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REVIEW ARTICLE

BISPHENOL A (BPA) IN FOOD CONTACT MATERIALS – NEW SCIENTIFIC OPINION FROM EFSA REGARDING PUBLIC HEALTH RISK

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ABSTRACT

The wide use of bisphenol A (BPA) as a monomer in plastics manufacture or epoxy resins intended for food contact materials (FCM) has triggered numerous concerns due to toxicological findings indicating possible endocrine disrupting properties. This article traces the evolution of the scientific opinions since 1986 when the Tolerable Daily Intake (TDI) for BPA and its specific migration limit (SML) from plastic FCM into food were proposed for the first time by the Scientific Committee for Food (SCF). Resent extensive scientific studies concerning refined data on toxicity and exposure to BPA from food and non-food sources (eg. dust, cosmetics, thermal paper), including the most vulnerable groups of population, allowed the European Food Safety Authority (EFSA) to reduce the TDI of BPA from previously 50 µg/kg bw/day to now 4 µg/kg bw/day. EFSA's latest scientific opinion published in 2015 concludes that basing on the current estimations of total exposure to BPA from dietary and non-dietary sources for infants, children and adolescents is below the temporary TDI of 4 µg/kg bw/day. EFSA has also underlined that BPA poses no health risk at the estimated exposure levels of any population age group, including unborn children and the elderly. However, EFSA has indicated that some data on exposure and toxicological effects still require clarifications.

Key words*: bisphenol A, BPA, food contact materials, toxicology, exposure, toxicity, TDI, specific migration limit, EFSA*

STRESZCZENIE

Szerokie zastosowanie bisfenolu A (BPA) jako monomeru w produkcji tworzyw sztucznych i żywic epoksydowych przeznaczonych do kontaktu z żywnością wywołało wiele obaw wynikających z badań toksykologicznych wskazujących na możliwe szkodliwe działanie, szczególnie odnoszące się do efektów endokrynnych. W artykule przedstawiono ewolucję podejścia do BPA oraz kolejnych opinii naukowych od 1986 roku, kiedy Naukowy Komitet ds. Żywności (SCF) po raz pierwszy zaproponował dla BPA wartość tolerowanego dziennego pobrania (TDI) i limit migracji specyficznej (SML) tego związku do żywności z materiałów z tworzyw sztucznych przeznaczonych do kontaktu z żywnością. Obszerne piśmiennictwo naukowe dotyczące pogłębionych badań toksycznego działania i narażenia na BPA, zarówno z żywności, jak i ze źródeł poza żywnościowych (kurz, kosmetyki, papier termiczny), uwzględniające najbardziej wrażliwe grupy populacji, umożliwiły EFSA obniżenie TDI z 50 µg/kg mc/dzień do 4 µg/kg mc/dzień. EFSA w swojej naukowej opinii z 2015 roku podkreśla, że na podstawie aktualnych oszacowań całkowite narażenie niemowląt, dzieci i młodzieży na BPA ze źródeł żywieniowych i poza żywieniowych jest poniżej tymczasowego TDI, wynoszącego 4 µg/kg mc/dzień. W opinii tej EFSA podkreśliła, że BPA nie stwarza ryzyka dla zdrowia, przy oszacowanych poziomach narażenia, dla żadnej z grup populacji, włączając również nienarodzone dzieci i osoby starsze. EFSA wskazała jednak na potrzebę wyjaśnienia niektórych danych dotyczących narażenia i badań toksykologicznych.

Słowa kluczowe*: bisfenol A, BPA, materiały do kontaktu z żywnością, narażenie, toksyczność, TDI, limit migracji specyficznej, EFSA*

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INTRODUCTION

Bisphenol A [2,2-bis(4-hydroxphenyl)propane, CAS No. 80-05-7, EEC packaging material Ref. No. 13480] commonly known as BPA is widely used as a monomer in the manufacture of polycarbonates (PC) and epoxy resins and as an additive in other polymeric materials. Due to their rigidity and transparency, polycarbonates are used in food contact materials, such as tableware, infant feeding bottles and reservoirs for water dispensers, and also in other applications such as toys and pacifiers. BPA-based epoxy resins can be used as internal protective coatings in cans for food and beverages and in drinking water storage tanks. BPA is also used in a number of non-food applications, e.g. epoxy resin-based paints, medical devices, dental materials, surface coatings, printing inks, thermal paper (eg. for cash receipts), flame retardants and common plastic products (eg. CDs, DVDs) [20, 22, 38].

In the last decade several objections concerning BPA-related delayed adverse health effects have been raised following the worldwide intensive discussion triggered by toxicological findings, mainly based on its endocrine disrupting properties [17, 20, 21, 24, 25]. The use of BPA in food contact materials (FCM) may thus cause a potential consumer exposure of this substance through food. A large number of research studies on toxicity and endocrine activity of BPA in animals have been published. However, there have been discrepancies in outcomes from different studies. This has led to the controversy about the BPA safety in the opinion of scientists and has resulted in different decisions concerning risk management being undertaken by the various national authorities [22, 23, 25].

Legal status related to BPA in FCM

The use of BPA in materials intended into contact with food is regulated at the European Union level. BPA was first evaluated in 1986 by the Scientific Committee on Food (SCF) for use in manufacturing of plastic FCM. The SCF allocated a Tolerable Daily Intake (TDI) for BPA at the level 0.05 mg/kg bw/day [52]. BPA was also placed on the list by the Commission Directive 90/128/EEC as a permitted substance which may be used in plastic food contact materials with a specific migration limit (SML) of 3.0 mg/kg food [9].

In 2002, the SCF [53] changed the status of BPA by setting a temporary TDI of 0.01 mg BPA/kg bw/day, and applying a 500-fold uncertainty factor (UF) (comprising 10 for interspecies differences, 10 for inter-individual differences and 5 for uncertainties in the toxicity database), due to the lack of complete toxicological data. The SCF recommended that the t-TDI should be reviewed when any significant new data becomes available [53]. This high UF was applied in the NOAEL (No-Observed-Adverse-Effect-Level) of 5 mg/kg bw/day identified in a three-generation study in the rat by *Tyl* et al. [59]. SML for BPA was accordingly reduced to 0.6 mg/kg of food which was reflected by the Commission Directive 2004/19/EC [11], amending Commission Directive 2002/72/EC [10].

In 2006, EFSA based on an extensive literature survey reduced the uncertainty factor to 100 and established a full TDI of 0.05 mg/kg bw/day. In the same evaluation the SML for BPA remained at the level of 0.6 mg/kg [20]. In 2008, EFSA re-confirmed the TDI (0.05 mg/kg bw/day) stating that the new data available did not provide convincing evidence to establish a lower value for TDI [21].

In 2011, the Commission Directive 2011/8/EU [12] prohibited, as a precautionary measure, the manufacture of polycarbonate infant feeding bottles with BPA as from 1 March 2011 and the placing on the market and import into the EU of such feeding bottles as from 1 June 2011.

Some European Union Member States banned the use of BPA in containers and packaging for food intended for children up to 3 years old and some of them extended this ban for other applications.

Denmark in 2010 banned the use of BPA in infant feeding bottles and cups and all containers for food products, such as breast milk substitutes and mixed substitutes intended for children for 0 -3 years of age [2]. Austria in 2011 published a decree forbidding the use of BPA in pacifiers and soothers [63]. Belgium in 2012 banned the marketing and putting on the market and manufacture of containers for food products, containing BPA, particularly intended for children between 0-3 years of age [44]. France in 2012 adopted the law suspending the manufacturing, import, export and putting on the market of all food contact materials containing BPA and also introduced labelling requirements for pregnant women, breastfeeding women and small children [48]. Sweden in 2013 banned the use of BPA or compounds containing BPA in varnishes or coatings in the packaging for food intended for children aged 0-3 years old [57].

Since 2006 much additional data including exposure and toxic aspects of BPA became available that justified refining previous assessments.

In 2015 EFSA published a new scientific opinion based on the assessment of health-related risks associated with human exposure to BPA [23, 23]. The external dietary and non-dietary exposure and internal exposure (absorbed dose of conjugated and unconjugated BPA) was included in this assessment and expressed as oral human equivalent dose (HED) referring to unconjugated BPA only. In this opinion based on new toxicological data EFSA adopted a total uncertainty factor of 150-

fold and the lowered previous TDI (50 μg/kg bw/day) to a temporary TDI of 4 μg/kg bw/day. This substantial change was made by EFSA because of new data and a refined risk assessment together with uncertainties in the database regarding mammary glands, reproductive, metabolic, neurobehavioral and immune systems [22]. Taking into account the t-TDI and the exposure and toxicity estimates EFSA concluded that there is no health risk from BPA dietary or aggregated exposure (diet, dust, cosmetics and thermal paper) for any age group of consumers, including unborn children, infant and adolescents. Dietary exposure and from the combined sources is considerably below the new t-TDI. [22, 23]. The t-TDI remains temporary pending the results of a long-term animal study, which will allow to reduce these uncertainties.

EFSA maintained the same specific migration limit (0.6 mg/kg food) with the restriction on the use of BPA in the infant feeding bottles.

The evolution history of the reference values: tolerable daily intakes and specific migration limits related to bisphenol A in plastic food contact materials is summarized in Table 1.

Table 1 Evolution of the reference values: TDI and SML related to BPA in plastic food contact materials

Year	TDI[1] (mg/kg bw/day)	SML[2] (mg/kg food or food simulant)	Reference
1986	0.05	3.0	[9, 52]
2002	0.01 (t-TDI)	0.6 SML(T)	[11, 53]
2006	0.05	0.6 SML(T)	[11, 20]
2010	0.05	0.6	[14, 21]
2011	0.05	0.6*	[12, 13]
2015	0.004 (t-TDI) (4 μg/kg bw/day)	0.6*	[13, 22]

* **Restriction**: BPA not to be used for the manufacture of polycarbonate infant feeding bottles [12, 13]

[1] TDI (Tolerable Daily Intake) is an estimate of the amount of a substance, expressed in milligrams on a body weight that can be ingested daily over a lifetime without appreciable risk. The TDI has been set to protect all human populations for lifetime exposure, including the most vulnerable groups such as pregnant and lactating women, infants and young children.

t-TDI (temporary Tolerable Daily Intake) is allocated if there are uncertainties in the data that may be resolved by further studies and it is known that significant new data will be available in the near future.

[2] SML - specific migration limit for individual substance fixed on the basis of a toxicological evaluation. It is set according to the TDI established by the SCF/EFSA. To set the limit, it is assumed that, every day throughout lifetime, a person of 60 kg body weight consumes 1kg of food packed in plastics containing the substance at the maximum permitted quantity. SML is expressed in mg/kg food or food simulant [14].

SML(T) - specific migration limit (total) in food or food simulant expressed as total of a substance indicated.

DIETARY AND NON-DIETARY EXPOSURE TO BPA

Sources of BPA and migration

The general population can be exposed to BPA from dietary (food, drinking water) and non-dietary (dust, air, thermal paper, cosmetics, toys etc.) sources.

The studies on the exposure to BPA showed that diet is the main source in all population groups. This is due to migration of BPA into the food from food contact materials such as polycarbonate (PC) plastics and epoxy resins. Food contact materials as a potential source of exposure to endocrine disruptors, including BPA were discussed by many authors [16, 34, 37, 40, 46]. Specifically, BPA can be released from PC into food products as residual monomer present in the plastic and epoxy resins, as well as by hydrolysis of ester bonds of the polymer, a reaction that is catalysed by hydroxide when the polymer is in contact with aqueous food [15, 37, 45].

Epoxy resins are low molecular weight prepolymers or higher molecular weight polymers which normally contain at least two epoxide groups. Since the epoxy resins are produced by O-alkylation of BPA with epichlorohydrin to form BPA-diglycidyl ether (BADGE) they may also contribute to the external exposure to BPA *via* food and water. The applications for epoxy-based materials are extensive and include coatings, adhesives, multilayer packaging and plastic components for direct food and beverage containers and composite materials such as those using carbon fibre and fiberglass reinforcements [38].

The wide use of polycarbonate plastics and epoxy resins triggers common concerns on the possible BPA migration into canned foods and into food having the contact with tableware [5, 15, 27, 28, 33, 39, 64]. Another source of concern may be the potential migration of BPA from vessels into food during microwave heating or potential migration of BPA into drinking water due to the use of PC and of epoxy-phenolic resins in water pipes and in water storage tanks [38].

The migration of BPA from commonly used food packaging and PC feeding bottles into food simulants was studied by many authors [6, 15, 27, 41, 43, 45, 50, 54, 55, 56, 65]. *Simoneau* et al. [54] reported BPA below limit of determination (0.1 μg/kg) in 32 out of 40 baby bottles made from PC sold in the European market when tested with 50% ethanol (used as a simulant for milk) for two hours at 70 °C after boiling for five minutes. The highest migration value was 1.83 μg/kg and most of the bottles did not release detectable levels of BPA in the second or third migration test carried out with this simulant. Also S*antillana* et al. [50] tested 72 baby bottles, taken from the market in Spain, for BPA migration into 50% ethanol and 3% acetic acid, for two hours at

70 °C followed by 24 hours at 40 °C by. In this study the highest value found in the third migration test into 3% acetic acid was 18 μg/kg and it occurred in only one of all tested bottles.

Brede et al. [6] found that brushing and boiling polycarbonate baby bottles causes increased BPA migration into food simulants. The effect of washing procedures on BPA migration into water simulants was also investigated by *Hoekstra* and *Simoneau* [37] who did not confirm that brushing polycarbonate bottles may increase BPA migration or that the migration from older bottles may be elevated as compared to the new ones. The studies generally show that under typical use conditions, the potential BPA migration from polycarbonate plastic articles intended into contact with food is rather low [45, 55, 56]. It depends on the food simulants used in the experiment, temperature and contact time. Most literature studies report a release of BPA into food simulant (3% acetic acid) below the specific migration limit (0.6 mg/kg).

Food contact articles made from polycarbonates such as kettles, coolers and filters for water may be the source of the additional dietary exposure to BPA. Literature data retrieved by EFSA reported BPA migration from such articles as follows: for coolers with PC reservoir - 0.81 μg/L, PC water kettles – 0.11 μg/L, PC filters – 0.04 μg/L in water [23].

Dietary exposure

Based on the literature data [24, 47, 51] EFSA estimated that average exposure to BPA for breastfed infants aged (1-5 days), (6 days-3 months) and (4-6 months) is 0.225, 0.165 and 0.145 μg/kg bw/day and the high exposure is 0.435, 0.600 and 0.528 μg/kg bw/day, respectively [22]. In the case of formula fed infants aged 0-6 months dietary exposure was considerably lower (0.030 μg/kg bw/day for average exposure and 0.080 μg/kg bw/day for the high exposure) compared to breastfed children. These estimates were based on the assumption that non-PC feeding bottles and water containing low level of BPA were used to reconstitute the formula product. Potential dietary exposure to BPA estimates in different age groups of the general population is presented in Table 2.

For the population aged over 6 months and up to 10 years of age the estimated dietary exposure was considerably higher: ranging from 0.290 to 0.375 μg/kg bw/day (for average exposure) and from 0.813 to 0.857 μg/kg bw/day (for high exposure) (Table 2). This was mainly due to higher consumption of food and beverages per kilogram body weight. Additionally, the highest assessed dietary exposure for infants and toddlers from food contact articles was 0.086 μg/kg bw/day (0.014 μg/kg bw/day from PC tableware, 0.046 μg/kg bw/day from PC cookware and 0.026 μg/kg bw/day - from water coolers and PC filters into the drinking water. The contribution of BPA from non-dietary sources such as dust and toys for infants and toddlers was 0.015 μg/kg bw/day (Table 4).

The modelled dietary exposure for adolescents (10-18 years of age), adults (including women of childbearing age) and elderly ranged from 0.116 to 0.159 μg/kg bw/day (average exposure) and from 0.335 to 0.388 μg/kg bw/day (high exposure) (Table 2).

The above dietary exposure estimations show considerably lower exposure as compared to previous EFSA estimations in 2006 [20], where a very conservative approach was applied due to the lack of data for consumption of canned food levels and the estimated BPA concentration in these foods.

The FAO/WHO Expert Meeting [25] which estimated international exposure to BPA, considered a variety possible scenarios of model diets, combining consumption from the best-case scenario (25% consumption from packaged food) to the worst-case scenario (100% of consumption from packaged food). The 'best-case estimate' refers to the scenario that results in the lowest realistic exposure and the 'worst-case estimate' refers to such scenario that results in the highest exposure, representing the most conservative estimate.

The results of the estimated potential international dietary exposure to BPA according to different possible scenarios for different population groups is presented in Table 3.

Table 2. Dietary exposure to BPA estimates for different age groups of the general population [22]

Population	Average exposure (μg/kg bw/day)	High exposure 95% percentile (μg/kg bw/day)
Infants (1 - 5 days) - *breastfed*	0.225	0.435
Infants (6 days - 3 months) - *breastfed*	0.165	0.600
Infants (4 - 6 months) - *breastfed*	0.145	0.528
Infant (0-6 months) – *formula fed, non-PC bottle*	0.030	0.080
Infants (6 - 12 months)	0.375	0.857
Toddlers (1-3 years)	0.375	0.857
Children (3-10 years)	0.290	0.813
Adolescents (10-18 years)	0.159	0.381
Adults (18-45 years)	0.132	0.388
Adults (45-65 years)	0.126	0.341
Elderly (65 years and over)	0.116	0.375

Table 3. International dietary exposures to PBA estimates from model diets for different age groups of the population [25, 26]

Population	Mean exposure (μg/kg bw/day)	High exposure (95th percentile) (μg/kg bw/day)
Infants (0-6 months) *exclusively breastfed*	0.3	1.3
Infants (0-6 months) *Formula (powder-liquid), PC bottle (best case - worst case)* [a]	2.0 - 2.4	2.7- 4.5
Infants (0-6 months) *formula (powder-liquid), no PC bottle (best case - worst case)* [a]	0.01 - 0.5	0.1-1.9
Toddlers (6-36 months) *breastfed + solid food (best case - worst case)* [a]	0.1	0.3-0.6 [c]
Toddlers (6-36 months) *formula, PC bottle + solid food (best case - worst case)* [b]	0.5 - 0.6	1.6 - 3.0 [c]
Toddlers (6-36 months) *formula, no PC bottle + solid food (best case - worst case)* [b]	0.01-0.1	0.1-1.5 [c]
Children (over 3 years old) *(fruits, vegetables, meat, soups, carbonated drinks etc.) (best case - worst case)* [b]	0.2-0.7	0.5-1.9 [c]
Adults *(fruits, vegetables, grains, meat, soups, carbonated drinks, tea, coffee, alcoholic beverages etc.) (best case - worst case)* [b]	0.4-1.4	1.1-1.2 [c]

[a] Formula only, no breast milk

[b] Best case scenario - 25% of the food consumed was in the packaging manufactured with BPA and worst case scenario - 100% of the food consumed was in the packaging manufactured with BPA.

[c] Budget method scenario was used: maximum consumption is reported in these upper range of exposure estimates.

The average exposure to BPA of infants (0-6 months) exclusively fed with breast milk was estimated 0.3 μg/kg bw/day and the high exposure (at 95% percentile) was estimated to be 1.3 μg/kg bw/day. However, when for infants 6-36 months of age solid food was introduced exposure to BPA decreased relative to body weight. Generally, exposure to BPA was higher for infants fed with liquid formula compared with powdered formula and for infants fed using polycarbonate bottles with non-polycarbonate bottles [26].

More refined dietary exposure assessment for infants applied by the EFSA in 2015 was possible because of much better data availability than in 2006. This resulted from the use, at that time, of very conservative assumptions on BPA concentration in infant formula and to BPA migration from PC feeding bottles to account for the lack of data [19, 20].

Expert opinion draws attention to the fact that food is the major contributor of total exposure to BPA for most population groups.

Non-dietary exposure

The non-dietary sources of BPA considered in the assessment of exposure were air (indoor and outdoor), dust, cosmetics, thermal paper, toys and other articles which may be put into the mouth [3, 22, 26, 40].

The data on the migration of BPA from these sources is relatively small: for air 1 ng/m^3, for dust 1460 μg/kg, for cosmetics (eg. body wash, body lotions) – 31 μg/kg. Migration of BPA from toys into saliva over 24 h period – 0.14 μg/toy (for rattles) and 0.98 μg/toy (for pacifiers with PC shields) [22, 25, 32, 42]. The transfer of BPA from thermal paper to fingers was estimated to be 1.4 μg/finger considering 10 seconds of contact with such paper [22]. BPA from thermal paper, cosmetics and dust can be absorbed through the skin and by inhalation. In the European Union countries BPA is

Table 4. Non-dietary exposure to BPA (μg/kg bw/day) in different age groups of the general population [22, 26]

Source and route of exposure	Age group of population	Average exposure (μg/kg bw/day)	High exposure (μg/kg bw/day)
Thermal paper (dermal)	Infants (0-1 year)	not applicable	not applicable
	Toddlers (1-3 years)	not applicable	not applicable
	Children (3-10 years)	0.069	0.550
	Adolescents (10-18 years)	0.094	0.863
	Adults	0.059	0.542
Cosmetics (dermal)	Infants	0.005	0.009
	Toddlers	0.003	0.005
	Children	0.002	0.004
	Adolescents	0.003	0.005
	Adults	0.002	0.004
Dust (oral/ingestion)	Infants	0.009	0.015
	Adults	0.0006	0.001
Toys (oral/ingestion)	Infants	0.0002	0.0006
	Toddlers	0.00001	0.00001
Air (inhalation)	Infants & toddlers	0.0007	0.0014
	Adults	0.0002	0.0003

not permitted in cosmetics and is placed on the list of substances prohibited in such products [49]. However, if their packaging contains BPA it can migrate into the cosmetic products.

For non-dietary sources of BPA inhalation is a relevant route for air, ingestion and inhalation for dust and dermal exposure for thermal paper and cosmetics.

Data on the modelled estimates of non-dietary exposure to BPA for infants, toddlers, children, adolescents and adults according to source and route of exposure are presented in Table 4.

Thermal paper was the largest external non-dietary exposure to BPA in all population groups above 3 years of age (children, adolescents, adults) ranging from 0.094 to 0.863 μg/kg bw/day for average and high exposure, respectively. However, in children under 3 years of age dust was the largest source of exposure to BPA, ranging from 0.009 to 0.015 μg/kg bw/day for average and high exposure, respectively. Estimated the highest exposure to BPA for children under 3 years of age from cosmetics was from 0.005 to 0.009 μg/kg bw/day for average and high exposure, respectively and from toys less than 0.001 μg/kg bw/day [22, 26].

Taking into account the external exposure to BPA from all dietary and non-dietary sources it was showed that diet is the main source of exposure in all population groups. The second largest source is the thermal paper in all population groups above 3 years of age and dust for the children below 3 years of age.

Comparing the highest estimates for aggregated exposure from dietary and non-dietary sources show that the total exposure will be below the t-TDI (4 μg/kg bw/day).

TOXICOLOGICAL DATA

The controversy over the toxicity of BPA has been reflected in the reports of numerous organisations [17, 18, 20, 26] and critical reviews [35, 40]. *Hengstler* et al. [35] in his critical review of key evidence on the human health hazards of exposure to bisphenol A wrote: "Despite the fact that more than 5 000 safety-related studies have been published on Bisphenol A there seem to be no resolution of the apparently dead-locked controversy as to whether exposure of the general population to BPA causes adverse effects due to its estrogenicity". More recent studies in mice have shown that *in utero* exposure to small doses of the oestrogen-like BPA will result in an enlarged prostate and a reduced sperm count [58, 65]. Higher doses of BPA resulted in the opposite effects on the prostate. However, these 'low-dose' results were negated by *Cagen* et al. [7] and by *Ashby* et al. [1] leaving doubts on this mode of action and by *Ho* et al. [36] who concluded that exposure to environmentally relevant doses of BPA did not result in the induction of prostatic hyperplasia. The combined exposure to BPA and X-rays and BPA to somatic cells of the bone marrow and liver of mice shoved that exposure to X rays may magnify the genotoxic effect measured in the bone marrow lymphocytes by the comet assay [30].

The results of another study performed by *Chevrier* et al. [8] suggested that exposure to BPA during pregnancy was related to reduced total T4 hormone in pregnant women and decreased TSH in male neonates. The maternal BPA concentrations was associated with reduced TSH in boys ($p<0.01$) but not in girls. This association was stronger when BPA was measured in the third trimester of pregnancy. Overall EFSA has noted some clinical relevancy of the study as a cause of concern but not for qualifying them as critical for establishing a reference dose. *Fujimoto* et al. [29] did not found associations between serum BPA and oocyte fertilization and embryo cell number [4]. Also *Galloway* et al. [31] study on daily BPA excretion and possible associations with sex hormone concentration did not shed more light on the potential endocrine effects; rather showing weak associations for all observed effects.

For hazard identification, the effects of BPA on kidney and liver weight reported in rats and mice in multi-generation studies [59, 60] have been regarded by EFSA [22, 23]. In these studies on male mice, the increased kidney weight was associated with nephropathy at the highest BPA dose and mild changes in kidney in female mice but not associated with nephropathy. The possibility of the low-dose effects of BPA, based on *in vitro* and *in vivo* experiments and epidemiological studies [61, 62] have been taken into account in the assessment.

CONCLUSIONS

EFSA concluded that based on the current estimations of exposure to BPA for infants, children and adolescents, which constitute the highest exposure groups, is below the temporary TDI of 4 μg/kg bw/day. This means that no health concern may be expected at the estimated levels of exposure to BPA, including prenatal and elderly exposure. This opinion has also been extended to consider exposure to BPA from non-dietary sources (thermal paper, dust, cosmetics and toys). However, considerable uncertainties and data gaps were indicated, resulting in the following suggested recommendations for the future.

Exposure data:

- data on BPA concentrations in unpackaged foods,
- data on the use of food contact materials containing BPA, including specific geographical differences,
- the contribution of dermal exposure to overall exposure,

- studies on the frequency and extent of dermal contact with materials containing BPA.

Toxicology data:

- refining the Human Equivalent Dose approach to improve extrapolation of the results in experimental animals to humans, including the toxicokinetics of BPA,
- studies on the toxicokinetics of BPA following dermal absorption in humans and experimental animals,
- studies in the kidney to determine the mode of action of BPA in this organ,
- further research on the significance of proliferative and morphological changes in mammary glands.

Despite the fact that many research studies on risk assessments have been done, there is still not yet full agreement on the impact of bisphenol A on human health.

Conflict of interest

The author declares no conflict of interest.

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