Background briefing on process of EFSA draft health assessment of BPA

EFSA conducted a comprehensive and systematic weight-of-evidence approach

EFSA looked at over 450 studies in a fully transparent process: the large guideline studies that already formed the basis for their 2006 opinion, those that were specially pointed out to them by critical groups such as the French NGO Réseau Environnement Santé (RES), as well as studies that became available more recently. A table lists each individual study with their strengths and weaknesses, any additional points to be mentioned, and the influence on likelihood of evidence as judged by the EFSA experts (page 425ff). Based on the evaluation of these studies EFSA defines the high quality guideline studies and a recent comprehensive NCTR/FDA study as the most reliable studies for their risk assessment, and uses these studies as a point of departure for their assessment. In the subsequent evaluation, EFSA chose the most conservative approach, and applied a sophisticated, and highly conservative, assessment method on the data.

EFSA assessed toxikokinetic study data on BPA

Toxikokinetic studies investigate the „behaviour" of a substance in the body, for example, what parts of the body or organs the substance may enter (e.g. fat, liver etc.), whether or not it is expected to be metabolized or excreted, and at what rate (absorption, distribution, metabolism and excretion). Toxicokinetic studies are also used for establishing relationships between experimental exposure in animals and the corresponding exposures in humans. Such studies are complex and costly, and not normally available for chemical substances. However, for BPA, a number of such toxikokinetik studies have been done in the past years. EFSA referred specially to three studies done by scientists of the US FDA NCTR in mice, rats, and monkeys, confirming efficient metabolism of BPA in all species investigated (*Doerge, 2010a, 2010b, 2011).

EFSA ranked all studies based on potential association of BPA to a particular health effect

EFSA looked at all endpoints investigated in the studies, and grouped them into areas. Then EFSA looked into each of these clusters in more detail, to assess, based on all available studies, whether a potential association between exposure to BPA and particular effects could be identified. The likelihood of such association of effects was classified in a six-staged ranking system, reaching from „very likely" to „very unlikely". This system is quite comparable to the one used by the US Center for Risks of Human Reproduction (CERHR), or to weight of evidence assessments in the medical arena.

In context of the overall weight of scientific evidence EFSA judged association with reproduction and fertility, brain and behavioural development, immune, cardiovascular, metabolic, genotoxic and carcinogenic effects to be "less than likely". These areas were therefore not specifically considered in the following human health assessment, but *are* explicitly mentioned to be covered by the conservative t-TDI.

Three areas were classified to show „likely" associations: liver, kidney and mammary gland (the latter with a larger amount of uncertainty on the likelihood) – although not at dose levels relevant to human exposure. It is important to note that with this assessment EFSA does not indicate a "likely" risk for humans but only defines the starting point for their risk assessment. The EFSA experts indicated that the "likely" associations on liver, kidney and mammary gland should be further risk assessed. This is because they considered that it is "likely" that an effect on the above mentioned organs might occur if animals are exposed to very high doses, i.e. doses above 3.6 mg/kg/day, 1000-fold above the t-TDI.

EFSA deliberately selected the most sensitive data for its assessment

EFSA identified general toxicity as the most sensitive endpoint (like in their previous assessments). For the three „likely associations" EFSA identified the lowest effect levels seen in the mouse (kidney 3.6 mg/kg bw/d,) and defined this dose as a starting point for their risk assessment. Effects on liver and mammary gland are only observed at substantially higher doses. This starting point is therefore considered to be conservative and covers all other endpoints. In effect, this low baseline ensures that any remaining uncertainty is covered in the evaluation.

It is interesting to note that the level defined by EFSA was the lowest level measured in a comprehensive two-generation study in one generation of adult male mice only, and only in the parent generation, not in their offspring. The values of the offspring or of the pregnant mother are

substantially higher in this study, indicating that EFSA took a very low value as a starting point for their risk assessment.

In addition, if EFSA would have taken toxikokinetic data from neonatal mice, or other species such as rat or monkey – in each case, the resulting TDI would have been even higher than the current one of 50 microgram/kg bw/d. However, again, EFSA deliberately selected the very most sensitive datapoints available to base their assessment on.

Transfer of data from mouse to human: EFSA used a more conservative baseline compared to previous assessment to calculate human equivalent dose

The toxikokinetic data provide a deeper understanding of the behaviour of BPA in the body, and also enable a more concrete calculation of the human equivalent level. Based on the most protectively defined low benchmark dose level (3.6 mg/kg bw/d), and the most conservative toxikokinetic factor reported in animal experiments (of 32) to convert the animal data into human relevance, EFSA calculated the so-called „human equivalent dose" to be 113 microgram/kg bw/day.

EFSA applied a high safety factor to manage uncertainties

In every scientific process, uncertainties or open questions will – by nature of science - always remain. Given the large amount of available scientific information on BPA, such remaining uncertainties however do not give any rise to concern for human health – otherwise EFSA would clearly have reacted much differently. The standard safety factor to account for uncertainties is 100 (10 for inter-, and another 10 for intra-species-variabilities). This safety factor is also included in the current TDI of 50 microgram/kg bw/d.

In its new assessment, EFSA applied a more conservative overall assessment factor of 800; after final rounding to derive a one-digit value for the t-TDI the overall resulting safety factor is 740:
EFSA uses a factor of 32 for toxikokinetic differences between mice and humans to define the human equivalent dose, a remaining inter-species factor of 2.5 and an unchanged factor 10 for intra-species variability, resulting in a remaining uncertainty factor of 25. Both values multiplied lead to an overall assessment factor of 800 and a very protective TDI of 4.52 microgram/kg bw/d, which is rounded up to 5 microgram/kg bw/d, thus including a final safety factor of ~740.

EFSA derived a highly conservative and overprotective t-TDI to cover all uncertainties, even the „less than likely" ones

In 2006, EFSA defined 5 mg/kg bw/d as lowest level to work with (the „starting point", also called NOAEL – no adverse effect level). Applying a safety factor of 100 resulted in the TDI of 50 microgram/kg bw/day.

The new temporary-TDI was derived by applying the remaining uncertainty factor of 25 on the „human equivalent dose" (HED), which was derived using a benchmark model in animal studies.
HED 113 microgram/kg bw/day divided by 25 = 4.52, i.e. ≈ t-TDI 5 microgram/kg bw/d.

After having derived the t-TDI, EFSA cross-checked with the values of each of the other endpoints to make sure no single endpoint was overlooked, and to confirm that the human equivalent dose used as starting point for all discussions would cover all other areas of potential toxicity. Given the extremely conservative approach in deriving such a highly protective TDI, EFSA concludes that this t-TDI covers also remaining uncertainty related to the endpoints liver and mammary gland as well as those endpoints which were considered „less than likely".

Therefore, the substantially reduced t-TDI is neither a result of increased uncertainty, nor of new scientific data that would have risen the concern. On the contrary: EFSA derived the t-TDI using worst case data (the most sensitive endpoint: kidney toxicity, in the most sensitive species: mice, at the lowest reported benchmark level derived in the first generation in a comprehensive study investigating three generations), and applying a modern, sophisticated mathematical model to define a benchmark dose to calculate the human equivalent dose (very conservative conversion factor from animal to humans). Still, the exposure of all groups of the population, including the most sensitive and the most highly exposed ones, is well below even this substantially reduced t-TDI. We therefore understand the fact that EFSA decided to amend the established safe intake levels for BPA as a sign of an abundance of caution at EFSA.

If there is reduced uncertainty based on the toxikokinetic data, why is the t-TDI so substantially reduced?

Uncertainties in the previous data could be reduced by new toxikokinetic data – therefore the previously used uncertainty factor of 100 could be reduced to 25. The new t-TDI is therefore more solid and provides high security for all age groups and exposure scenarios.

New and better comprehensive toxikokinetic animal data enabled EFSA to define a human equivalent level. The availability of new toxikokinetik data (which were not available in the previous EFSA assessment), provided a better understanding of the behaviour of BPA in the metabolism. EFSA evaluated these new toxikokinetic data and lowered the remaining overall uncertainty in their assessment by applying a worst-case animal-human conversion factor based on animal experiments.

Toxikokinetik studies on BPA are available in three animal species: in mouse, rat and monkey. The monkey test-system is the one most near to the human system, while the mouse system is the most far away. Authorities have a scope of discretion as to which system/data to select. EFSA choose the mouse, thus being consistent with previous European risk assessments of BPA which also used the mouse test-system as reference.

The specific data starting point used by EFSA (adult mouse) lead to an adjustment of the previously used animal-human conversion factor. (4->32).

By using the most sensitive data point from the mouse test system as starting point and calculating a benchmark level using the increased animal-human conversion factor, the new t-TDI was derived. EFSA used in each assessment step the most protective scenario, resulting in a „very conservatively derived“ t-TDI.

The new t-TDI is scientifically very conservative and provides solid protection, as it is further substantiated by new scientific data. Earlier uncertainties due to lacking scientific knowledge have been substantially reduced. During the evaluation of the available studies an extremely conservative approach was taken by EFSA and therefore, the new t-TDI should be regarded as highly protective. Still, all age groups and exposure scenarios are well below even the t-TDI.

The new TDI for BPA is based on a large safety factor and is temporary

A „temporary TDI“ is established for a specified, limited period of time to enable additional biochemical, toxicological or other data to be obtained as may be required for estimating a tolerable daily intake. A temporary TDI involves the application of a safety factor larger than that used in establishing a permanent TDI. http://www.codexalimentarius.net/pestres/data/reference/glossary.html

EFSA defined the new safety value as temporary TDI pending the outcome of the long-term study in rats involving prenatal as well as postnatal exposure to BPA, which is currently being undertaken by the US National Toxicology Program (NTP). This study will also clarify open questions re mammary gland effects. We would expect that EFSA would re-consider and decide on a permanent TDI once these data have become available for regulatory assessment.

Uncertainty factor

EFSA default (2006)	New EFSA draft assessment (Jan 2014)
Interspecies variability: 10 ***4 (toxicokinetic)*** x 2.5 (toxicodynamic, also called „additional uncertainty“) = 10	**Inter**species variability: 80 ***32 (toxicokinetic data adult mouse)*** x 2.5 (toxicodynamic, also called „additional uncertainty“) = 80
Intraspecies variability: 10	**Intra**species variability: 10
uncertainty factor => 10 x 10 = **100**	**overall assessment factor** => 80 x 10 = **800**

TDI

EFSA default (2006)	**New EFSA draft assessment (Jan 2014)**
starting point: 5000 microgram (NOAEL) (NOAEL = no adverse effect level)	starting point**: 3600 microgram** (BMDL10 adult mouse) (BMDL = benchmark dose low)
	Human equivalent dose (HED): **113 microgram** (3600 ./. 32 = 112,5 -> ≈ 113), already includes the toxikokinetic data
Uncertainty factor: 100	**Remaining uncertainty factor 25** (800 ./. 32 = 25; due to availability of toxicokinetic data)
5000 ./. 100 = **TDI 50 microgram/kg bw/d**	113 ./. 25 = 4.52 i.e. **≈ t-TDI 5 microgram/kg bw/d.**
Safety factor: 100	Safety factor: 740

* Doerge DR, Twaddle NC, Vanlandingham M and Fisher JW, 2010a. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology, 247, 158-165.

Doerge DR, Twaddle NC, Vanlandingham M and Fisher JW, 2011. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicology Letters, 207, 298-305.

Doerge DR, Twaddle NC, Woodling KA and Fisher JW, 2010b. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology, 248, 1-11.