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Update on Bisphenol A

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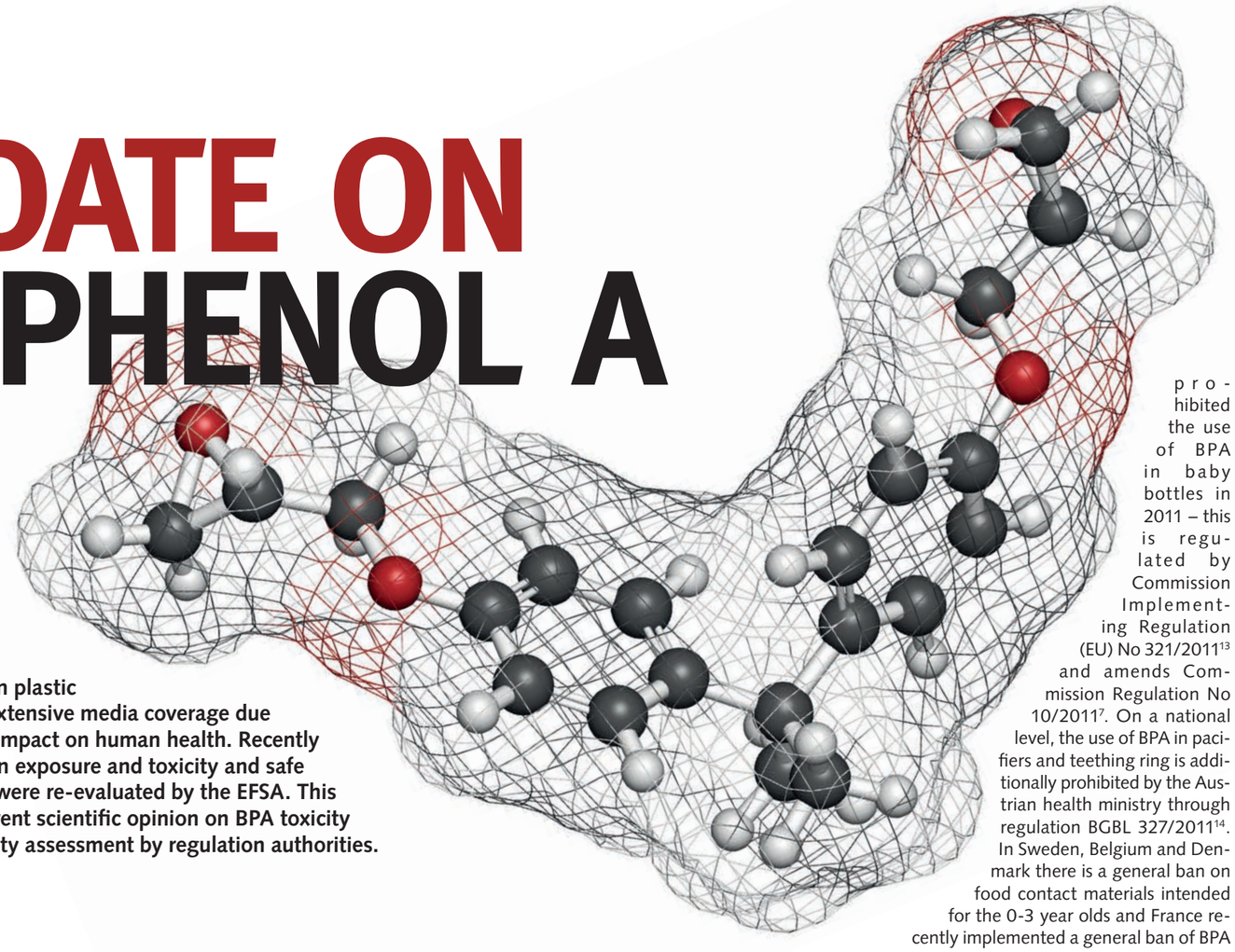
UPDATE ON BISPHENOL A



Bisphenol A (BPA) as a ubiquitous compound in plastic products has reached extensive media coverage due to its possible harmful impact on human health. Recently BPA-related concerns on exposure and toxicity and safe levels of incorporation were re-evaluated by the EFSA. This article presents the current scientific opinion on BPA toxicity and discusses the toxicity assessment by regulation authorities.

Wolfgang Gunzer

Bisphenol A is a ubiquitous compound[1] and is one of the most produced chemicals worldwide with an estimated production volume of 5.5 million tons in 2011[2]. It is widely used in consumer products and humans are exposed to Bisphenol A (BPA) via different ways such as food, air, dust and plastic products of everyday use[3,4]. Over the last decade food contact materials such as BPA has reached considerable scientific attention due to their possible harmful impact on human health especially in vulnerable groups such as infants and young children. Figure 1 highlights the exponential growth of research related to Bisphenol A from the 1990s to 2014.

In addition the European Food Safety Authority (EFSA) re-evaluated recently their previously released scientific opinions from 2006, 2008 and 2010 on BPA-related concerns (exposure and toxicity) and safe levels of incorporation and reduced the Tolerable Daily Intake (TDI) from 50 µg/kg bw per day to 4µg/kg bw per day[5]. The following sections will give a concise overview on the latest scientific results and opinions on BPA and the role of European-wide and international regulation authorities.

BPA IN FOOD CONTACT MATERIALS, AIN SOURCES, EXPOSURE

Bisphenol A is a widely used chemical compound for the production of polymers such as polycarbonate[3] and due to this the ways of exposition to humans are multiple[1]. Polycarbonate is used for different everyday products for example polycarbonate containers for food stuffs (storage containers, microwave ovenware, tableware) and beverages (resin cups, reusable bottles, baby bottles). BPA is also used on the inner side of metal food and beverage cans and thermal paper from cash register receipts[1;6]. The use of BPA and other permitted chemicals in food contact materials is regulated through European legislation (Commission Regulation No 10/2011; 7).

It is known that chemical substances (including BPA) can leach from plastic material and migrate in small amounts into food[1] - due to this specific migration limits (SML) exist. SML is defined as '…the maximum permitted amount of a given substance released from a material or article into food or food simulants'[7] and is 0.6mg/kg food for BPA[5]. Due to such migration mechanisms food and beverages are believed to be the main source for BPA intake in humans[8] and the use of BPA in food contact materials plays a vital role in the discussion. Others report that there is a controversy regarding total BPA exposure due to extensive use of BPA in thermal paper and other products of every-day use[8;9]. Migration processes of BPA from different plastic sources into food has been reported by several studies[10;11;12]: They showed that migration can be enhanced under some circumstances such as higher temperatures in heating and longer contact time between food and package material (canned products) and frequent reuse of containers.

As a result to keep contamination risk as low as possible for susceptible age groups such as infants, the European Commission prohibited the use of BPA in baby bottles in 2011 – this is regulated by Commission Implementing Regulation (EU) No 321/2011[13] and amends Commission Regulation No 10/2011[7]. On a national level, the use of BPA in pacifiers and teething ring is additionally prohibited by the Austrian health ministry through regulation BGBL 327/2011[14]. In Sweden, Belgium and Denmark there is a general ban on food contact materials intended for the 0-3 year olds and France recently implemented a general ban of BPA use for all food contact materials covering all age groups[15]. In the US the Food and Drug Administration (FDA) also banned the use of BPA in baby bottle production and furthermore the use of BPA in inner coatings of infant formula packaging[16;17]. Interestingly a recently published study from a Canadian research group found significantly higher urinary BPA levels in exclusively formula-fed infants than in mixed or breast-fed infants[18]. Figure 2 depicts mean BPA levels in different kind of foods and water and it can be seen that bottled water and canned foods may contain higher amounts of BPA than fresh foods, which was recently confirmed by Lorber et al.[19].

The recent review from the EFSA on BPA evaluated new data on dietary and non-dietary exposure in humans and found that intake of BPA from food is four to fifteen times lower than estimated nine years ago[5]. The estimation of total exposure levels of BPA among different age groups in general population is not easy to assess due to the multiple ways of exposure and the ubiquitous character of BPA. Total exposure levels are mainly estimated and are subsumed by the EFSA under the term 'aggregated exposure'[5]. Figure 3 depicts examples of BPA exposure levels from the recent EFSA report. It shows that the mean aggregated exposure levels in women (0.388 + 0.675 = 1.063µg/kg bw per day) and men (0.335 + 0.675 = 1.010µg/kg bw per day) is nearly equal. The aggregated exposure for children 3-10 years (0.813 + 0.445 = 1.258µg/kg bw per day) and adolescents (0.381 + 1.068 = 1.449µg/kg bw per day) is higher than those in adults. The EFSA concluded that in comparison to their newly proposed temporary TDI of 4µg/kg bw per day total BPA exposure levels are 4-times lower in general population. At this point it has to be said that the EFSA recognized that considerable uncertainties in estimation of non-dietary exposure levels exist[5].

BIOLOGICAL CHARACTERISTICS AND ADVERSE EFFECTS

BPA is known to have different cellular and molecular mechanisms in mammals and humans[8]. It is an endocrine disruptor (endocrine disrupting chemical – EDC) which means it can disturb endocrine function and it can interact with oestrogen receptors[1;4;6]. It is also known that BPA leads to altered cell signalling, genetic alterations and mitochondrial dysfunction[8]. EDCs may have endocrine functions at the same low doses as human endogenous hormones are present[20].

Due to its biological properties and molecular characteristics, BPA's potential harmful impact on humans has been extensively investigated – a large body of evidence is coming from animal studies and in vitro models[20]. Much less human data exist – mainly from epidemiological studies of human exposure measurements (measurement of urinary BPA levels). Biological effects from dose-related interactions with tissues come from animal studies. Studies examining the possible deleterious impact of BPA on human health have been extensively reviewed by several authors[8;9;20]. It has been summarised that BPA may have a negative impact on the (male and female) reproductive system, blunts the immune system, boosts oxidative stress and inflammation, and plays a role in the development of chronic and cardiovascular diseases[20]. A study from Wang et al.[21] showed for the first time a possible direct association between thyroid hormone function and urinary BPA levels in occupational exposed workers. In addition since foetuses, infants and children are most susceptible to exposure to BPA, there is broad consensus that this may lead to altered behaviour and neurobiological development[20]. However a recent study showed that neonates are able to effective metabolize BPA to its biologically inactive and readily excretable form BPA glucuronide[22].

Rezg and colleagues[8] argue that the evidence on the impact of BPA on human health in the case of human development and development of chronic diseases such as diabetes is not definitive but they conclude that it is robust enough to raise serious concerns. Similar conclusions were proposed recently by Mirmara and Evans-Molina[9] – They found from cross-sectional studies that urinary BPA levels are positively associated with obesity and diabetes, although they limit their findings due to quality issues and caveats in interpreta-

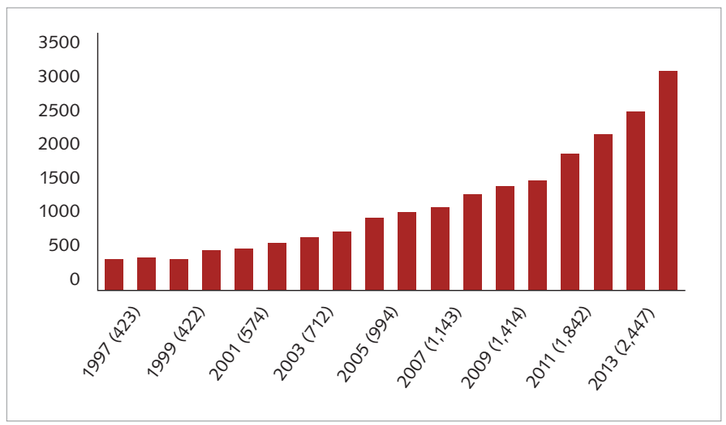


Figure 1: Number of scientific publications per year related to BPA (Data source: sciencedirect.com; search term: Bisphenol A; time range: 1997-2014).

tion of results. The FDA published a review on available new literature and found that there is a strong association between BPA exposure and cardiovascular disease-related factors, neurodevelopment and reproductive system[23]. Contrary to that the recent risk assessment from the EFSA found that there is only a weak association between BPA toxicity and named factors[5].

REGULATION AUTHORITIES AND TOXICITY ASSESSMENT

The recent re-evaluation of BPA toxicity and exposure levels lead to a reduction of the TDI to 4µg/kg bw per day and the EFSA stated that the estimated aggregated exposure levels in all age groups in the general population are 4 times lower and therefore there is no health risk[5]. But someone might have a critical look at the assessment of this new TDI – How did the EFSA established this new TDI? After reviewing the existing evidence on adverse BPA effects (hazard identification) the EFSA experts came to the conclusion that the only critical endpoints in BPA toxicity characterization are high-dose effects in kidney, liver and mammary glands in animals and took this into consideration[5]. The EFSA also stated that they found methodological shortcomings in so called low-dose studies so they did not took these results direct into consideration for the new value[5]. There are considerable issues regarding risk assessment of EDCs. In general toxicity assessment of substances often follows assumptions of a linear dose-response[3]. In the case of EDCs they follow a non-monotonic-dose response curve in the form of a 'U'-shaped curve (so called 'low-dose hypotheses')[20], which make it challenging assessing toxicity risk of BPA. Another issue is the possible different mode of action of BPA in different species[3]. For example a recent low-dose study by Barry-Delclos et al.[24] did not found any low-dose related adverse effects from BPA in rat models. They administered BPA from gestation day 6 through postnatal day 90 in doses below the NOAEL (2.5-2,700µg/kg bw/day) up to doses to 300,000µg/kg bw/day (as a control) to induce already known adverse effects from BPA with the aim to reveal adverse effects from BPA doses below the NOAEL[24].

So the EFSA used only the above stated endpoint from a two-generation mice study and did a Benchmark Dose calculation (BMDL10 of 8.960µg/kg bw per day). From this a Human Equivalent Dose (HED) was estimated (609µg/kg bw per day), which was the reference point for the new value. An uncertainty analysis was conducted and an overall uncertainty factor of 150 was then applied on the HED and resulted in the new value of 4µg/kg bw per day[5]. So it can be summarised that this new value is mainly based on results from few animal studies, and to take the results from all other (human and animal) studies into account they applied a high uncertainty factor to be on the "safe" side. Although it has been stated from others that results from low-dose studies are contradictory[25], it should be taken into account that endocrine disrupting chemicals such as BPA may exhibit greater effects at lower doses due to synergistic effects with other substances[4,8,19,20]. With this background The Danish National Food Institute evaluated the EFSA report a few weeks after publication and criticised the same points and found the EFSA uncertainty analysis insufficient[26]. They took results from low dose studies and the endocrine disrupting effects into account and proposed a much lower TDI of 0.7µg/kg bw per day[26]. Institutions from other EU member states such as the German Bundesinstitut für Riskobewertung (BfR) supported the recent EFSA conclusions[27].

*Note: This TDI was based on the NOAEL (No Observed Adverse Effect Level) of 5mg/kg body weight per day from rodent studies with an uncertainty factor of 100.

CONCLUSION

A lot of uncertainty due to numerous factors exists still to date in the risk assessment of Bisphenol A. The EFSA stated that no health risk exist to any consumer at current exposure levels. They reduced due to new and refined risk assessment methods the TDI to 4µg/kg of bw/day, although they found that there are no conclusive results from low-dose studies. In addition they say that the new TDI is provisional and will be reconsidered depending on the outcome of a long-term study in rats which is currently examined. This research conducted by the US National Toxicology Program is expected to bring new insights in BPA's toxicity[5]. Similar to that the US FDA also found uncertainties with low-dose toxicity studies in their recent review on BPA toxicity and did not reduce their current NOAEL (No Observed Adverse Effect Level) of 5mg/kg of bw/day23. To sum up, Mirmara and Evans[9] and Rochester[20] pointed out, that to define the impact level of BPA on human health accurately it is necessary a) to perform studies collecting longitudinal data to define BPA exposure in human tissue exactly and b) coupling it with prospective data of disease development.

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Drinking water (µg/dm³)	
Tap water (Europe, Asia, North America)	0.099-0.317
Bottled water (France)	0.07-4.21
Food (µg/kg)	
Cereals	1-3.8
Meat	0.49-56
Fish	7.1-102.7
Vegetables and fruits	11-95.3
Canned seafood	1-99.9
Canned vegetables and fruits	3.7-265.6
Tinned soft drinks	0.032-4
Milk	1.32-176

Figure 2: Different levels of BPA in drinking water and different food groups (adapted from 6)

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Age group	Exposure level	Dietary	Non-dietary			
		Oral	Oral	Dermal		Sum of non-dietary
		Food & beverage	Dust & Toys	Thermal paper	Cosmetics	
Children 3-10 years	A	0.290	0.003	0.053	0.008	0.064
	H	0.813	0.005	0.424	0.016	0.445
Adolescents 10-18 years	A	0.159	0.002	0.113	0.015	0.13
	H	0.381	0.003	1.036	0.029	1.068
Women 18-45 years	A	0.132	0.0006	0.071	0.012	0.084
	H	0.388	0.001	0.650*	0.024*	0.675*
Men 18-45 years	A	0.126	0.0006	0.071	0.012	0.084
	H	0.335	0.001	0.650	0.024	0.675

Figure 3: Examples of average (A) and high (H) exposure (µg/kg bw per day) levels from dietary and non-dietary sources to BPA in the different age groups of the general population (adapted from 5)