U.S. FDA Comments on EFSA's Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs

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at the

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Methods

Comprehensive, detailed evaluation

Appropriate methodology

- Clear criteria for hazard identification and risk assessment
- Standardized critique of individual studies
- Comprehensive Weight of Evidence (WoE) for individual and related endpoints
- Use and discussion of toxicokinetic and pharmacokinetic data in reducing uncertainty

Hazard Assessment

Overly-conservative approach

- Weighted endpoints more toward “likely” than in previous EFSA assessments
- Carried over concern for certain endpoints into risk assessment consideration despite not identifying concern (or likely effects) for the endpoints in the hazard assessment
- Balanced overly-conservative conclusions of the hazard assessment with uncertainty discussion

Uncertainty

Evaluating uncertainty invaluable in characterizing confidence in conclusions

Uncertainty in current EFSA hazard evaluation increased despite new data

- Multiple species pharmacokinetic/toxicokinetic evaluations
- Advances in analytical methods
- Toxicological studies

EFSA evaluation limited its application of new data in reducing the levels of uncertainty

Uncertainty

Analytical methods and pharmacokinetics

- Identified clear potential and sources for testing and sample contamination
  - May decrease uncertainty around conflicting results from studies not addressing or measuring potential contamination
  - Reduces uncertainty in inter-species extrapolation as well as bio-monitoring reports

Toxicology

- NCTR GLP / NTP Technical Report E2176.01: evaluated wide range of “low” doses and endpoints across multiple systems
  - No clear treatment-related effects were observed in the low-dose range of the study

NMDR

- U.S.EPA *State of the Science Evaluation: Nonmonotonic Dose Responses as They Apply to Estrogen, Androgen, and Thyroid Pathways and EPA Testing and Assessment Procedures*.
  - Potential for nonmonotonic dose responses due to BPA concluded to be unlikely for hormone related toxicity endpoints.

Toxicokinetics and HED

EFSA appropriately identified uncertainty related to the toxicokinetics of BPA in mice

Mouse PK dietary study needed to fill data gap

Inappropriate to calculate HED at this time based on mouse data

- Potentially results in excessively low HED value

TDI

Pharmacokinetics/toxicokinetics, advancements in analytical methods, and new toxicological data aid in (1) reducing uncertainty in evaluation of studies, (2) in interpretation of conflicting reports, and (3) characterizing conservative nature of interspecies (rodent to primate) extrapolation

Hazard evaluation

- Supports reduction of hazard concern levels for many endpoints in current EFSA assessment.

Risk assessment

- Supports previous TDI, reduced t-TDI not warranted
- Support large margin of safety in comparison to very conservative EFSA exposure estimates for all population