No health risk for consumers from Bisphenol A exposure - the BfR endorses the conclusion of the new EFSA assessment

BfR communication No. 005/2015, 19 February 2015

In January 2015, the European Food Safety Authority (EFSA) published a new opinion on the assessment of the health risks associated with Bisphenol A (BPA) in foods and from other, non-dietary sources. In this opinion, the EFSA experts conclude that based on the current scientific evidence and given the current levels of consumer exposure, BPA does not pose a health risk for any age group. This also applies to unborn children, infants and young adolescents. New data and more sophisticated methods have led the EFSA experts to significantly reduce the tolerable daily intake (TDI) for BPA - from 50 micrograms per kilogramme of bodyweight per day (µg/kg bw/day) to 4 µg/kg bw/day. In view of this new assessment, the highest estimates of the exposure derived from foods alone or in combination with other sources (diet, house dust, cosmetics and thermal paper) are 3 to 5 times below the new TDI value. Uncertainties regarding possible health effects of BPA on the mammary gland, the reproductive, metabolic and immune systems and in relation to neurobehavioural disorders have been analysed and taken into account in the calculation of the TDI. The TDI must be seen as a temporary value as long as the results of a long-term study on rats, a study which aims to eliminate those uncertainties, are still pending. The BfR welcomes the fact that extensive data from Europe was taken into account in the exposure calculation and, given the uncertainties of the overall BPA data situation, endorses the derivation of the new temporary TDI.

The scientific opinion of the EFSA consists of three documents: an overview (Executive Summary), an exposure assessment (Part I) and a toxicological risk assessment (Part II). Draft versions for Part I (2013) and Part II (2014) were published for public consultation and were discussed with stakeholders on the occasion of an EFSA stakeholder meeting. The information and comments obtained through this process have been taken into consideration in the final version of the opinion and have additionally been published in the form of a technical report along with the answers of the EFSA.

Part I contains the exposure evaluation for the different age groups of the population. For this purpose, the EFSA calculated the so-called “external exposure” via diet taking into account the consumption habits and the BPA contents in foods. To estimate consumers’ external exposure from other sources (e.g. thermal paper, cosmetic products and toys), the BPA release from these products was considered together with behavioural patterns such as the use and handling of these products. It is now clear that canned foods generally have higher BPA contents than fresh foods. Overall, food is the most important source of external BPA exposure, followed by thermal paper as the second-most important source - with the exception of children under 3 years old for whom house dust is the second-most important source. In terms of quantity, the absorption of BPA through inhalation only plays a minor role.

In addition, the EFSA also estimated the exposure to the toxicologically active, free (i.e. non-metabolised) BPA, the so-called “aggregate exposure”, taking into account the specific toxicokinetics for the different routes of exposure. Since the magnitude of BPA detoxification varies depending on the route of exposure (oral, dermal), the EFSA has converted the external dermal exposure to BPA (e.g. from thermal paper) into oral equivalents, thereby making it possible to add these values to the dietary exposure estimates. Based on the aggregated exposure estimates, the EFSA has, by making conservative (worst-case) assumptions for children aged 3 to 10 years, calculated a maximum daily BPA intake of

about 1.3 micrograms per kg of bodyweight. For younger children, the EFSA expects a significantly lower intake. The maximum aggregate exposure for all age groups is 1.5 micrograms per kg of bodyweight and day.

In addition, the EFSA has estimated the so-called “internal exposure” to total BPA (i.e. free plus conjugated BPA) from all sources and over all routes, taking into consideration the lower absorption rate for the dermal route in comparison to the oral route. This internal exposure to total BPA was then compared with the results from human biomonitoring studies on the urinary excretion of the absorbed BPA. Data from the Environmental Survey for Children (Kinder-Umwelt-Survey) conducted by the German Federal Environmental Agency (Umweltbundesamt) were incorporated in the analysis of the biomonitoring data as well. A comparison of both approaches showed that the internal exposure estimates agreed well with the estimates from the human biomonitoring. This allows the conclusion that no significant exposure sources were overlooked in the calculation of internal exposure.

The BfR welcomes these estimates, which are based on extensive data from Europe, as a reliable compilation and weighting of possible BPA exposure sources.

In Part II, the EFSA evaluated the results from epidemiological, animal experiment and cell culture studies based on extensive research of the relevant literature. Taking a so-called Weight of Evidence approach, the EFSA then determined the relevance of these findings for human health. It was emphasised that BPA is “likely” to have health-relevant effects on the kidneys, liver and mammary glands. In contrast, other BPA effects (i.e. effects on reproduction and development at low doses, adverse effects on the neurobehavioural, metabolic, immune and cardiovascular systems, and mutagenic and carcinogenic effects) were rated as less likely. The BfR already agreed with the assessment of the effects on the liver and kidneys in the past. More recent animal experiments conducted in the last few years have put a renewed focus on mammary gland changes.

Recent studies on the toxicokinetics of BPA in different test animal species have been crucial for the extrapolation of data from animal studies to humans. These notably revealed a faster BPA metabolism in mice compared to humans. On the basis of these new insights, the EFSA has derived a conversion factor for the comparison of the exposure of mice and humans to the toxicologically active, free BPA. This experimentally determined, BPA-specific factor for the toxicokinetic differences between mice and humans was used instead of the usual uncertainty factor. It was thus possible to calculate, on the basis of an oral BPA dose which is harmless to mice, a corresponding (equivalent) dose for humans (“Human Equivalent Dose”, HED).

The evaluation by EFSA of the toxic effects of BPA on the kidneys and liver of rodents has not changed fundamentally. Already in its opinions of 2006 and 2010, the EFSA used the kidney effects from a multigeneration study in mice as a basis for its assessment. The newly introduced reduction in the tolerable daily intake (TDI) as compared to earlier EFSA opinions is due to the following changes: the current derivation used a new statistical method (benchmark dose approach) to establish the critical dose for the kidney effects in mice. The dose thereby established was then converted into an HED by means of the factor determined from the new toxicokinetic data. The HED thus derived amounts to 609 micrograms per kg of bodyweight and day and was used as a reference point for determining a temporary tolerable daily intake (t-TDI).

The possible occurrence of so-called low-dose effects (i.e. changes in the mammary gland, immunological, metabolic and reprotoxic effects as well as neurobehavioural effects) would

no longer be covered, if the usual uncertainty factors for interspecies extrapolation and intra-individual variability were used. For this reason, uncertainty analyses were conducted for the purpose of assessing these low-dose effects. These analyses took into account the reliability of the study results. In addition, the relevance of the reported effects in animals for humans was also considered. From an HED of 100 micrograms per kg of bodyweight and day upwards, the occurrence of changes in the mammary glands and other low-dose effects could no longer be reliably ruled out. This HED was then taken into consideration in the derivation of the t-TDI, i.e. the EFSA even incorporated study results with yet unclear relevance for human health in its risk assessment of BPA.

TDI values are usually derived with uncertainty factors (UF) which are applied to the reference point. Since the HED already makes allowance for toxicokinetic interspecies differences, it is sufficient to take into account only the UFs of 2.5 for the toxicodynamic difference between the species and of 10 for the variability in the human population. This results in an overall UF of 25 to which an additional factor of 6 was applied in order to take into consideration possible low-dose effects at an HED of 100 micrograms per kg of bodyweight and day or higher. The HED value for the reference point (kidney effects: 609 micrograms per kg of bodyweight and day) was thus divided by an overall factor of 150. This results in a t-TDI of 4 micrograms per kg of bodyweight and day.

In view of the uncertainties in the overall data situation on BPA, the BfR endorses the derivation of the t-TDI.

In the context of the temporary validity of the TDI, the EFSA draws attention to the studies on BPA currently undertaken in the USA (by the NTP/FDA). The aim of these new studies (including a two-year study in rats with prenatal exposure and toxicokinetic studies in humans with oral and dermal exposure) is to further clarify the current uncertainties with regard to mammary gland effects and also concerning those low-dose effects that have been categorised as less likely by the EFSA.

Assuming a worst-case scenario of aggregate high exposure (food plus other sources) the BPA intake of consumers is approximately between 1 and 1.5 micrograms of BPA per kg of bodyweight per day. This means that for all population groups - including children, adolescents and women of child-bearing age - the BPA intake values are below the EFSA-derived t-TDI value of 4 micrograms per kg of bodyweight per day.

The crucial point for exposure to BPA from food contact materials is the statement of the EFSA that the risk for human health is low, since consumer exposure to BPA is below the temporary TDI value (t-TDI).

The decision whether the t-TDI laid down by the EFSA is to be used as a basis for a new specific migration limit or, if applicable, for other regulatory measures in the EU regulation on plastic materials and articles intended to come into contact with food lies with the EU Commission and the member states.

Further information

FAQs on bisphenol A in consumer products
BfR FAQ
http://www.bfr.bund.de/en/frequently_asked_questions_on_bisphenol_a_in_consumer_products-60837.html

Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs

EFSA Journal 2015;13(1):3978 doi:10.2903/j.efsa.2015.3978
http://www.efsa.europa.eu/de/efsajournal/pub/3978.htm