Draft Assessment of Bisphenol A for Use In Food Contact Applications Update

FDA Science Board
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Reassessing Safety

A Multistep Process

- Reviewing and considering new data, information, and interpretations
- Developing or requiring the development of new data
- Seeking expert input
- Completing reviews
- Determining and taking appropriate action

Science Board Comments on the Draft Assessment

- Expand/Update exposure assessment
- Consider dose modeling for point of departure
- Clarify uncertainty factors used
- Reevaluate toxicity studies deemed "adequate"
- Consider the value of meta-analysis
- Expand discussion of biomonitoring data
- Carefully consider planned toxicological studies to ensure they may clarify remaining uncertainties

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Outline

- Update on Toxicology Assessment
  - Dose Modeling and Point of Departure Analysis
  - Uncertainty Factors
- Update on Infant Exposure Assessment
  - New exposure assessment model
  - Develop data to assess uncertainties in parameters used for the exposure assessment
- Ongoing Activities

Toxicology Assessment
Update

Point of Departure (POD) Analysis (Tyl Study)

- Draft Assessment: Based point of departure on NOAELs from the Tyl et al. (2002, 2008).
- Science Board: Suggested a Benchmark Dose analysis using available software as basis for POD.

Point of Departure (POD) Analysis

- Several BMDL analyses of Tyl et al. data already published including: Draft Assessment NOAEL 5 mg/kg bw/day
  - JNIAIST BMDL 23 mg/kg bw/day in mice
    multinucleated giant hepatocytes
  - Willhite *et al.* $BMDL_{10}$ 75 mg/kg bw/day in female mice
    ovarian cysts
  - CERHR $BMDL_{10}$ 35 mg/kg bw/day in rats
    decreased terminal body weight
    $BMDL_{10}$ 12 mg/kg bw/day in mice
    centrilobular hepatocyte hypertrophy

Results of BMDL Analysis To Date

- Thus far, the BMDL approach does not indicate a more protective POD than FDA previously developed using NOAELs from Tyl et al. (2002, 2008).
- Analysis and conclusions are limited to the endpoints examined in the Tyl et al. (2002, 2008) studies.
- Considering value of further BMDL/POD analysis.

Uncertainty (Safety) Factors

- Draft Assessment: Margin of safety developed from NOAELs of Tyl et al. (2002, 2008) using uncertainty factors for:
  - Systemic toxicity
  - Reproductive toxicity
  - Developmental toxicity
- Science Board: Suggested a more thorough description of the uncertainty factors used.

Uncertainty (Safety) Factors Revised Discussion

Repeated Dose (Systemic) Toxicity

- Intraspecies variability (human variation)
- Interspecies variability (animal-to-human uncertainty)
- Duration (subchronic-to-chronic uncertainty)
- Availability of Multispecies data

Developmental and Reproductive Toxicity

- Choice of UF depends on severity of the findings:
  - Permanent (irreversible) changes
  - Nonpermanent (reversible) changes

Exposure Assessment

Update

New Exposure Model

Existing Data

- Initial work based on the data available on BPA in IF
  - FDA (1997): 14 concentrates
    - 0.1-13.2 μg/kg food
  - HC (2008): 18 concentrates, 3 RTF
    - 2.3-10.2 μg/kg food
  - EWG (2007): 6 concentrates
    - ND-17 μg/kg food
- Total of 36 liquid samples representative of US market
  - 5 from Europe omitted
  - 0.04-8.6 μg/kg food (at use concentrations)

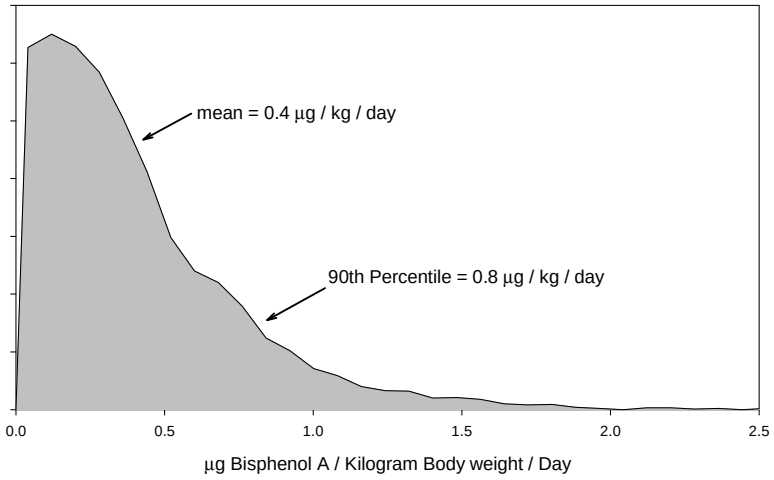
New Exposure Model

Existing Data

- Formula consumption
  - Food Intakes derived from the 1994-96, 98 USDA Continuing Survey of Food Intakes by Individuals (CSFII)
  - 2-Day Survey
  - Approximately 1200 Infants (age 0 to 12 months)

Probabilistic Exposure Model

- Distributions used in place of point estimates for BPA in infant formula
- Infant Formula (food) consumption
  - Typically Lognormal
- Concentration data (BPA in infant formula)
  - Determined Experimentally
  - Distribution model fit to data
- Distributions sampled by Monte Carlo process
- Intake calculations performed in multiple iterations
- Provides an intake distribution



Exposure Modeling Results

Existing Data

- Estimated Daily Intake of BPA from liquid formula
  - Mean : 0.4 μg / kg body weight / day
  - 90th Percentile : 0.8 μg / kg body weight / day
- Assumptions underlying model
  - 2-day average intake data reflects usual intake
  - Analytical BPA concentration data set is representative of all infant formula

Developing New Infant Formula Data

- Robust analysis of several infant formula brands and products as a function of formula type, container size, geographic location and storage time
- Infant formula sampling plan & collection worksheet
  - Major Brands
  - Milk & soy
  - Ready-to-feed (RTF), concentrate & powder
  - Containers of various sizes and types
  - East Coast and West Coast major markets
  - Several cans within lots and different lots

Developing New Infant Formula Data

- Method development
  - Updated 1997 method
  - Updated, modified method to allow for rapid analysis
    - Utilizes tandem mass spec detection (LC-MS/MS with a stable isotope internal standard)
    - Modified sample preparation
  - Completed in-house validation with spiked samples

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- Initial analytical results
  - Recent results on 57 samples
  - 0.02-10.55 μg/kg food
  - Comparable to existing data
  - No statistically significant geographic variation

Reexamining Assumptions

- Expand discussions on:
  - Studies on BPA migrating from PC bottles into formula
  - BPA migrating to infant formula from microwave reheating or resulting from excessive dishwasher use
  - BPA migration from PC bottles based on terminal sterilization
  - The impact of brand loyalty on exposure
  - The impact of the use of powder versus liquid concentrate formula

Infant Feeding Practices Study II

- Infant Feeding Practices Study (IFPS)
  - Collaborative study by FDA and CDC consisting of a mail survey of mothers of infants from pregnancy to 1st birthday
  - IFPS II (2005-7) included >2000 infants including participants in the Women Infants Children (WIC) Program
  - Provided detailed information about general infant feeding patterns and infant health
  - Questions on formula purchased, label reading, mixing, handling, and other practices

IFPS II Results

- Question- Do you heat the bottle in a microwave oven?
  - 65% of "all mothers" reported "rarely/never" over all ages
  - 85% of "WIC mothers" reported "rarely/never"
- Question- Do you boil water for formula?
  - Most mothers did not boil tap (70%) or bottled (83%) water used to reconstitute formula
  - Surmise that % not using terminal sterilization are even higher
- Question- Did you switch formula in the last 2 weeks?
  - % mothers responding "yes" decreases as infant matures
  - 27% (1 month) and decreasing to 10% (9 months)
- Question- What type of formula did you use?
  - 85-90% powder for "all mothers"

BPA from PC Bottles

Expanded analysis considering experimental conditions

- Recommended use (WHO, CFSAN, AAP)
  - Water boiled & cooled, no microwave heating, refrigerated or used within 2 hours
  - <1 μg/kg food
- Current practices
  - Use of microwave oven and dishwashers
  - Reheating <1 μg/kg food, dishwasher <2.4 μg/kg food
- Expanded analysis continue to support the same or lower levels than our original assumptions
  - <1 μg/kg food (typical) and <10 μg/kg food (terminal sterilization)

Ongoing Activities
Infant Exposure

- Laboratory analysis
  - Complete analysis of remaining liquid IF samples to conclusively determine variability
  - Complete analysis of powder IF samples
- Exposure Analysis
  - Update exposure with new laboratory data on liquid and powder IF samples
  - Incorporate information from IFPS II, expanded PC bottle analysis, and other relevant data on infant formula consumption into probabilistic modeling
- Evaluation of existing biomonitoring data and incorporation into overall exposure discussion.

Ongoing Activities
Engaging Industry

- Code of Practice Collaboration
  - Minimizing BPA migration from existing packaging materials into infant formula
- Ongoing discussions with polycarbonate manufacturers regarding the future marketing of polycarbonate infant bottles
- Consultations with infant formula manufacturers regarding the use of alternative packaging

Ongoing Activities
Toxicology

- Re-evaluating studies deemed 'adequate' by CERHR for highlighted endpoints with clearer evaluation criteria.
- Evaluation of new data identified by the SB, or published since the SB meeting.
- Consideration of value of meta data analysis

Ongoing Activities
Additional Toxicity Studies

- Finalized protocol to address the pharmacokinetic uncertainties
  - Adult, neonatal and fetal rats
  - Neonatal and adult primates
- Tiered approach to address the potential carcinogenicity and chronic toxicity of BPA
  - Protocol development for subchronic perinatal rodent study
    - NCTR SD rat
    - Expanded doses, termination times, endpoints
  - Results will be used to design *in utero* 2-year combined chronic toxicity and carcinogenicity study
- Protocol development for a neurodevelopmental study in rats
- Protocol development for a study on growth and cognitive and pubertal development in rhesus monkeys.

Ongoing Activities
Epidemiology

- FDA and NIH are collaborating to identify available extant cohort studies at NIH for assessment of the temporal association of urinary concentrations of BPA with incidence of specific diseases.
- Three FDA-NIH working groups are currently evaluating:
  - Laboratory analyses to measure BPA,
  - Epidemiology studies of adults (Coronary Heart Disease, Stroke, Diabetes and Cancer)
  - Epidemiology studies of children (Onset of puberty, Obesity and Diabetes)

These Slides, the Draft Assessment of Bisphenol A (BPA) for Use in Food Contact Applications, and the Science Board(SB) report as well as FDA' preliminary response in the December 3rd, 2008 letter to the SB can be accessed at FDA's website (http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_00_index.htm).

•The information presented is part of an on-going effort to reassess the safety of BPA.

•This presentation focuses on updating our progress in a few areas highlighted in FDA's SB review and the December 3, 2008 letter which are accessible at the web site above.

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