Follow-up Meeting on the Web-Based Public Consulting on Bisphenol A

Brussels, April 23 2014

Comments from PlasticsEurope

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Overview

- EFSA's conclusion is based on a comprehensive, transparent and sound Weight-of-Evidence approach
  - All relevant data are systematically evaluated
  - Low-dose effects/NMDR curves were neither consistent nor corroborated
  - Estimated dermal exposure is adequately conservative
- Opportunities are available for improvement
  - EFSA's benchmark dose analysis should be refined
  - More scientifically defensible Human-Equivalent-Dose-Factor (HEDF) values are available
- **Overall, EFSA Should**
  - **Retain the Current TDI of 50 µg/kg/day**
  - **Re-evaluate and finalize the TDI once the results of anticipated significant FDA and NTP studies are available**

EFSA's Hazard Identification Process Is Sound

- Hazard identification process is thorough and well documented
  - Comprehensively included all relevant animal and human studies
  - Both positive and negative studies included
  - Strengths and weaknesses of each individual study consistently evaluated
  - Assessed whether specific effects were corroborated and cohesive within and among studies
- Defensible selection of critical toxicological effects for hazard characterization
  - General toxicity endpoints (i.e., kidney and liver weight) are appropriate
  - Mammary gland effects are not suitable based on FDA/NCTR's large-scale subchronic study*
    - Effects reported in Murray et al. (2007) exploratory study were not confirmed and methodology found to be highly variable
    - Recent gene-expression data in mammary gland

* Murray et al. 2007. Reproductive Toxicology. 23(3):383-390; NCTR GLP/NTP Technical Report for Project No. 2176.01. PI K. Barry Delclos – May 2013; and Basavarajappa et al. 2014. SOT Poster

Low-Dose Effects/NMDR Curve Not Corroborated

- EFSA applied its data quality assessment and WoE approach to studies reporting low-dose effects and nonmonotonic dose response (NMDR) curves
- EFSA noted that the low-dose/NMDR studies:
  - Lacked a well described dose response curve
  - Observed statistically significant effects for only one or two doses
  - Reported inconsistent study results
  - Were not corroborated by two multi-generation studies and US FDA/NCTR's large-scale subchronic study, all three of which reported only monotonic dose-responses and no low-dose effects
- As EFSA noted, until low-dose/NMDR findings are substantiated, they should not be included in a WoE assessment
  - EFSA's conclusion is consistent with other government agencies worldwide

BMD Analysis is Appropriate, But Can Be Improved

- Use of benchmark dose methodology to establish a Point of Departure is appropriate
  - Accounts for shape of dose-response curve
  - Less sensitive to actual dose levels tested

- Selection of benchmark response (BMR) = 10% change in kidney weight is valid
  - The effect level of BPA is driven by systemic toxicity
  - Less than 10% kidney weight change not considered adverse
  - BMR = 5% change is within range of normal variability
  - Standard alternative approach to select BMR (one control SD from the control mean) supports the use of BMR = 10%

BMD Analysis is Appropriate, But Can Be Improved

- Several opportunities available to improve EFSA's BMD analysis:
  1. "[I]ndividual observations should ideally serve as the input for a BMD analysis" (EFSA, 2009)
     - EFSA analysis relied on available summarized data (mean, SD)
  2. Analyze average kidney weight adjusted for body weight
     - No biological basis for difference between left and right kidneys
     - Accounts for concurrent effects on body weight
  3. Most importantly, independent analysis of each dataset to identify best statistical fit with lowest uncertainty
     - Combined analysis distorted by lack of F1 female dose-response and high F1 male variability
     - Female mice less sensitive than males; will not drive the outcome
     - Very good statistical fit with low uncertainty for F0 males
- Recommended $BMDL_{10}$ values for F0 males range from 23.5 (PROAST) – 35.6 (BMDS) mg/kg-bw/day

Analyses Show More Appropriate HEDFs

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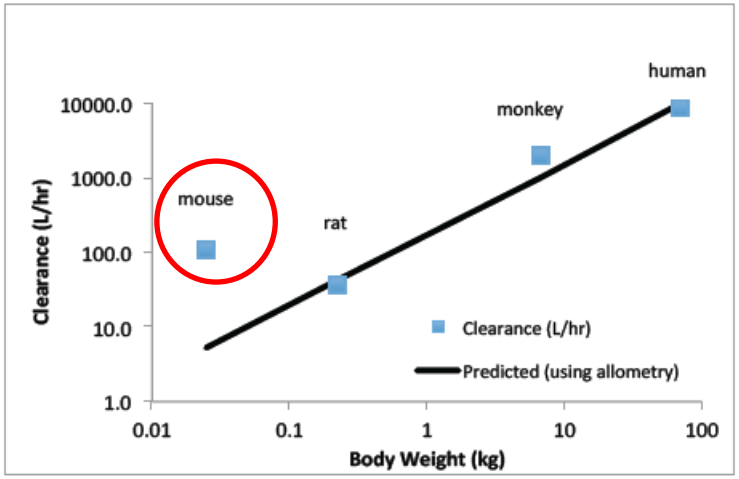
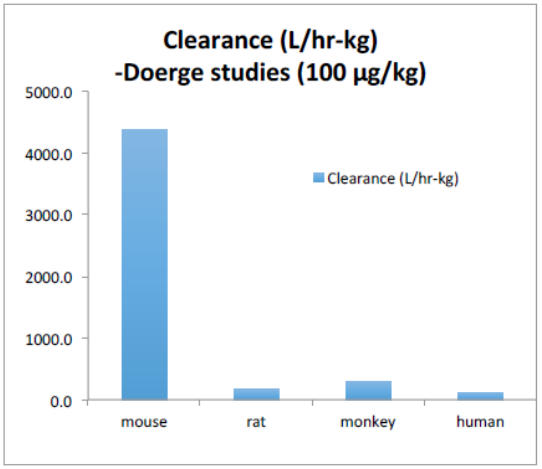
Analysis 1 – Unconjugated BPA HEDF = 0.6

- EFSA assigned "zero unconjugated BPA" to samples below the LOD in Doerge 2011
  - Result is significant underestimate of AUC for mice
  - Clearance estimates reveal significant, unexplained inter-species inconsistency





- Allometric relationship between clearance and body weight provides sound alternative approach
  - Predicted clearance of unconjugated BPA in mice = 206 L/hr-kg and AUC = 2.1 nmol-hr/L
  - HEDF = 0.6, which is more consistent with the HEDF derived from rats (0.42) and monkeys (0.72)

Analyses Show More Appropriate HEDFs

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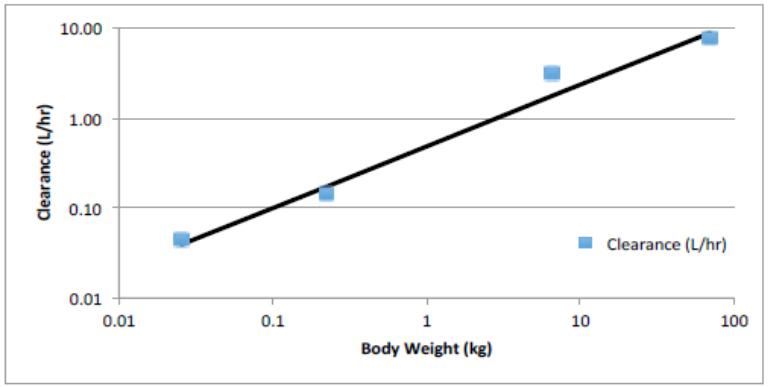
Analysis 2 – Total BPA HEDF = 0.06

- Reliable total BPA AUC values for humans and mice are available
  - Mice: 247 nmol--hr/L from Doerge 2011; not limited by analytical LOD
  - Humans: 4000 nmol-hr/L from Völkel 2002 (calculated from reported clearance)
- Total BPA clearance estimates show concordance across species, as expected:



- HEDF based on total BPA is 0.06

Therefore, a more scientifically defensible Human-Equivalent-Dose-Factor is between 0.06 (for total BPA) and 0.6 (for unconjugated BPA)

EFSA Should Retain the Current TDI

- Based on the $BMDL_{10}$ and HEDF values presented, a range of scientifically defensible TDI values are possible.*

(HEDF x $BMDL_{10}$)	÷	25	=	**TDI**
(0.6 x 35,599)	÷	25	=	**854 µg/kg-bw/day**
(0.6 x 23,530)	÷	25	=	**565 µg/kg-bw/day**
(0.06 x 35,599)	÷	25	=	**85 µg/kg-bw/day**
(0.06 x 23,530)	÷	25	=	**57 µg/kg-bw/day**

- EFSA should reconfirm the current TDI of 50 µg/kg-bw/day as a temporary TDI, which is supported by:
  - Range of defensible TDI values above 50 µg/kg-bw/day
  - Significant ongoing research available in near future from FDA and NTP**

* All of the TDI values are calculated with an uncertainty factor of 25 as used in the Draft Opinion.
** Schug et al., 2013. Reproductive Toxicology. 40:35-40.

Conclusion

EFSA FAQs, January 2014: "*EFSA finds there is no health concern as the highest estimates for combined oral and non-oral exposure to BPA are 3-5 times lower than the proposed TDI*" *

- The approach taken by EFSA to characterize hazards and establish a TDI is scientifically sound, but does not justify a revision of the TDI at the present time.

- Overall, it is most appropriate for EFSA to:
  - **Reconfirm the TDI of 50 µg/kg-bw/day as a temporary TDI**
  - **Re-evaluate and finalize the TDI once the results of anticipated significant FDA and NTP studies are available**

*http://www.efsa.europa.eu/en/faqs/faqbisphenol.htm?wtrl=01

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Thank you

Backup

US FDA: “Is BPA safe? Yes.” (June 2013)

How does FDA regulate BPA?

The agency regulates all food packaging materials from which components can reasonably be expected to migrate into a food. The original authorizations for food contact uses of BPA were issued under FDA’s food additive regulations. In general, FDA now reviews food contact substances under a notification process, which is manufacturer specific. For all food contact materials, there must be sufficient scientific information to demonstrate that the use of the substances is safe. . . . .

Is BPA safe?

Yes. Based on FDA’s ongoing safety review of scientific evidence, the available information continues to support the safety of BPA for the currently approved uses in food containers and packaging. People are exposed to low levels of BPA because, like many packaging components, very small amounts of BPA may migrate from the food packaging into foods or beverages.

http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm355155.htm

Food Safety Authorities Consistently Assess BPA as Safe

Japanese Ministries MHLW, METI (2001/2004/2005/2011)

Food contact materials based on BPA are safe for their intended uses.

http://www.aist-riss.jp/main/modules/product/index.php?content_id=73&ml_lang=en

U.S. Food and Drug Administration (2005/2007/2008/2010/2012/2013)

No evidence of harm to children or adults from the current levels of BPA-exposure, and at the same time provided guidance on how parents can minimise infant exposure to BPA if they choose to do so

"FDA's current assessment is that BPA is safe at the very low levels that occur in some foods."

http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm

Health Canada (2008/2009/2010/2012)

"[…] current dietary exposure to BPA through food packaging uses is not expected to pose a health risk to the general population, including newborns and young children."

http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/bpa_hra-ers-2012-09-eng.php

Canadian government officially added BPA to Schedule 1 of the Canadian Environmental Protection Act (CEPA)

United Kingdom

(October 2012)

"We are advised by the Food Standards Agency (FSA) that in its view and in line with international scientific consensus, low dose exposure to Bisphenol A (BPA) from food contact materials does not represent a health risk to consumers, including potentially vulnerable groups."

http://www.publications.parliament.uk/pa/cm201213/cmhansrd/cm121015/text/121015w0006.htm/

Food Safety Authorities Consistently Assess BPA as Safe

Germany

(March 2014)

"Entscheidend für die Bewertung des BfR ist die Aussage der EFSA, dass das Risiko für die menschliche Gesundheit gering ist, da die Verbraucherexposition gegenüber Bisphenol A unterhalb des vorläufigen TDI-Werts (t-TDI) liegt."

http://www.bfr.bund.de/cm/343/fragen-und-antworten-zu-bisphenol-a-in-verbrauchernahen-produkten.pdf

Hong Kong

December 2011

"According to risk assessments on BPA by food safety authorities in Europe, USA , Canada , Australia and New Zealand, the amount of BPA that people including infants currently absorb from all food and drinks is very low and is not expected to pose a health risk."

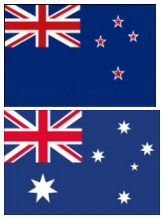
http://www.cfs.gov.hk/english/programme/programme_rafs/programme_rafs_fc_02_17.html

Switzerland

December 2011

"The BAG has evaluated the scientific reports of various food safety authorities and believes that the exposure to bisphenol A from food represents no risk for consumers. This also applies to newborns and infants."

http://www.bag.admin.ch/themen/lebensmittel/04861/06170/index.html?lang=de



Australia
New Zealand

April 2014

"…the overwhelming weight of scientific opinion is that there is no health or safety issue at the levels people are exposed to."

"Replacing long standing, extensively studied chemicals with newer alternatives with a more limited safety database does not necessarily lead to safer products."

http://www.foodstandards.gov.au/consumerinformation/bisphenolabpa/

http://www.foodstandards.gov.au/_srcfiles/BPA%20paper%20October%202010%20FINAL.pdf