

REVIEW

Bisphenol A exposure pathways in early childhood: Reviewing the need for improved risk assessment models

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Bisphenol A (BPA) is a plasticiser found in a number of household plastics, electronics, and food-packaging materials. Over the past 5 years, several human epidemiological studies have reported a positive association between BPA exposure and adverse health outcomes in children, including obesity, asthma, preterm birth, and neuro-behavioural disturbances. These findings are in conflict with international environmental risk assessment models, which predict daily exposure levels to BPA should not pose a risk to child health. The aim of this review is to provide an overview of the evidence for different exposure sources and potential exposure pathways of BPA in early childhood. By collating the findings from experimental models and exposure associations observed in human bio-monitoring studies, we affirm the potential for non-dietary sources to make a substantial contribution to total daily exposure in young children. Infants and toddlers have distinctive exposure sources, physiology, and metabolism of endocrine-disrupting chemicals. We recommend risk-assessment models implement new frameworks, which specifically address exposure and hazard in early childhood. This is particularly important for BPA, which is present in numerous products in the home and day-care environments, and for which animal studies report contradictory findings on its safety at environmentally relevant levels of exposure.

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INTRODUCTION

Bisphenol A (BPA) is a high-production chemical commonly found in polycarbonate plastics and in epoxy resins to line the inside of food cans. Although BPA in infant feeding bottles has been either banned or voluntarily phased out in some countries, it is still used as a monomer in a number of polycarbonate plastics designed for use by infants and young children. These include children's toys, feeding utensils, pacifiers, and teething rings.^{1–3} BPA is also used in numerous other household plastics and electronics, such as food storage containers, chopping boards, cooking utensils, plastic food wrap, mobile phones, computers, sunglasses, CDs, DVDs, electrical and electronic equipment, automobiles, sports equipment and bicycle helmets, dental composites and sealants, and is widely used as an additive in thermal print paper for receipts, magazines, and books.^{4,5}

Over the past two decades, numerous lines of evidence have demonstrated that BPA is an endocrine-disrupting chemical with the capacity to disrupt a variety of hormonal signalling pathways. Animal studies indicate a positive dose–response relationship between post-natal early life exposure to BPA and excess adiposity.^{6,7} BPA exposure in pregnant mice has been observed to increase abnormal inflammatory processes and the risk of development of atopic asthma in offspring.⁸ Prenatal exposure in rodents has also been associated with altered behavioural activities and sexual dimorphism.⁹ Human and animal *in vitro* studies have further demonstrated that BPA has the capacity to alter thyroid functioning, promote insulin resistance, and trigger

immune dysfunction at the cellular level.^{6,10} However, conflicting results showing no effect have been reported in some toxicology studies¹¹ and there remains considerable uncertainty on how the findings from experimental models relate to health outcomes and onset of disease in human populations.

International biomonitoring studies confirm that >90% of children in the United States, Europe, Asia, and Australia are exposed to BPA.^{12–19} On a global scale, urinary BPA concentrations are frequently observed to be higher in young children than those reported in the general population from the same or similar geographical locations (Figure 1), raising concern as to the potential health effects of exposure during critical windows of early childhood development.^{20,21} A major limitation in the interpretation of human biomonitoring studies is that long-term exposure patterns to BPA is difficult to assess, in part due to the high within-day and between-day temporal variability in urinary BPA concentration observed in adults.^{22–24} Exposure assessment based on spot urine sampling may be less prone to exposure misclassification in preschool children, with a recent study of 2- to 5-year-old children in Australia reporting an interclass correlation coefficient of 0.51 for short-term variability in urinary BPA concentration across a 48-h period,²⁵ although further assessment of urinary BPA variability in infants and toddlers over longer periods of time and during developmental milestones is warranted.

The tolerable daily intake, or reference dose, is determined by governmental regulatory agencies by risk-assessment modelling.

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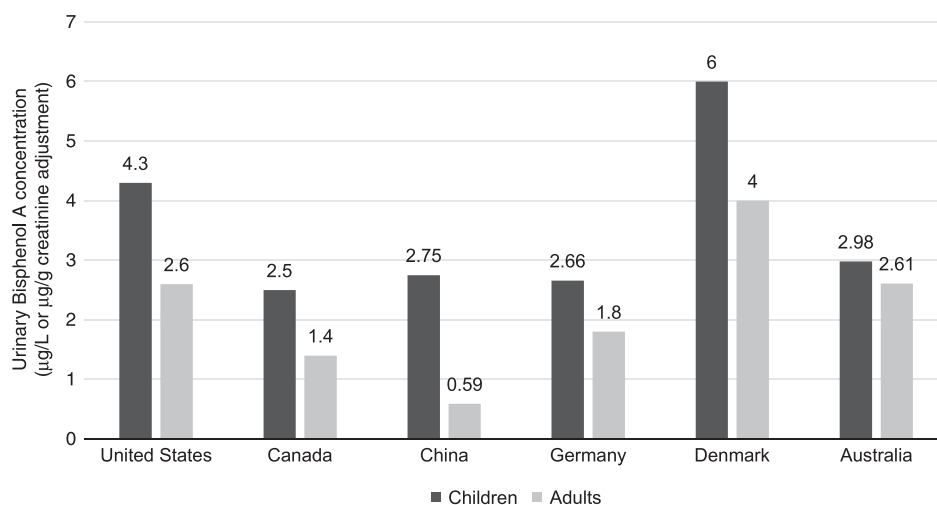


Figure 1. Comparison of urinary bisphenol A concentrations between children and the general population by country.^{12–19}

The reference dose represents a recommended daily limit of exposure for the human population, and in the case of BPA was built on the assumption that the predominant exposure pathway in humans is through the ingestion of contaminated dietary sources, followed by gastrointestinal (GI) absorption in the small intestine.²⁶ As non-dietary sources of exposure are presumed under these models to make only a minor or negligible contribution to total daily exposure, their potential contribution is generally excluded from BPA risk characterisation. As a result, the leaching of BPA from food-packaging materials and daily estimates of consumption of contaminated foods have been well studied;^{27,28} however, there are fewer studies assessing the potential for BPA exposure from non-dietary exposure sources. This is despite only 5% of the annual production of BPA in the United States being used in the manufacturing of food contact materials.²⁹

Within a child's daily living environment, there are numerous consumer products which contain BPA. The degradation of these consumer products under normal conditions of use eventually leads to BPA being released into dust, air, and contact surfaces within the home and day-care environments.³⁰ It is therefore plausible that multiple exposure sources, pathways, and especially exposure routes (Figure 2) contribute to the total internal concentration of young children to BPA. Exposure route is an important consideration in BPA risk assessment, as different exposure routes may influence the bioavailability of free BPA in the systemic circulation. In mammals, BPA absorbed through the GI system is subject to first-pass metabolism in the liver, predominately via the UDP-glucuronosyltransferase family of enzymes.^{31,32} Conjugated BPA is more water soluble than free BPA and this helps facilitate renal elimination.

The presence of unconjugated and conjugated BPA in the systemic circulation has been the topic of much debate with regards to BPA's potential to elicit biological activity and endocrine disruptive effects.³³ As the predominant exposure pathway in humans is assumed to be via GI absorption, it has been argued that the presence of unconjugated BPA in human serum most likely represents external sample contamination or sample degradation during storage and laboratory analysis.³⁴ However, many research groups and laboratories have gone to considerable efforts to minimise the risk of sample contamination and have developed sensitive and accurate methods by which to test for and quantify unconjugated serum BPA concentration.³³

Free BPA, which is absorbed through alternative exposure routes, such as the skin, oral mucosa, or respiratory epithelium, represent another possible explanation for the presence of

unconjugated BPA being detectable in the systemic circulation. BPA absorption through the skin, oral mucosa, and respiratory epithelium would be expected to bypass first-pass metabolism in the liver (Figure 2) and would thus lead to unconjugated BPA being present in the systemic circulation for more prolonged periods than is observed with GI absorption.^{4,35,36} Dermal, sublingual, and inhalational exposures to BPA would therefore be expected to result in increased potential for unconjugated BPA to reach target organs and elicit deleterious biological and endocrine disruptive effects. This is a particularly important consideration in infants and toddlers, who continue to undergo rapid growth and development after birth and throughout the early childhood years.

The aim of this review is to provide an overview of the relevant exposure pathways for BPA in early childhood, specifically in infants and toddlers, with an emphasis on how and why these may differ to the general population. We undertook a scoping literature search of over 8000 peer-reviewed articles from Pubmed and Embase, which allowed us to collate the available evidence from animal and human experimental models, as well as associations seen in BPA exposure patterns from human biomonitoring and longitudinal cohort studies. We discuss the significance of excluding relevant exposure pathways from risk-assessment modelling of human exposure to BPA. We also consider the importance of designing and implementing risk-assessment frameworks specific for exposure to young children, as at the present time risk estimates for early childhood are largely based on either extrapolation from animal studies or modelled on human adult studies of exposure.

DIVERSE SOURCES OF EXPOSURE BY INGESTION AND ABSORPTION VIA THE GI TRACT

Dietary Exposure Sources

Although much of this review focuses on non-dietary exposure sources in early childhood, it is worth noting that dietary exposure remains a major concern in infants and toddlers, who have a significantly higher dietary intake for their body weight than the general population.³⁷ In the first 4–6 months after birth, neonates rely solely on either infant formula or breast milk — or a combination of the two — as their primary nutritional source. Significant contamination of this primary source therefore has the potential to magnify daily exposure concentrations.

Although BPA has been banned from use in infant feeding bottles in some countries, there are still no regulations on its use

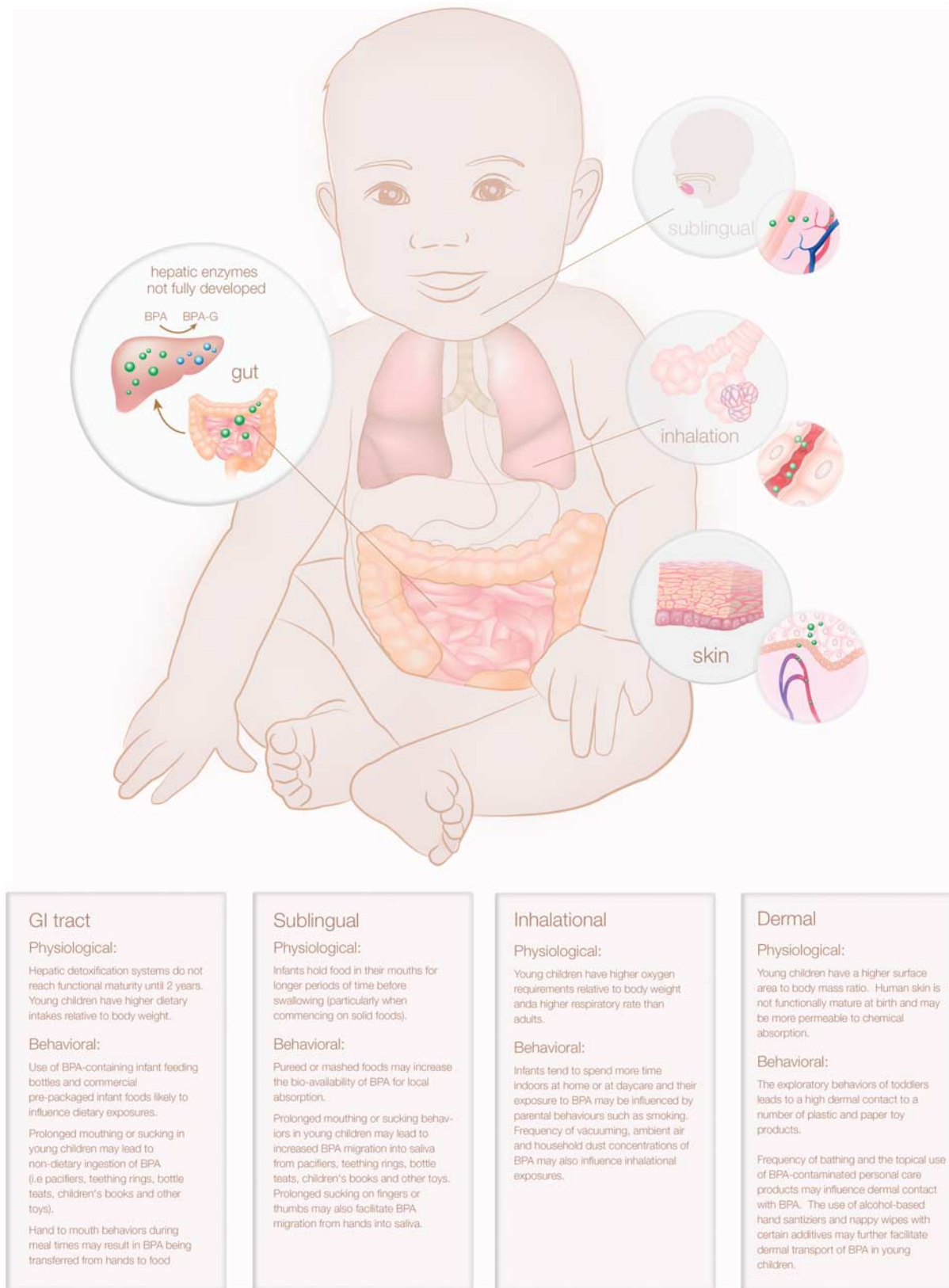


Figure 2. Physiological and behavioural differences, and how they may influence potential exposure routes for bisphenol A absorption in young children.

Table 1. BPA concentrations (ng/ml) reported in studies of human breast milk.

Author	Year	Country	Method	Sample size	Total BPA concentrations (ng/ml)	Free BPA concentrations (ng/ml)
Kuruto-Niwa et al. ⁵⁶	2007	Japan	ELISA	101	3.41 ± 0.13 (Mean ± SD)	—
Sun et al. ⁶⁰	2004	Japan	HPLC	23	—	0.61 ± 0.2 (Mean ± SD)
Ye et al. ⁵⁷	2006	United States	HPLC	20	1.9 (Median)	1.3 (Median)
Yi et al. ⁵⁹	2010	Korea	HPLC	100	10.4 (Median)	6.6 (Median)
Mendonca et al. ⁵⁸	2012	United States	HPLC	23	2.1 ± 4.9 (Mean ± SD)	1.7 ± 5.2 (Mean ± SD)
Zimmers et al. ⁶¹	2014	United States	LC/MS/MS	21	—	0.68 (Median) 3.13 (Mean)
Cao et al. ⁶²	2015	Canada	GC/MS/MS	278	0.11 ng/g (Median)	0.1 ng/g (Median)

in a number of developed and developing countries. Residual BPA monomers in polycarbonate plastics are generally reported in the range of 1–140 mg/kg, although higher concentrations of up to the maximum recommended migration level set by the European Food Safety Authority (EFSA) of 600 mg/kg have occasionally been reported.³⁸ The interpretation of the laboratory-based migration studies should take into consideration that experimental use of ultrapure water or 10% ethanol as a simulant of food sources may underestimate actual BPA migration in real-world scenarios, as micronutrients and enzymes contained within breast milk and infant formula may facilitate increased release of BPA from polycarbonate than is observed in laboratory-based studies.

Practices such as repeated steam sterilizing, microwaving, dishwasher cleaning, or leaving the bottle in direct sunlight will accelerate the rate of degradation of polymer links within polycarbonate plastic and will facilitate BPA leaching from infant feeding bottles into the food source contained within.^{39–47} Labelling polycarbonate bottles or containers as microwave or dishwasher ‘safe’ does not translate into reduced migration of BPA into foods, as these products have been observed to still leach considerable quantities of BPA during repeated use in the microwave or dishwasher, regardless of the product labelling.^{40,47} The re-use of plastic bottles or containers across successive siblings may result in the release of increasing levels of BPA as the product ages, in particular if the plastic shows visible signs of wear.⁴⁸

BPA exposure in neonates is not limited to the use of polycarbonate feeding bottles, as samples of canned and powdered infant formulas in the United States and Canada have been observed to be contaminated with variable concentrations of BPA, ranging up to 113 ng/g.^{49–51} Longer storage of liquid formula at room temperature has been observed to increase BPA migration over a 10-month period in some samples.⁴⁹ In general, BPA concentrations in the United States in canned liquid formula range between 0.48 and 11 ng/g, and in powdered formula BPA concentrations range from not-detectable to 0.4 ng/g.⁵¹ However, a recent study of liquid and powdered infant formulas in Italy observed higher BPA concentrations, ranging between not-detectable and 169 ng/g per dry weight, with a median of 8 ng/g.⁵² In this study, BPA concentrations were not significantly different between powdered and liquid formula preparations.

The practice in the home for reconstitution of powdered infant formulas must also be considered, in part owing to the use of BPA-containing resin coatings of several domestic water supply pipes and storage tanks,⁵³ as well as the use of bottled water to prepare powdered formula in some regions of the world.⁵⁴ Indeed, a recent Chinese study estimated that drinking tap water from a polycarbonate baby bottle heated to 40 °C would result in an average intake in Chinese infants of 1340 ng/day of BPA,⁵⁵ suggesting that the water supply may be a more relevant exposure source to BPA in infants receiving powdered formula as their primary nutritional source rather than the powder itself.

BPA can also partition into human breast milk, and both unconjugated and conjugated BPA have been detected in

samples of human breast milk at varying concentrations (Table 1).^{56–62} Studies of BPA in human breast milk suggest that unconjugated BPA makes up 50% or more of the total detectable BPA in human breast milk samples, although it is difficult to establish to what degree the presence of unconjugated BPA in breast milk samples may have been due to external contamination from sample storage and processing. The largest of these studies, performed in 278 Canadian women, is the only study to have compared exposure estimates from samples of human breast milk with samples of infant formula processed in the same laboratory and using the same analytical techniques.⁶² The authors reported that for Canadian breast-fed infants, daily dietary exposure to BPA is likely to be somewhat lower compared with infants receiving infant formula.⁴⁹ For most other regions of the world, small sample sizes and differences in laboratory analyses limit the ability to make direct comparisons in dietary exposure based on whether infants receive breast milk or infant formula as their primary nutritional source.

A recent Korean study observed significantly higher serum BPA concentrations in infants who were primarily fed with a plastic feeding bottle, compared with children who directly fed from the breast (mean of 96.6 vs 45.5 pg/ml respectively).⁶³ The higher serum BPA concentrations observed in bottle-fed infants were regardless of whether the child received breast milk or infant formula through the bottle, implying that mode of feeding may be an important predictor of exposure than the actual food source in some regions of the world. We could find only one study that has investigated neonatal exposure from human breast milk using paired samples of breast milk and infant urine.⁵⁸ In this study, Mendonca et al.⁵⁸ reported no correlation between BPA concentrations in breast milk and BPA concentrations in infant urine, although the timing of urine collection to that of maternal breast milk was somewhat unclear and the small sample size means the study may have been underpowered to detect a difference. Whether maternal dietary intake of BPA in lactating mothers is a significant predictor of neonatal exposure remains unclear but from a public health perspective is worth further investigation.

Exposure assessments for older infants and toddlers need additional consideration of the wide variety of dietary sources that young children may consume following the introduction of solid foods. Commercial infant and toddler foods come in a range of food-packaging materials that may contain BPA, such as glass jars with aluminium lids, tetrapacks, food cans, polyethylene terephthalate containers, and squeezable pouches with plastic linings.^{64–66} Infant and toddler foods are usually packaged in smaller volumes, leading to a greater surface area to volume ratio between the food and the packaging material. Two Australian surveys of canned foods observed the highest levels of BPA migration into foods occurred in canned infant custards and deserts (up to a maximum of 420 ng/g), compared with other canned food options, including fruit, vegetables, soup, and tuna, which were generally under 200 ng/g.^{65,66} At the global level, the World Health Organization has estimated that dietary intake of BPA in young children is highest in 6- to 36-month-old infants

Table 2. Comparison of maximum BPA content ($\mu\text{g/g}$ or $\mu\text{g/l}$) reported in canned foods vs other household products.

<i>Canned foods</i> ^{65–66} ($\mu\text{g/g}$)	<i>Paper products</i> ^{71,73} ($\mu\text{g/g}$)	<i>Personal care and cleaning products</i> ^{89,90} ($\mu\text{g/g}$)	<i>Household plastics</i> ⁷⁰ ($\mu\text{g/l}$)
Canned vegetables 0.103	Receipts 14,700	Body washes 0.0443	Child's spoon 0.221
Canned fruit 0.024	Magazines 55	Hair-care products 0.0006	Child's toy 0.279
Canned infant custard 0.400	Tickets 14,400	Makeup 0.0412	Silicone teat 259
Canned infant dairy desert 0.290	Airplane board pass 415	Skin lotions 0.167	CD 0.157
	Flyers 598	Toilet soap 0.0493	DVD 0.267
	Newspapers 658	Toothpaste 0.0028	Infant teether 5.865
	Napkins 3 340		
	Kitchen paper towels 24.1		
	Toilet paper 180		
	Paper money 77,100		

Table 3. Studies assessing the concentration of BPA in household dust samples.

<i>Author</i>	<i>Year</i>	<i>Region</i>	<i>Median BPA concentration in dust (ng/g)</i>	<i>Maximum BPA concentration in dust (ng/g)</i>	<i>Detection rate (%)</i>
Rudel et al. ⁷⁹	2003	USA	820	17,600	86
Wilson et al. ⁷⁷	2007	USA	< LOD ^a	707	25–47
Geens et al. ⁷⁸	2009	Belgium	1460	9730	100
Loganathan et al. ⁷⁵	2011	USA	422	10,200	95
Blanchard et al. ⁷⁴	2014	France	4700	20,000	88
Liao et al. ⁷⁶	2012	USA	1600	9380	100
		China	630	8350	96.4
		Japan	2700	21,800	100
		Korea	3260	39,100	100

^aMedian level below the lower limit of detection.

following commencement on solid foods, in whom daily dietary intakes are estimated to range between 0.6 and 3 μg BPA/kg/day.⁶⁷

An important limitation of this approach to dietary assessment of daily exposure is that it does not address concurrent exposure patterns to other synthetic or natural endocrine disruptors also found within infant and toddler food sources. Soy-based infant formula now makes up a third of the United States formula market,⁶⁸ raising concerns regarding the potential for synergistic endocrine-disrupting effects of combined exposure to genistein and BPA. Phthalate plasticisers are also commonly used in food-packaging materials and have also been observed within samples of human breast milk and infant formula.⁵² Concurrent exposure to other endocrine-disrupting substances contained in infant and toddler nutritional sources is an important consideration if the risk of dietary ingestion of BPA is to be accurately characterised within the context it is received in early childhood.

Non-dietary Exposure Sources

A distinguishing feature between adults and young children is that ingestion of BPA is not necessarily limited to dietary exposure sources. Sucking and chewing are normal developmental behaviours in early childhood⁶⁹ and can include mouthing on plastics and other BPA-containing consumer products, which are generally not considered dietary exposure sources, such as pacifiers, teething rings, toys, and books. The frequent hand-to-mouth behaviours of infants and toddlers may indirectly increase ingestion of BPA, following the transfer of BPA to the hands and food, which are then placed in the mouth.³⁷ One study of BPA migration from household plastic products observed that migration concentrations were generally in the range of 150–300 ng/l, which included an infant spoon, a toy, a CD, and a DVD. However, some products released considerably higher BPA

concentrations under testing conditions, including an infant teething aide, which was reported to leach 5865 ng/l of BPA.⁷⁰

Thermal print paper is another important exposure source to BPA, where it is widely used as a colour developer.⁷¹ BPA is contained in materials applied to the outer layer, so relatively high quantities of BPA can be found on the surface of thermal print paper, which is not chemically bound within the product.⁷² Surveys of BPA content in consumer products have reported that several paper products contain between a 100 to a 1000 times the BPA content reported in canned foods (Table 2). For example, whereas the maximum reported BPA concentration in canned infant foods from an Australian food survey was 0.42 $\mu\text{g/g}$,⁶⁶ the BPA content in supermarket receipts is reported to be as high as 14,700 and 77,100 $\mu\text{g/g}$ in paper currency.^{71,73} Thermal paper is also extensively recycled and BPA may be present in a range of paper and cardboard products made from recycled materials, such as magazines, books, and newspapers.⁷¹ Exposure to BPA has the potential to be significant in young children who ingest BPA-containing paper and cardboard products, such as chewing on a magazine or children's book made from recycled thermal paper. This has important public health implications, as many parents may not be aware of the relatively high BPA content in common paper and cardboard materials from around the home. It is possible that parents may even encourage their child to suck or chew on various paper products, in the belief that this is a 'safer' option than sucking on plastic toys.

As infants and toddlers in most developed countries spend more than 90% of their time indoors, house dust composition may be an under-recognised exposure source of BPA in young children. Analyses of dust samples collected from the home environment have demonstrated that BPA is a pervasive contaminant of household dust, although considerable variations exist in dust BPA concentrations, even in dust samples collected in the same city or region (Table 3).^{74–79} Recent studies from the

United States and France report BPA concentrations in household dust ranging up to a maximum of 10,200 and 20,000 ng/g, respectively.^{74,75} Within Asia, studies from Japan and Korea report the highest levels of BPA concentrations in household dust, ranging up to 21,800 ng/g in Japan and 31,900 ng/g in Korea.⁷⁶ Ingestion of dust is estimated to be ~60 mg/day in young children.⁸⁰ Thus, children exposed to environments with the highest dust concentrations of BPA would be expected to ingest in the range of 500–2300 ng BPA/day, which is higher than the estimates of many infant dietary sources.

NON-DIETARY EXPOSURE SOURCES MAY HAVE MULTIPLE EXPOSURE ROUTES

Dermal Absorption

There are a number of factors that are known to influence the transfer of exogenous compounds across human skin. These include the molecular weight and lipophilicity of the compound, as well as differences in permeability of human skin based on age, gender, ethnic background, and location of the skin on the body.⁸¹ Drug compounds suitable for transdermal delivery are generally those with a log *P* of > 1.5 and with a molecular weight of under 500 Da.⁸² As BPA is a small compound (288 Da), which is also lipophilic (log *P* of 3.4), it would be expected that BPA would pass through human skin with relative ease.⁸³

Viable skin models have undeniably demonstrated that BPA applied directly to the skin is absorbed through the epidermis and dermis. Studies of human skin explants to assess skin penetration of BPA have observed that ~9.5–33% of the applied dose is transferred through the skin as free BPA within 24–48 h of topical application.^{84–86} However, it is uncertain how these findings relate to living tissue, in particular in young children. The skin of human neonates is immature at birth and takes at least 3–5 months to attain similar barrier properties as those of adults.⁸¹ The skin of neonates may therefore be more permeable to lipophilic chemical absorption than in the general population. Infants and toddlers also have a comparatively higher surface area to body mass ratio than adults and older children.³⁷

BPA is known to transfer from thermal receipt paper to the skin of the fingers in adults. Biedermann *et al.*⁸⁷ observed that handling thermal print paper transferred an average of 1.13 µg BPA to the pad of the finger, up to a maximum of 23 µg per finger. Based on the proportion of BPA initially transferred to the skin and the fact that it could no longer be washed off after 2 h, the fraction absorbed from the fingertips was estimated to be 27%, which is in keeping with the findings of the human skin explant models, although the study did not access for how much BPA transferred into the systemic circulation. Handling thermal receipt paper for as short a time as 30 s has been observed to result in between 0.1 and 0.5 µg BPA being transferred to fingers and the thumb.⁷⁰

BPA is also known to transfer to the hands of pre-school children.⁸⁸ The exploratory behaviours of older infants and toddlers will lead them to have high dermal contact to a myriad of plastic, cardboard, and paper products throughout the course of any 1 day, including toys, children's books, and recycled papers used for recreational activities. Dust is also a potential source of dermal exposure to BPA in this age group, in particular when present in the 'crawl zone' of an infant and the 'reach zone' of a toddler. A study of pre-school children in the United States reported a median BPA concentration of 5600 ng/m² present on the hands of the children.⁸⁸ In comparison, surface wipes collected from the home and day-care environment generally tended to range between 260 and 500 ng/m². Such a high BPA concentration from the hand wipes of preschool children implies frequent contact with BPA-containing materials across the course of the day, and when modelling of the transdermal flux was applied (estimated as ~1600 ng/m²/h), the authors predicted that up to a

third of the total daily BPA exposure initially presumed to be from oral intake could have plausibly come from dermal absorption instead.⁸⁸

Personal care products and household cleaning products have also been documented to contain variable levels of BPA, including bar soaps, facial and body lotions, shampoos, dishwashing and laundry detergent, and toilet bowl cleaner.^{89,90} The presence of BPA in personal care products marketed for use in infants and children is not immediately obvious, as it is not listed as an ingredient on the label. The addition of water is well known to increase the transdermal flux of many synthetic chemicals,⁹¹ which has important implications for BPA exposure in infants and toddlers during bath time, as both personal care products and the bath water itself may be contaminated with BPA.

Alcohol-based chemical additives commonly found in infant and toddler personal care products such as nappy wipes, hand sanitisers, and moisturisers may further influence dermal absorptive capacity of BPA when they are applied to the skin of young children. Chemical additives in products such as moisturisers and hand sanitisers include isopropyl, propylene glycol, and ethanol.⁸³ These additives are known to interact with human skin, disrupting the highly ordered lipid bilayer structure that forms the primary barrier and increasing transport of exogenous compounds across the skin.⁸²

In a recent study by Hormann *et al.*,⁸³ the influence of a common household brand of hand sanitiser was investigated in facilitating transdermal transfer of BPA from thermal receipt paper in a sample of 10 adult participants. The study observed that up to 581 µg of BPA was transferred to the hands after topical application of hand sanitiser, followed by holding a restaurant receipt in the hands for less than a minute. Transfer of BPA from receipt paper to hands was around an order of magnitude lower when the same brand of receipt paper was held in dry hands without application of hand sanitiser. These findings have particular relevance to infants and toddlers, as use of hand sanitisers or alcohol-based wet wipes may be seen by parents as a quick and convenient means to clean children's hands when dirty and before meals. Furthermore, infants and toddlers rely heavily on hand to mouth behaviours for food consumption,³⁷ which is likely to additionally increase dietary exposure if BPA present on hands is then transferred to food before consumption.⁸³

In summary, further studies are required to determine the absorptive capacity of the skin in human children, as well as the dermal bioavailability of BPA from regular daytime contact with toys, books, and dust. Dermal absorption may be particularly relevant in infants, in whom the barrier functions seen in adult skin may not yet have fully developed and it is possible that exposure pathway models based on the permeability and transdermal absorption of human adults may substantially underestimate dermal penetration of BPA in young children. BPA, which penetrates through the stratum corneum, would have the capacity to enter the systemic circulation in its unconjugated form via the skin's capillary network. Given the popularity of hand sanitisers, moisturisers, and other alcohol-based personal care products designed for use in infant and toddlers, there is also a need to design age-specific exposure studies to assess the role that chemical additives contained within these products may have in enhancing the transdermal absorption of BPA.

Inhalation

Infants and toddlers have higher oxygen requirements per kg body weight and a higher respiratory rate compared with adults, which makes them particularly susceptible to inhalational toxicants.³⁷ The mucosal surface area of the respiratory tract is several hundreds of times that of the external skin barrier and the absorptive capacity of the respiratory epithelium to synthetic chemicals and other exogenous substances is well documented.⁹²

Despite advances in the knowledge of respiratory epithelial permeability, there is little known about how and where many exogenous compounds are absorbed at a cellular level and how long they reside in the lung. In order to assist in rapid gas transfer, the terminal bronchioles and alveolar sacs lay within close proximity of end capillaries (Figure 2), and as with the dermal exposure route absorption of BPA from the respiratory epithelium would be expected to enter the systemic circulation in its free form.

There are several lines of indirect evidence, suggesting that inhalational exposure to BPA in air, dust, or smoke may be an important but under-recognised exposure route in the human population. Pregnant women in the United States with frequent exposure to tobacco smoke have on average 20% higher urinary BPA concentrations compared with those with no history of smoking,⁹³ and second-hand smoke exposure has also been reported to be a significant predictor of BPA exposure in human children.^{17,94} This is likely on the basis of BPA making up around 25–30% dry weight in some cigarette filters.²² Free BPA within the cigarette filter, which attaches to combusted particulate matter of the cigarette, would be expected to deposit on the respiratory epithelium when inhaled.

Environmental sampling from the home environment suggests that BPA readily adheres to dust particles, with the highest ambient environmental concentrations of BPA observed in settled dust, followed by in airborne particulate matter, but with low-to-negligible concentrations in the gas phase.⁷⁴ BPA has been found in indoor air samples at low concentrations ranging up to 30.3 ng/m³, but with considerably higher concentrations noted in several studies of household dust (Table 3).^{74–79} We could only find one study that has attempted to estimate BPA exposure from dust inhalation in pre-school children. However, as the median dust and ambient air concentrations in this study were below the laboratory limits of detection,⁷⁷ the prediction that dust inhalation is low in preschool children from this study is not relevant to most regions of the world, in which substantially higher concentrations of BPA have been observed within household dust.^{74–76,78,79} Repeat measurement studies modelling exposure from BPA concentrations of dust and ambient air within the living spaces of infants and toddlers would be of benefit to further characterise the potential for inhalational exposure from households and day-care centres.

When modelling inhalation, it is also important to consider that some larger particulate matter may settle more proximally in the respiratory tract. This includes nasal deposition, which is also known to be highly permeable to exogenous substances.⁹⁵ Intra-nasal absorption has gained recognition in recent years as an effective mechanism for delivery of therapeutic drugs to the central nervous system, as absorption of exogenous substances by the intranasal route are known to travel directly to the brain via the olfactory and trigeminal nerves, which innervate the nasal passages, and in doing so bypasses the blood–brain barrier.⁹⁶ This is a potentially important exposure pathway when considering the association seen in human epidemiological studies of BPA exposure in children and neurobehavioural health outcomes,^{97–102} as neonates are preferential nose breathers.

Byproducts of the combustion of plastics, receipts, and thermal printer paper in open domestic fireplaces may be an additional source of ambient BPA exposure in some households. In a scenario mimicking domestic opening burning of household wastes, including food-packing materials and non-recyclable plastics, BPA was observed to have an emission rate of 9.66 mg/kg and a concentration 58.3 p.p.m.¹⁰³ It has been further estimated that ~79,000 kg of BPA is emitted annually as a result of domestic open barrel burning in the United States alone. Consideration also needs to be given to outdoor air contamination in homes adjacent to industrial settings, as an estimated

100,000 kg of BPA is released into the atmosphere each year in the United States as a pollutant from manufacturing processes.²⁹

Inhalation is a well-established exposure route in young children to a number of toxicants, including several phthalate plasticisers.¹⁰⁴ Despite this, inhalation is usually discounted as a contributing exposure route for BPA from theoretical pharmacokinetic models. As far as we are aware, this is the first time that inhalation and absorption of BPA via the human respiratory epithelium is being proposed as a relevant exposure route for BPA. Specific instances in which inhalation of BPA may lead to significant internal exposure to BPA include houses reporting the highest BPA concentrations in household dust or ambient air and prolonged or repeated exposure to second-hand cigarette smoke. Further research modelling potential inhalational exposure and BPA uptake from the respiratory tract in humans is warranted.

Sublingual Absorption

Recent reviews have suggested that sublingual absorption may represent another important exposure route for BPA in humans,^{36,72} following the confirmation of sublingual absorption in an animal model using dogs.¹⁰⁵ A comparison of administrative route in studies of rhesus monkeys observed that dosing schedules using gastric gavage (which bypasses the oral mucosa) generally had detectable levels of unconjugated BPA in serum of < 1%, whereas studies in which BPA was administered as part of the animal's food sources resulted in ~7% of the administered dose being detected as unconjugated BPA in the blood.¹⁰⁶ At the time of this review, there have not been any studies published on the human capacity for sublingual absorption for BPA, although sublingual absorption is well-recognised in human pharmacology for the rapid delivery of drugs such as glyceryl trinitrate.¹⁰⁷ The oral mucosa lies within close proximity to densely packed capillary networks, and thus absorption by this exposure route would also be expected to lead to free BPA directly entering the systemic circulation.¹⁰⁸

Although further research is needed to confirm the capacity for sublingual absorption in human children, it is an important consideration for BPA-risk assessment in the context of early childhood. Infants and toddlers often have their food provided in a pureed or mashed form and they hold food in their mouths for longer periods of time than adults before swallowing. Furthermore, the use of pacifiers and teething aids in infants is highly prevalent in some developed countries, with a study from New Zealand reporting 79% of parents introduced a pacifier at some point in the first year, often for 6 or more hours a day.¹⁰⁹ A Japanese study has also assessed the potential for BPA exposure when infants suck or chew on children's books, with up to 43.4 ng/ml of BPA being released from pages of children's books into artificial saliva over a 2-h period.²

Here we propose that prolonged sucking or mouthing behaviours on teething aids, toys, books, and pacifiers may increase the bioavailability of BPA in human saliva in infants and toddlers. Similarly, prolonged periods of time sucking fingers or thumbs may also increase the bioavailability of BPA in human saliva, which is a well-recognised developmental phase seen in many young children, which is eventually outgrown. Both of these scenarios, which are common in young children, may lead to extremely high concentrations of BPA in saliva which would not be expected to be observed to the same degree in studies modelling sublingual uptake of BPA from animals ingesting feed or in the general adult population.

DISCUSSION: THE NEED FOR AN IMPROVED RISK-ASSESSMENT APPROACH

In early childhood, even subtle alterations in hormonal signalling have the potential to fundamentally alter normal growth and

development trajectories in sensitive end organs, including the developing brain and lungs. BPA is a known endocrine disrupting chemical, which has sparked considerable debate over the past decade. Although ingestion of BPA-containing food as a contaminant from food packaging and storage materials is inarguably an important exposure route for BPA, it is becoming increasingly clear that dietary exposure sources alone do not provide a complete picture of BPA exposure in the human population. In this review, we have highlighted significant gaps in the knowledge of how exposure to BPA occurs within the infant and toddler age groups. Extrapolation of exposure assessments performed in adults is unlikely to capture the more varied exposure sources of infants and toddlers, and there is a clear need for more thorough exposure assessments to be performed in this subgroup in order to better inform the risk-assessment process.

It is worth noting that much of what is known on BPA pharmacokinetics in humans came from two early pharmacokinetic studies in adults.^{31,110} These studies indicated that orally administered BPA is rapidly absorbed from the GI tract, following which it undergoes a first-pass metabolism in the liver, which facilitates rapid conjugation of free BPA. From these two pharmacokinetic studies, the biological half-life of BPA in the human body was estimated to be between 4 and 6 h, with nearly complete elimination after 24 h. However, only the GI route of exposure was assessed in these studies and other potential exposure routes were excluded in both the study design and interpretation of the data.

As these early pharmacokinetic studies were only performed in adults,^{31,110} they cannot be assumed to be accurate pharmacokinetic models for exposure to BPA in early childhood. It is well established that hepatic detoxification systems do not reach maturity until 2 years of age, including the UDP-glucuronosyltransferase family of enzymes responsible for the predominant conjugation of free BPA in humans.¹¹¹ As a result, human newborns are predicted to have three times higher serum BPA concentration than an adult.¹¹² Although some capacity to conjugate BPA has been observed in term newborns,¹¹³ risk-assessment modelling based on adult pharmacokinetic models of rapid and complete conjugation has the potential to underestimate the internal exposure to BPA in infants and toddlers.^{111,114}

The overarching aim of risk analysis is to assess the health risk posed to humans by a toxicant. The initial hazard assessments for BPA were mostly based on third-generation and second-generation toxicology studies in rodents, with a toxicological endpoint of reduced liver weight.¹¹⁵ From these studies, an overall no-observed adverse effect level of 5 mg/kg/day was determined by the hazard assessments performed by the EFSA.²⁶ An uncertainty factor was then applied, to allow for varying differences in risk within the human population. This led to a "tolerable daily intake" of 50 µg BPA/kg/day being set by the EFSA in 2006. The United States Environmental Protection Agency then derived a reference dose of 50 µg BPA/kg/day shortly thereafter. Other countries have also derived their own national reference doses, either by adopting those of the EFSA or the United States, or by performing their own toxicology-based risk assessment.

There are now more than 30 human epidemiological studies reporting an association between pre-natal or post-natal BPA exposure in children and the development of childhood diseases such as obesity, asthma, and neurobehavioural disturbances.^{97–102,116–119} These findings pose a challenge for regulatory decision making in regards to BPA, as there is increasing evidence to support wide-ranging health effects from a variety of environmentally relevant exposure sources, pathways, and routes, which are not plausibly predicted from the current risk-assessment approach, even with the application of an uncertainty factor.¹²⁰ Although the EFSA reduced the tolerable

daily intake to 4 µg BPA/kg/day in 2014, the United States has maintained its original reference dose of 50 µg BPA/kg/day.

The World Health Organization predicts that in 6- to 36-month-old infants, total daily BPA exposure may reach 3 µg/kg/day based on dietary exposures alone.⁶⁷ Despite the World Health Organization predictions that daily dietary exposures alone will potentially approach the EFSA's recommended tolerable daily limit of 4 µg BPA/kg/day in some infants, many regulatory agencies continue to inform the general public that current human exposure levels to BPA do not pose a threat to human health.^{121–123} It is also worth noting that estimates of total daily exposure have traditionally relied on a single urine sampling protocol by which to base their calculations, ignoring the known variability in urinary BPA concentration across the course of the day and across longer periods of time. This approach may lead to significant inaccuracies in total daily exposure estimates and is likely to underestimate total daily exposure if calculations are based on an early morning or fasting urine sample.

At the national level, most countries within the European Union have adopted the initial EFSA's tolerable daily intake for their own regulatory purposes; however, it is unclear how many European countries have followed through with the EFSA's most recent recommendations to reduce recommended daily exposure limits from 50 to 4 µg BPA/kg/day. Furthermore, there is considerable variation as to the implementation of regulatory action to restrict BPA exposure in young children outside of Europe. In Australia and New Zealand, there are no regulatory requirements for manufacturers to remove BPA from food contact materials or infant products.¹²³ Meanwhile, Canada and the United States have banned the use of BPA in infant feeding bottles and sippy cups, Japan has regulatory restrictions in place to reduce the use of BPA in canned foods, and Japanese plastics manufacturers phased out the use of BPA in children's plastic tableware over a decade ago.^{122–125}

It is also uncertain as to whether current regulatory restrictions on the use of BPA have effectively reduced exposure levels in early childhood. We could find no published national surveillance biomonitoring studies from before and after restrictions were enforced to assess the success of these policies in reducing total daily exposure patterns to BPA in populations of infants and toddlers. Furthermore, as regulatory decisions fall into the jurisdiction of national Food Standards Authorities in many countries, regulatory policies thus far have predominantly focused on dietary exposure sources and food contact materials. National and international regulatory policies, which address the broad range of potential exposure sources to BPA within the wider home and day-care environments, have yet to be developed.

The collective implications of epidemiological studies assessing BPA exposure and child health are concerning and raise the question as to whether current risk-assessment models may be making several fundamental misassumptions. Here we build on the work by Vandenberg *et al.*³⁶ and propose that non-dietary exposure pathways in combination with a reduced capacity to conjugate BPA in early childhood make up part of the missing puzzle pieces. The typical developmental behaviours of infants and toddlers discussed throughout this review indicate this subgroup of the population may be at increased public health risk because of considerable unaccounted incidences for uptake of BPA via non-dietary exposure pathways. This includes activities such as mouthing or sucking on polycarbonate plastics, handling of recycled thermal receipt paper in children's books, and exposure to second-hand cigarette smoke. Dietary exposure in early childhood may also be underestimated if adult dietary consumption patterns are used to predict BPA ingestion in infants and toddlers.

We argue that in order to improve risk assessment of BPA exposure in early childhood, the application of a universal uncertainty factor should be replaced by risk-assessment

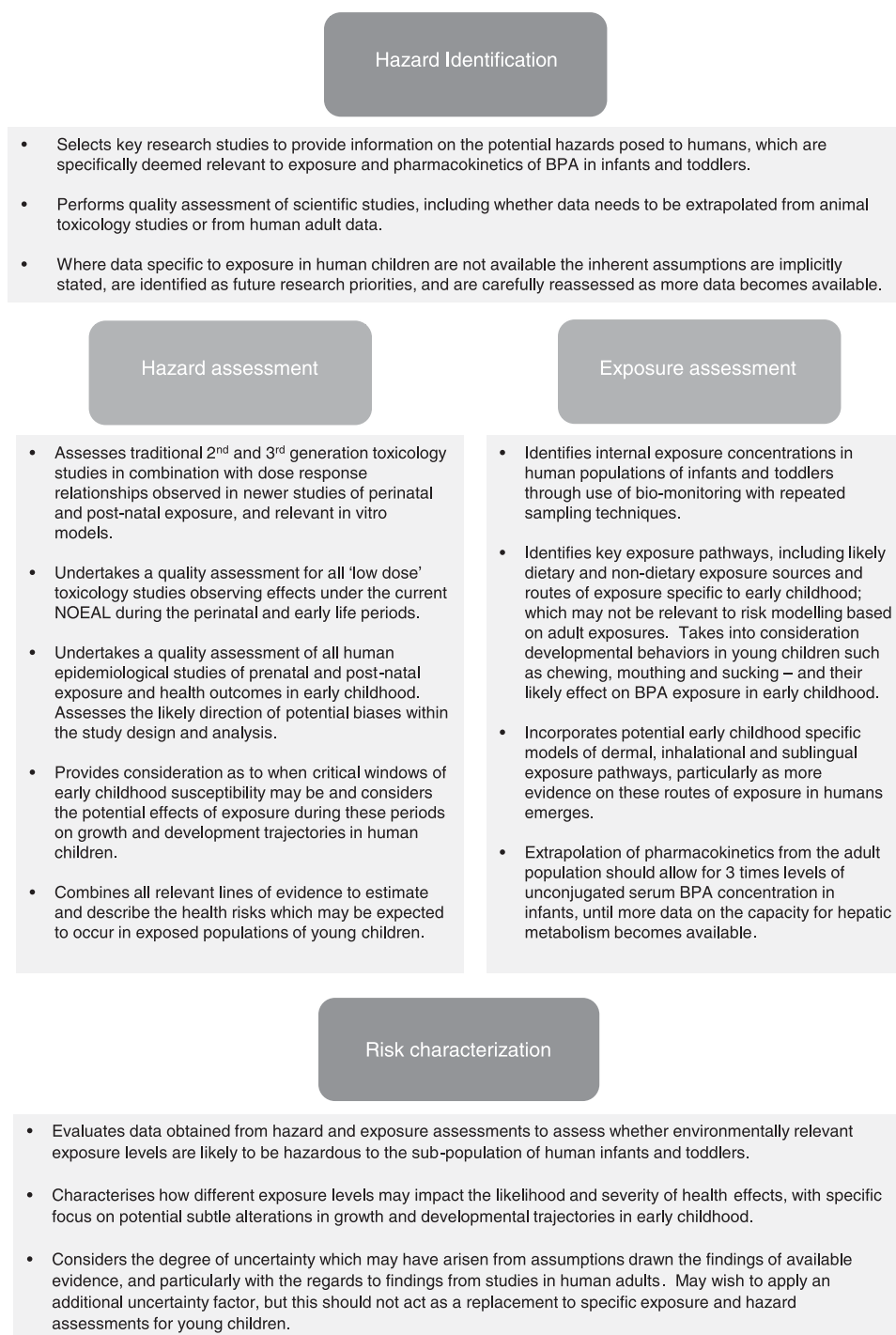


Figure 3. Considerations for an Early Childhood Specific Environmental Health Risk Assessment Model.

frameworks, which are specific for exposure in early childhood at each step in the assessment process (Figure 3). We further recommend that early-childhood-specific risk-assessment models take into consideration epidemiological evidence relating BPA exposure in human children and its association to childhood disease, preferably through the grouping of studies assessing specific health endpoints with meta-analysis. There needs to be increased recognition of the wide variety of BPA-containing consumer products in the home and day-care environments, which are potential exposure sources, and modelling should allow

for the possibility that a third of the estimated total daily exposure to BPA in pre-school children may come from dermal uptake of the skin.⁸⁸ Improved human biomonitoring, which specifically assesses BPA concentrations in infant blood and urine, the temporal variability of BPA concentrations in young children, and the degree to which young children are able to conjugate BPA are also important considerations if the exposure is to be more accurately characterised in the early childhood years.

Further research is required into the potential health effects of conjugated BPA in the systemic circulation in young children. As

initial toxicology studies observed that BPA glucuronide does not bind to the classical oestrogen nuclear receptor pathways, it has long been assumed that glucuronide BPA conjugates lack biological activity.¹²⁶ In reality, there is very little published data on the potential biological actions (or lack of biological action) for human BPA-glucuronide and BPA-sulphate conjugates, and they may still have the potential to disrupt normal growth and development in early childhood through other biological pathways.¹²⁷

Lastly, it is important to consider the increasing use of BPA analogues and derivatives as BPA replacements in consumer products. These include bisphenol S (BPS), bisphenol B, and bisphenol F. Substitution of BPA with another bisphenol analogue allows for the product to then be advertised and marketed as 'BPA free'. BPS, in particular, appears to be gaining in popularity in thermal receipt paper as a replacement for BPA. A study of receipt papers from the United States observed that about half of the receipt papers surveyed had substituted similar concentrations of BPS for BPA, with only 4% of receipt papers sampled containing neither BPA nor BPS.⁸³ Although much less research has been undertaken on the toxicity of exposure to alternative bisphenol analogues in plastics and paper, a recent systematic review suggests that BPS and bisphenol B appear to have similar hormonal activity to that of BPA.¹²⁸ Meanwhile, household dust has been reported to have relatively high concentrations of tetrabromobisphenol A and BPA bis (disphenylphosphate),^{129,130} highlighting the increasing use of bisphenol analogues and derivatives as flame retardant replacements to polybrominated diphenyl ethers. Public health policy and debate therefore needs to take into consideration that young children are likely to be exposed not just to BPA but to multiple bisphenol compounds through both dietary and non-dietary exposure sources. Mixture effects of concurrent exposure to multiple bisphenol compounds with similar endocrine-disrupting properties may not be deducible from the single compound analyses used in traditional chemical risk assessment and regulatory decision making.

In conclusion, further research is required if we are to better understand the relevant sources, pathways, and routes that constitute exposure to endocrine disruptors such as BPA in early childhood, as they cannot be assumed to be the same as in older children and adults. Exclusion of non-dietary exposure sources and their relevant exposure routes from risk-assessment processes and regulatory decision making will substantially underestimate the risk of BPA exposure in early childhood and the application of an uncertainty factor in current risk assessment models may not be sufficient to account for differences of exposure patterns and metabolism in young children.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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