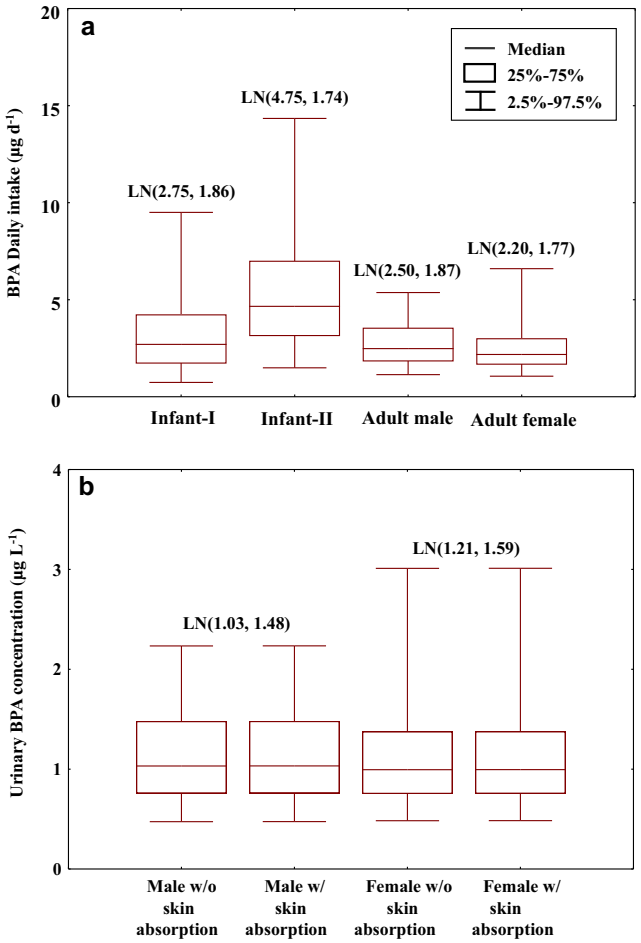

Fig. 4 Distributions of **a** BPA daily intake and **b** urinary BPA concentrations for Chinese subgroups

BPA with and without skin absorption at steady state was found (Supplementary Fig. S1).

Discussion

Exposure and dose-response modeling

The precise exposure estimation was the crucial step for accurate assessment of the risk. Until now, two approaches were often used to determine the daily BPA intake. The aggregated approach accounted for all possible exposure routes, but some exposure routes were still negligible. This approach may produce the derivation for correct risk assessment to compensate for the poor or incomplete exposure data. On the other hand, the backward approach was considered as a more precise estimation due to existing functional relationships between BPA ingestion and urinary excretion based on experimental data or the PBPK model.

However, we can hardly confirm each exposure pathway using the backward approach. The daily average BPA intake (ng kg^{-1} day^{-1}) for Chinese in this study was similar to the Swiss reported by von Goetz et al. (2010) (male 30.4 ng kg^{-1} day^{-1} and female 33.0 ng kg^{-1} day^{-1}). However, an obvious difference was found in Japanese (male and female 430 ng kg^{-1} day^{-1}) (Miyamoto and Kotake 2006), implicating the varieties in dietary habits among different countries. Dekant and Völkel (2008) concluded that the daily intake of BPA was considered below 6 μg per person (<0.1 μg kg^{-1} day^{-1}) in the majority of adult populations

Table 3 Summary of Hill-based fitting results to data in the animal studies for BPA in the low-dose exposure ranges

Species	Exposure	Response	Fitted parameters	Data source
Mice (adult)	Oral dose 0, 3, 30, 300, 3000 μg kg^{-1}	Immune response: anti-HEL IgG (1/1000 dilution)	$r^2 = 0.99$; $E_{max} = 0.62$-fold, $EC_{50} = 811$ (95 % CI 693–933) μg kg^{-1}, $n = 1.06$, baseline = 0.26 (dimensionless)	Yoshino et al. (2003)
Rat (neonatal)	Oral dose 0, 40, 160, 800 mg kg^{-1}	Reproduction: uterotrophic assay	$r^2 = 0.99$; $E_{max} = 0.72$-fold, $EC_{50} = 408$ (388–426) mg kg^{-1}, $n = 1.43$, baseline = 27.7 mg	Yamasaki et al. (2000)
Human (adult)	Urine 0.8, 2.23, 4.56, 11.06 μg L^{-1}	Cardiovascular disease: odds ratio of cardiovascular disease	$r^2 = 0.99$; $E_{max} = 6.16$-fold, $EC_{50} = 15.00$ (11.86–18.13) μg L^{-1}, $n = 2.67$, baseline OR = 1.0 (dimensionless)	Exposure: Melzer et al. (2010); effect: Lang et al. (2008)
Human (adult)	Urine 0.8, 2.23, 4.56, 11.06 μg L^{-1}	Diabetes: odds ratio of diabetes	$r^2 = 0.99$; $E_{max} = 3.66$-fold, $EC_{50} = 10.83$ (10.51–11.16) μg L^{-1}, $n = 3.10$, baseline OR = 1.0 (dimensionless)	Exposure: Melzer et al. (2010); effect: Lang et al. (2008)
Human (adult female)	Urine 0.8, 1.4, 2.1, 4.7 μg L^{-1}[a]	Behavior: BASC-2 score	$r^2 = 0.96$; $E_{max} = 0.19$-fold, $EC_{50} = 1.59$ (1.21–1.97) μg L^{-1}, $n = 2.29$, baseline = 42.2 (dimensionless)	Braun et al. (2009)

[a] Urinary BPA had been adjusted back to the original measurement with average adjusted factor of 1.0 adopted from Zhang et al. (2011) for the Chinese subgroup

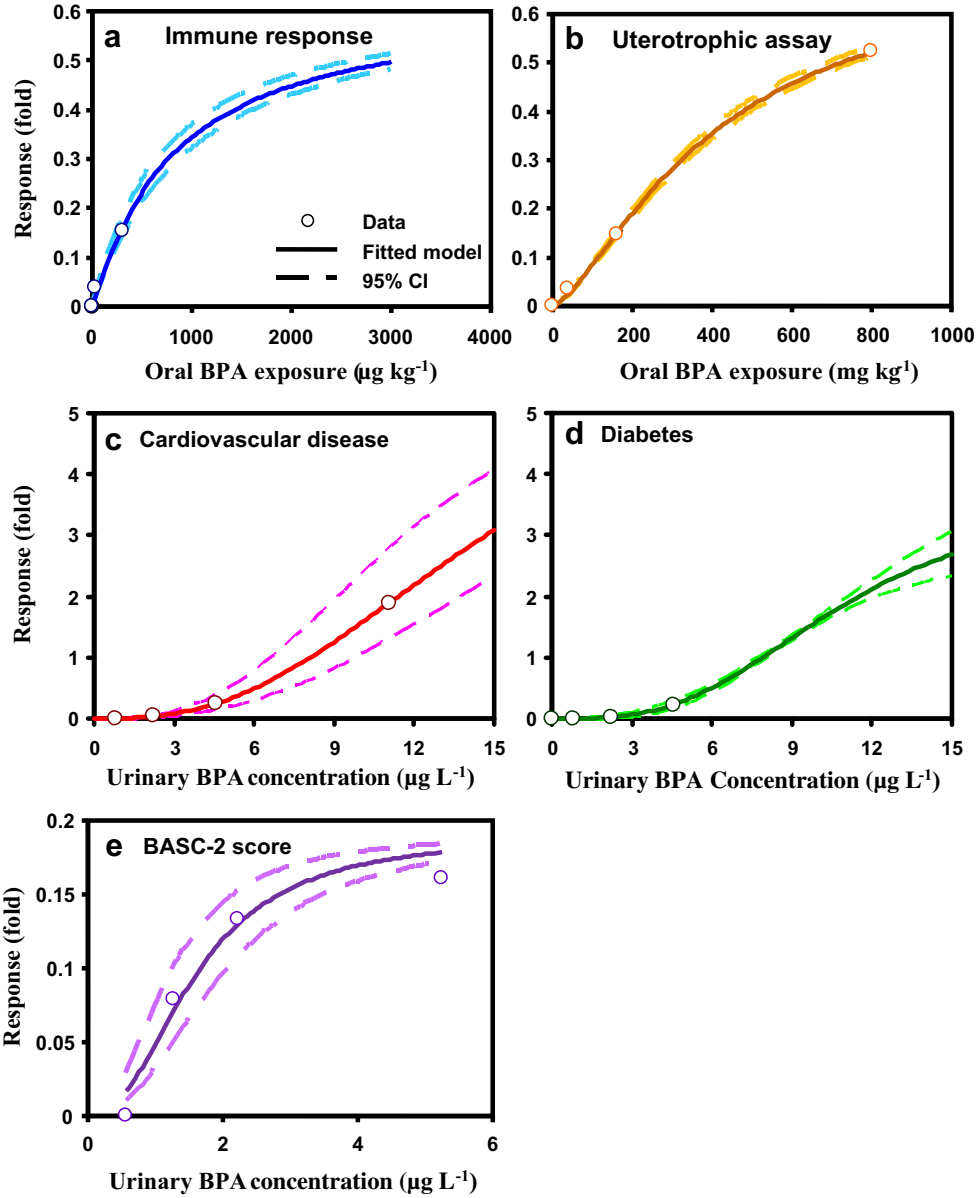

Fig. 5 Dose-response curves for BPA with five health outcomes from animal and epidemiological studies. **a** Mice immune response, **b** rat uterotrophic assay, **c** human cardiovascular disease, **d** human diabetes, and **e** human behavior (BASC-2 score)

using backward calculation. Meanwhile, the median daily intake of the overall population was nearly 34 ng kg^{-1} day^{-1} based on the backward calculation of the 2005–2006 NHANES urinary detection (Lakind and Naiman 2011).

Therefore, most of the data estimated by the forward (von Goetz et al. 2010) and backward approaches (Chen et al. 2016; Dekant and Völkel 2008; Lakind and Naiman 2011; Miyamoto and Kotake 2006) revealed similar daily intake compared with our estimated results (Table 5). On the other hand, the median adult male and female urinary BPA concentrations estimated by our proposed PBPK model are appropriate compared with the monitoring data from Zhang et al. (2005) for Chinese and Asians.

Meanwhile, the Hill model-based dose-response data along with fitted coefficients can be used to infer risk probability (Braun et al. 2009; Lang et al. 2008; Yamasaki et al. 2000; Yoshino et al. 2003). The lowest external dose or quartile urinary concentration that led to health effects was suggested as baselines. Moreover, we estimated Hill-based dose-response relationships for the total increased proportion of incidence of health outcome at certain BPA concentrations.

We showed that the fitted dose-response curves of five health outcomes had good coefficients of determination ($r^2 > 0.95$), revealing a significant association of the cumulative proportion of incidence of health outcomes with BPA concentration. The values of EC_{50} in urinary BPA concentration producing epidemiological responses ranged from 1.59 to

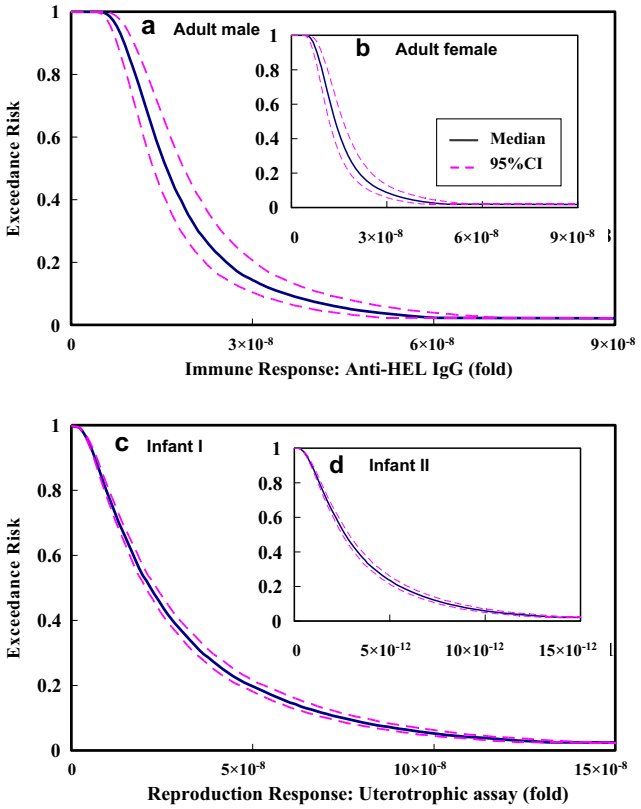

Fig. 6 Estimated exceedance risk curves with 95 % CI based on BPA daily intake. **a**, **b** Anti-hexanoyl-lys (HEL) IgG antibody elevated effect as immune response for adult male and female, respectively. **c**, **d** Uterine weight elevated effect as reproduction effect for infant I and infant II, respectively

15.02 μg L^{-1}. Besides, the value of EC_{50} in the external dose for increasing uterus weight was nearly 500-fold higher than that for inducing immune response.

BPA guideline and risk assessment

Miyamoto and Kotake (2006) indicated that Japanese aged 1–6 years had the highest BPA exposure with the highest exposure (95th percentile) of 3.9 and 4.1 μg kg^{-1} day^{-1} for males and females, respectively, approximate to TDI of 4 μg kg^{-1} day^{-1}. On the other hand, von Goetz et al. (2010) found that the highest BPA exposure occurred at the infant population with 1.7 μg kg^{-1} day^{-1} (aged 0.5–1 year), which occupied 42.5 % of TDI. In our study, the highest BPA exposure occurred at infant II subgroup (0.5–1 year) with the highest exposure of 1.4 μg kg^{-1} day^{-1}, which is similar to the value from von Goetz et al. (2010).

Braun et al. (2011) investigated 389 pregnant women, and the highest BPA was found to be 2.8 μg g^{-1} of creatinine-standardized urinary BPA concentration measured from cashiers, which was significantly higher than that from other occupations (1.2–2.1 μg g^{-1}). Therefore, skin absorption through contact with thermal printer paper may be a critical route in determining the internal BPA burdens. The cashiers had 1.47-fold higher urinary BPA concentration compared to the unemployed population with 1.9 μg g^{-1} urinary BPA concentration.

The conversion ratios for skin absorption into venous blood were estimated to be 0.006 % for female and male adults (Braun et al. 2011). From a skin absorption study, Biedermann et al. (2010) estimated the worst exposed case with a daily intake rate of 71 μg day^{-1}, whereas Marquet et al. (2011) estimated approximately 40 μg day^{-1}. They occupied approximately 12.5–25 % of the TDI under the above estimation. There are no increased adverse probabilities compared with the risk estimation without skin absorption. The risk curves shown in Figs. 5, 6, and 7 were the critical results for public policy.

Limitations and implications

The present model has some limitations related to the inherent problems of uncertainty, variability, and data gaps. Besides, the most relevant exposure sources that contributed to all the exposure routes of BPA were difficult, if not impossible, to obtain completely. As a result, the strength and robustness of the proposed constructed Hill models as well as the PBPK model could be greatly improved to predict health risk more precisely.

Some endpoints such as semen activity exhibiting a U-shape dose-response relationship may not be suitable for this model. The cause of this phenomenon may link to more complex mechanisms that are needed to be further investigated. However, our parsimonious model provided essential approaches in scientific risk evaluation and was flexible enough to integrate effects applicable at different environmental criteria.

There were several implications in our established model. First, the skin model simulated by realistic assumption via the PBPK model can help us to correctly estimate risk from skin absorption through the physiological process. Second, the dose-response profiles were selected from other health outcomes associated with BPA. They could be applied in the hazard-based toxicity studies to assess risks in particular aspects. Furthermore, our approach combining the Hill model and the PBPK model can serve as a theoretically based assessment than traditional hazard quotient models to achieve scientific evidence.

Meanwhile, some chemicals such as phthalate or dioxin also raised great concern on estrogenic effects. Their potential risk can also be evaluated by our approach in a similar manner. Our results showed that urinary BPA

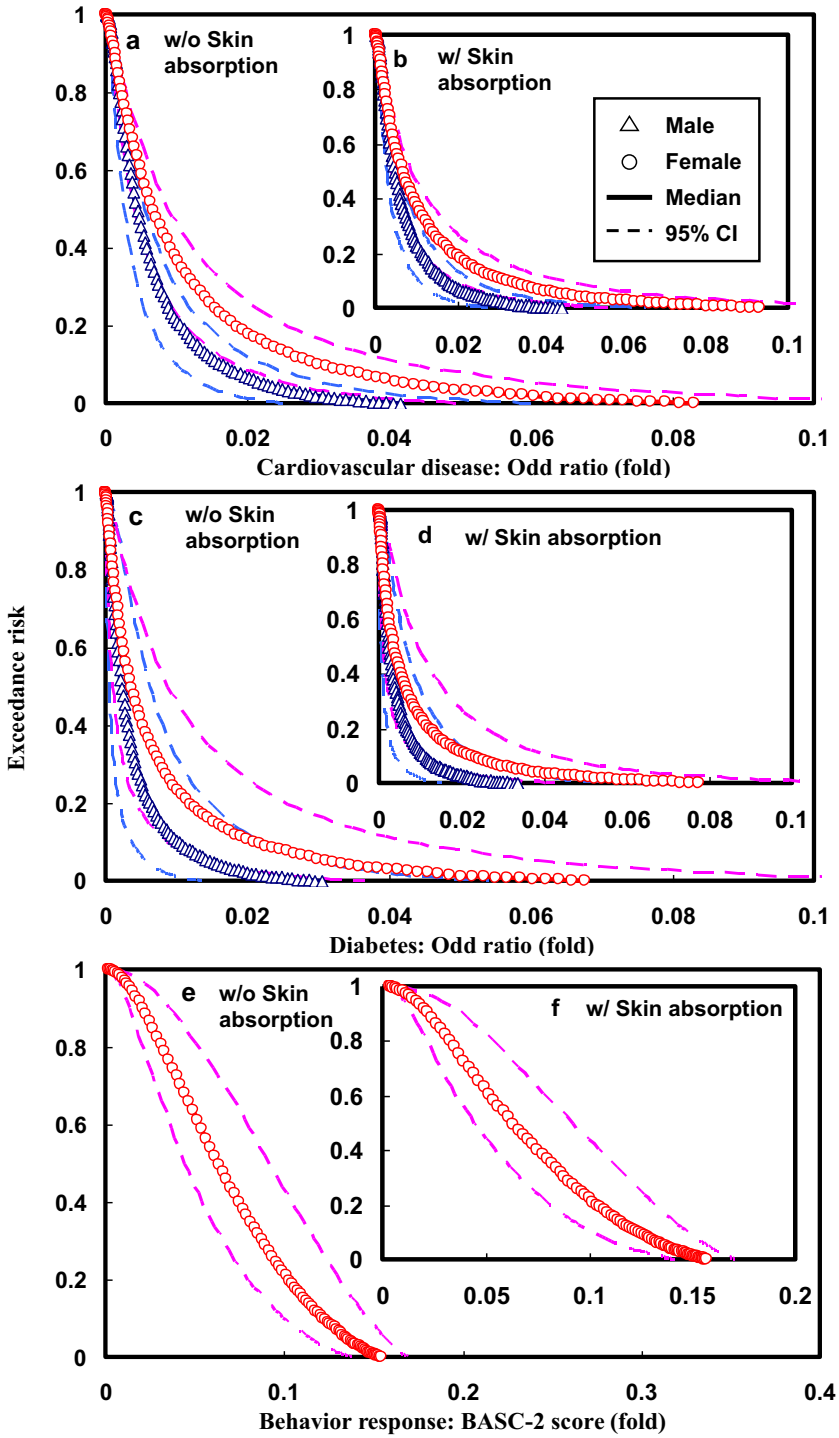

Fig. 7 Estimated exceedance risk curves with 95 % CI based on urinary BPA concentration. **a**, **c**, **e** BPA exposure without and **b**, **d**, **f** with skin absorption for adult male and adult female on cardiovascular disease, diabetes, and BASC-2 score elevated effects, respectively

estimates by the PBPK model can be validated by comparing with recently published biomonitoring studies, indicating that a well-established model and key parameters can depict a real-world setting in BPA estimation. In our model, skin absorption can be easily involved in our PBPK model and results show insignificant contribution to BPA body burden compared with that from oral dose administration.

Conclusions

We developed an age- and gender-specific PBPK model either with skin absorption being considered that allows the assessment of environmental BPA exposure in a Chinese population based on five health responses, namely immune response, uterotrophic assay, CVD, diabetes, and behavior change. We reconstructed the Hill-based dose-response relationships

Table 4 Estimated BPA-associated responses in fold increase compared with control

	Exceedance risk		
	0.8	0.5	0.2
Without skin absorption			
Immune response (male/female)	1.06 (0.92–1.26)[a] × 10^{-8}	1.58 (1.36–1.87) × 10^{-8}	2.57 (2.22–3.04) × 10^{-8}
	1.10 (0.95–1.30) × 10^{-8}	1.58 (1.36–1.87) × 10^{-8}	2.44 (2.11–2.89) × 10^{-8}
Uterus weight increase (infant I/infant II)	0.97 (0.91–1.04) × 10^{-12}	2.18 (2.05–2.35) × 10^{-12}	4.94 (4.65–5.31) × 10^{-12}
	1.31 (1.23–1.41) × 10^{-12}	2.67 (2.51–2.87) × 10^{-12}	5.54 (5.21–5.96) × 10^{-12}
Cardiovascular disease (male/female)	1.85 (1.12–2.24) × 10^{-3}	4.41 (2.65–5.60) × 10^{-3}	1.05 (0.63–1.40) × 10^{-2}
	2.26 (1.36–2.76) × 10^{-3}	6.78 (4.08–8.83) × 10^{-3}	1.77 (1.07–2.44) × 10^{-2}
Diabetes (male/female)	0.83 (0.16–2.73) × 10^{-3}	2.25 (0.56–6.28) × 10^{-3}	0.62 (0.19–1.44) × 10^{-2}
	1.04 (0.22–3.31) × 10^{-3}	3.72 (1.03–9.50) × 10^{-3}	1.13 (0.41–2.39) × 10^{-2}
BASC-2 (female)[b]	3.10 (2.03–5.07) × 10^{-2}	6.33 (4.45–9.17) × 10^{-2}	1.01 (0.78–1.29) × 10^{-1}
With skin absorption			
Cardiovascular disease (male/female)	1.82 (1.09–2.19) × 10^{-3}	4.58 (2.76–5.84) × 10^{-3}	1.12 (0.67–1.50) × 10^{-2}
	2.44 (1.47–2.99) × 10^{-4}	6.83 (4.11–8.90) × 10^{-3}	1.90 (1.14–2.63) × 10^{-2}
Diabetes (male/female)	0.81 (0.16–2.68) × 10^{-3}	2.36 (0.59–6.52) × 10^{-3}	0.67 (0.21–1.54) × 10^{-2}
	1.14 (0.24–3.56) × 10^{-3}	3.75 (1.04–9.56) × 10^{-3}	1.23 (0.45–2.56) × 10^{-2}
BASC-2 (female)[b]	3.27 (2.15–5.32) × 10^{-2}	6.35 (4.47–9.20) × 10^{-2}	1.04 (0.81–1.32) × 10^{-1}

[a] Median (95 % CI)

[b] Indicated as pregnant female

calibrated with animal and epidemiological data. We found that (*i*) BPA exposures were less likely to pose a significant risk for infants (0–1 year) and adults (male and female >20 years) with less than 10^{-6}-fold increase in uterus weight gain and immune response outcomes, respectively, and (*ii*) the adverse health risks show no significant influence (<10^{-6}-fold

Table 5 Comparison of the average daily BPA intake per body weight and median urinary BPA concentration among this study and other published data

Population	Infant I	Infant II	Adult		Reference
	0–0.5 year	0.5–1 year	Male	Female	
Average daily BPA intake per body weight (ng kg^{-1} day^{-1})					
Chinese	555[a]	615[a]	46.2[a]	44.7[a]	This study
Japanese	55	180	430, 28–49[b]	430, 34–59[b]	Miyamoto and Kotake (2006)
Swiss	143.4	792.1	30.4	33.0	von Goetz et al. (2010)
Nonspecific			<100[b]		Dekant and Völkel (2008)
American			34[b]		Lakind and Naiman (2011)
Median urinary BPA concentration (ng mL^{-1})					
Chinese	NA	NA	1.03[c]	1.00[c]	This study
Chinese	NA	NA	1.40	1.00	Zhang et al. (2011)
Asian	NA	NA	1.27	1.13	Zhang et al. (2011)

NA not available

[a] Calculated by dividing the subpopulation-specific body weight

[b] Calculated by backward estimation from urinary BPA concentration

[c] Calculated by the PBPK model with BPA metabolic ratio of 0.9995 based on Krishnan et al. (2010)

increase) on uterus weight gain and immune response. We conclude that our approach provides a powerful tool for tracking and managing human long-term BPA susceptibility in relation to multiple exposure pathways, and for informing the public of the magnitude of environmental BPA pollution impacts on human health. Most importantly, effective monitoring of environmental BPA pollution sources is urgently needed to guide management strategies into the future.

Acknowledgments This work was supported by the National Science Council of Republic of China under Grant NSC 100-2313-B-002-012-MY3.

Compliance with ethical standards The article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Biedermann S, Tschudin P, Grob K (2010) Transfer of bisphenol A from thermal printer paper to the skin. Anal Bioanal Chem 398:571–576

Biles JE, McNeal TP, Begley TH (1997) Determination of bisphenol A migrating from epoxy can coatings to infant formula liquid concentrates. J Agric Food Chem 45:4697–4700

Bois FY, Jamei M, Clewell HJ (2010) PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology 278:256–267

Braun JM, Kalkbrenner AE, Calafat AM, Bernert JT, Ye X, Silva MJ (2011) Variability and predictors of urinary bisphenol A concentrations during pregnancy. Environ Health Perspect 119:131–137

Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, Venners SA (2014) Early-life bisphenol A exposure and child body mass index: a prospective cohort study. Environ Health Perspect 122:1239–1245

Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM (2009) Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect 117:1945–1952

Brenn-Struckhofova Z, Cichna-Markl M (2006) Determination of bisphenol A in wine by sol-gel immunoaffinity chromatography, HPLC and fluorescence detection. Food Addit Contam Part A-Chem 23:1227–1235

Centers for Disease Control and Prevention (CDC) (2013) Biomonitoring summary: bisphenol A. Available at: http://www.cdc.gov/biomonitoring/BisphenolA_ BiomonitoringSummary.html. Accessed May 2016

Chen WY, Shen YP, Chen SC (2016) Assessing bisphenol A (BPA) exposure risk from long-term dietary intakes in Taiwan. Sci Total Environ 543:140–146

Cho CY, Shin BS, Jung JH, Kim DH, Lee KC, Han SY (2002) Pharmacokinetic scaling of bisphenol A by species-invariant time methods. Xenobiotica 32:925–934

Dekant W, Völkel W (2008) Human exposure to bisphenol A by biomonitoring: methods, results and assessment of environmental exposures. Toxicol Appl Pharmacol 28:114–134

Duffy E, Hearty AP, Flynn A, McCarthy S, Gibney MJ (2006) Estimation of exposure to food-packaging materials. 2: Patterns of intakes of packaged foods in Irish children aged 5–12 years. Food Addit Contam Part A-Chem 23:715–725

European Food Safety Authority (EFSA) Factsheets: EFSA explains the safety of bisphenol A. Available at: http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/factsheetbpa150121.pdf. Accessed May 2016

Fu P, Kawamura K (2010) Ubiquity of bisphenol A in the atmosphere. Environ Pollut 158:3138–3143

Gajewska M, Worth A, Urani C, Briesen H, Schramm KW (2014) Application of physiologically-based toxicokinetic modelling in oral-to-dermal extrapolation of threshold doses of cosmetic ingredients. Toxicol Lett 227:189–202

Kaddar N, Harthe C, Déchaud H, Mappus E, Pugeat M (2008) Cutaneous penetration of bisphenol A in pig skin. J Toxicol Env Health Part A 71:471–473

Krishnan K, Gagné M, Nong A, Aylward LL, Hays SM (2010) Biomonitoring equivalents for bisphenol A (BPA). Regul Toxicol Pharmacol 58:18–24

Kubwabo C, Kosarac I, Stewart B, Gauthier BR, Lalonde K, Lalonde PJ (2009) Migration of bisphenol A from plastic baby bottles, baby bottle liners and reusable polycarbonate drinking bottles. Food Addit Contam Part A-Chem 26:928–937

Kundakovic M, Champagne FA (2011) Epigenetic perspective on the developmental effects of bisphenol A. Brain Behav Immun 25:1084–1093

Lacroix MZ, Puel S, Collet SH, Corbel T, Picard-Hagen N, Toutain PL (2011) Simultaneous quantification of bisphenol A and its glucuronide metabolite (BPA-G) in plasma and urine: applicability to toxicokinetic investigations. Talanta 85:2053–2059

Lakind JS, Naiman DQ (2011) Daily intake of bisphenol A and potential sources of exposure: 2005–2006 National Health and Nutrition Examination Survey. J Expo Sci Environ Epidemiol 1:272–279

Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB (2008) Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA-J Am Med Assoc 300:1303–1310

Li DK, Zhou Z, Miao M, He Y, Wang J, Ferber J (2011) Urine bisphenol-A (BPA) level in relation to semen quality. Fertil Steril 5:625–630

Li X, Ying GG, Su HC, Yang XB, Wang L (2010) Simultaneous determination and assessment of 4-nonylphenol, bisphenol A and triclosan in tap water, bottled water and baby bottles. Environ Int 36:557–562

Lim DS, Kwack SJ, Kim KB, Kim HS, Lee BM (2009) Potential risk of bisphenol A migration from polycarbonate containers after heating, boiling, and microwaving. J Toxicol Environ Health Part A 72:1285–1291

Maragou NC, Makri A, Lampi EN, Thomaidis NS, Koupparis MA (2007) Migration of bisphenol A from polycarbonate baby bottles under real use conditions. Food Addit Contam Part A-Chem 25:373–383

Marquet F, Payan JP, Beydon D, Wathier L, Grandclaude MC, Ferrari E (2011) In vivo and ex vivo percutaneous absorption of [(14) C]-bisphenol A in rats: a possible extrapolation to human absorption? Arch Toxicol 85:1035–1043

Meiji Dairies Corporation (2002) Oishi Milk No Tsukurikata: best way to prepare powdered formula. Available at: http://www.meiji-hohoemi.com/info/catalog/ makemilk.html. Accessed Jan 2016

Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS (2010) Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. PLoS One 5, e8673

Miao M, Yuan W, Zhu G, He X, Li DK (2011) In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod Toxicol 32:64–68

Michałowicz J, Mokra K, Bąk A (2015) Bisphenol A and its analogs induce morphological and biochemical alterations in human peripheral blood mononuclear cells (in vitro study). Toxicol In Vitro 29: 1464–1472

Mielke H, Gundert-Remy U (2012) Physiologically based toxicokinetic modelling as a tool to support risk assessment: three case studies. Toxicol Lett 204:190–198

Mielke H, Partosch F, Gundert-Remy U (2011) The contribution of dermal exposure to the internal exposure of bisphenol A in man. Toxicol Lett 204:190–198

Mileva G, Baker SL, Konkle AT, Bielajew C (2014) Bisphenol-A: epigenetic reprogramming and effects on reproduction and behavior. Int J Environ Res Public Health 11:7537–7561

Miyamoto K, Kotake M (2006) Estimation of daily bisphenol A intake of Japanese individuals with emphasis on uncertainty and variability. Environ Sci 13:15–29

Naciff JM, Khambatta ZS, Reichling TD, Carr GJ, Tiesman JP, Singleton DW (2010) The genomic response of Ishikawa cells to bisphenol A exposure is dose- and time-dependent. Toxicology 270:137–149

Noonan GO, Ackerman LK, Begley TH (2011) Concentration of bisphenol A in highly consumed canned foods on the U.S. market. J Agric Food Chem 59:7178–7185

Ren J, Jiang SJ (2010) An investigation on pollution situation of 4-nonylphenol and bisphenol A in some vegetable products in Haikou city. Modern Prev Med 37:451–455

Rocha BA, Azevedo LF, Gallimberti M, Campiglia AD, Barbosa F Jr (2015) High levels of bisphenol A and bisphenol S in Brazilian thermal paper receipts and estimation of daily exposure. J Toxicol Environ Health A 78:1181–1188

Shao B, Han H, Li DM, Ma YL, Tu XM, Wu YG (2007a) Analysis of alkylphenol and bisphenol A in meat by accelerated solvent extraction and liquid chromatography with tandem mass spectrometry. Food Chem 105:1236–1241

Shao B, Han H, Tu X, Huang L (2007b) Analysis of alkylphenol and bisphenol A in eggs and milk by matrix solid phase dispersion extraction and liquid chromatography with tandem mass spectrometry. J Chromatogr B 850:412–416

Shin BS, Hwang SW, Bulitta JB, Lee JB, Yang SD, Park JS (2010) Assessment of bisphenol A exposure in Korean pregnant women by physiologically based pharmacokinetic modeling. J Toxicol Env Health Part A 73:1586–1598

Shin BS, Kim CH, Jun YS, Kim DH, Lee BM, Yoon CH (2004) Physiologically based pharmacokinetics of bisphenol A. J Toxicol Env Health Part A 67:1971–1985

Stahlhut RW, Welshons WV, Swan SH (2009) Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. Environ Health Perspect 117:784–789

Sun CY, Zhang KR, Cheng XY, Zheng B (2006) Study on the migration behavior of seven estrogens in plastic toys through simulated sweat and saliva. Chinese J Health Lab Technol 16:32–34

Sun Y, Irie M, Kishikawa N, Wada M, Kuroda N, Nakashima K (2004) Determination of bisphenol A in human breast milk by HPLC with column-switching and fluoresence detection. Biomed Chromatogr 18:501–507

Travis C (1987) Interspecies and dose-route extrapolations. Pharmacokinetics in risk assessment. Drinking water and health. National Academy Press, Washington, pp 208–220

United States Environmental Protection Agency (USEPA) (1998) Guidelines for ecological risk assessment. USEPA, Washington

Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV (2007) Human exposure to bisphenol A (BPA). Reprod Toxicol 24:139–177

Villegas R, Yang G, Liu D, Xiang YB, Cai H, Zheng W (2007) Validity and reproducibility of the food-frequency questionnaire used in the Shanghai men's health study. Br J Nutr 97:993–1000

von Goetz N, Wormuth M, Scheringer M, Hungerbühler K (2010) Bisphenol A: how the most relevant exposure sources contribute to total consumer exposure. Risk Anal 30:473–487

Wang C, Hou XH, Zhang ML, Bao YQ, Zou YH, Zhong WH (2010) Comparison of body mass index with body fat percentage in the evaluation of obesity in Chinese. Biomed Environ Sci 23:173–179

Welshons WV, Nagel SC, Vom Saal FS (2006) Large effects from small exposures, III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology 147: S56–S69

Xiao J, Shao B, Wu YN, Wang ZT, Hou W (2007) Determination of bisphenol A and alkyl phenols in canned food with high performance liquid chromatography-fluorescence. Zhonghua Yu Fang Yi Xue Za Zhi 1:449–52

Yamasaki K, Sawaki M, Takatsuki M (2000) Immature rat uterotrophic assay of bisphenol A. Environ Health Perspect 108:1147–1150

Yoshino S, Yamaki K, Yanagisawa R, Takano H, Hayashi H, Mori Y (2003) Effects of bisphenol A on antigen-specific antibody production, proliferative responses of lymphoid cells, and TH1 and TH2 immune responses in mice. Br J Pharmacol 138:1271–1276

Zhang CX, Ho SC (2009) Validity and reproducibility of a food frequency questionnaire among Chinese women in Guangdong province. Asia Pac J Clin Nutr 18:240–250

Zhang M, Binns CW, Lee AH (2005) A quantitative food frequency questionnaire for women in southeast China: development and reproducibility. Asia-Pac J Public Health 17:29–35

Zhang Z, Alomirah H, Cho HS, Li YF, Liao C, Minh TB (2011) Urinary bisphenol A concentrations and their implications for human exposure in several Asian countries. Environ Sci Technol 45:7044–7050

Zimmerman-Downs JM, Shuman D, Stull SC, Ratzlaff RE (2010) Bisphenol A blood and saliva levels prior to and after dental sealant placement in adults. Int J Dent Hyg 84:145–150