Draft Assessment of Bisphenol A for Use In Food Contact Applications

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Outline

- Introduction
- Exposure Assessment
- Toxicology Assessment
  - Pharmacokinetics
  - Reproductive and developmental toxicity
  - Carcinogenesis
  - Other developmental endpoints
- Conclusions
- Recommendations

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The Draft Assessment of Bisphenol A for Use in Food Contact Applications described in this presentation can be accessed at FDA's website at:

The information in the draft assessment has been distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by FDA. The draft assessment should not be construed to represent, any agency determination or policy.

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BPA Background

- Used in food packaging
  - Molded objects such as polycarbonate baby bottles
  - Epoxy can linings such as those used for vegetable cans
- Monomer used in the manufacture of food additives:
  - Potential exposure due to migration of unreacted material or depolymerized material through the use of food contact materials.
  - Food additive impurity/constituent (not an impurity/constituent of food).

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Safety Assessment Approach

Food Additive Safety Standard:

Safe or safety means that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.

21CFR§170.3(i)

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Food Contact Materials

Premarket

- Submitter's assessment:

  Safety assessment performed by industry and submitted to FDA:

  - Performance and submission of full studies to FDA.
- FDA's assessment:

  Full review of all relevant data, submitted and acquired, with a critical assessment regarding performance and conclusions.

Postmarket

- FDA continually monitors and reviews scientific data
- Postmarket reporting of adverse findings
- Engagement of the regulated industry
- Appropriate action based on safety concern.

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Exposure Driven Approach

Low Exposure:

- Cumulative exposure ≤ 150 μg/person/day
- Focus: carcinogenicity and genetic toxicity
- Other endpoints – existing data

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BPA Mode(s) of Action

- Binds to estrogen receptors (ERα and ERβ)
- May also interact with other receptors, including membrane bound ER and estrogen-related receptor γ

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BPA Reassessment

- FDA reassessment:
  - Rat multigeneration study
  - Mouse multigeneration study
  - Pharmacokinetic assessment

Why these studies?

- FDA considered the Tyl *et al.* (2002, 2008) studies pivotal and more weighted then published studies examining the same or similar endpoints due to their:
  - robust study design
  - large sample size
  - lifetime exposure regimen
  - large dose range
  - expanded protocol
  - full availability of supporting data

FDA Task Force

- Reported concerns for current consumer exposure:
  - Neural and behavioral effects;
  - Prostate gland and mammary gland;
  - Acceleration of the age at which females attain puberty; and
  - Accuracy of infant exposure assessment.
- Establishment of FDA Task Force:
  - Review new data and examine infant exposure assumptions.
  - Expand review of toxicity data to newly identified endpoints of discussion.
  - Consider all FDA regulated products.

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Infant Exposure Assessment

- Maximum exposure estimate: 2.42 μg/kg bw/day
- Conservatisms in estimate:
  - all formula is in a liquid form as purchased and used by the consumer;
  - all liquid infant formula is packed in cans coated with BPA-based enamels;
  - consumers prepare and deliver all formula in thermally sterilized PC bottles;
  - repeated use of PC baby bottles results in the 10 μg/kg level at every use; and
  - consumption occurs at the maximum level as opposed to an average.
- This maximum exposure is the value we used in the assessment.

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Infant EDI Background

- Updated EDI: 0.15 - 2.42 μg/kg bw/day
  - Review of data from numerous sources
    - literature, EFSA, EC, HC, other groups and FDA
- PC bottle contribution:
  - months 0-2: 10 μg/kg released with sterilization of a bottle containing formula by boiling
  - months 3-12: 1 μg/kg released with every use of a room temperature bottle containing formula
- Our final assessment only considers the maximum exposure resulting from sterilizing bottles.

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Infant EDI Assumptions

- Conservatisms in infant formula contribution:
  - Liquid formula packaged in epoxy can coatings
    - 2.5 ppb
- Conservatisms in formula intake:
  - Consumption data were evaluated on a per month basis up to 12 months of age to obtain the maximum exposure as adjusted for body weight.

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Adult Exposure

- Exposure: 0.185 μg/kg bw/d
  - BPA migration studies from canned (epoxy-coated) foods:
    - Survey data indicated a mean of 22 ppb
  - 17% of all food available to consumers for purchase is packaged in polymer coated metal packaging
  - Estimate:
    - 22 ppb x 0.17 = 3.7 ppb
    - 3.7 ppb x ((3 kg food/p/d) ÷ (60 kg/person)) = 0.185 μg/kg bw/d
  - Conservatisms: that all food and *beverages* which are packaged in cans are packed in cans coated with BPA-based coatings and BPA levels in both are as high as 22 ppb.
  - Contribution from PC-based articles is low and does not contribute to the total BPA exposure.

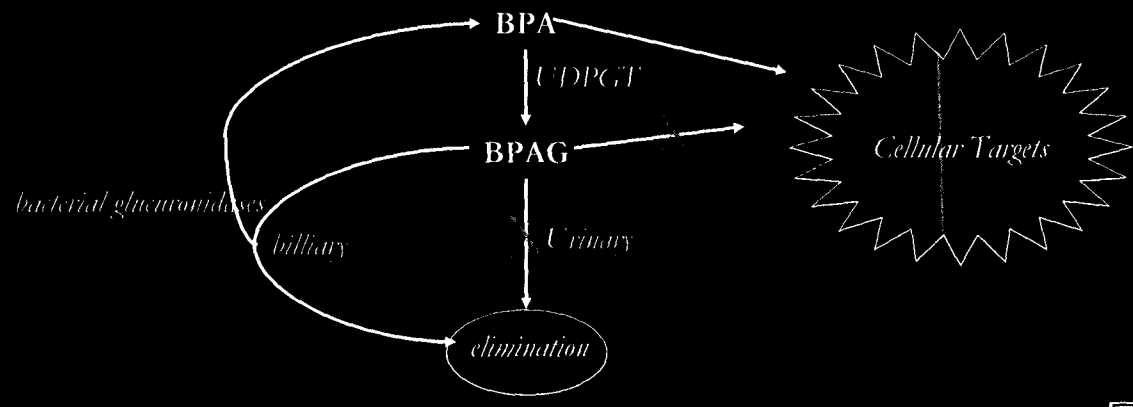
Pharmacokinetics

- Adult absorption and metabolism:
  - BPA uptake is rapid and significant.
  - Rapid metabolism to BPA glucuronide (BPAG).
    - BPAG has no significant estrogenic activity.
- Fetal/neonatal absorption and metabolism:
  - *In utero* via placental transfer.
  - BPA appears in the milk of lactating animals in substantial quantities.
    - Primarily BPAG; however, newer reports indicate some free BPA.
    - BPAG may be hydrolyzed by intestinal (bacterial) glucuronidases to form free BPA which would be rapidly absorbed by the neonate.
  - Glucuronidating capability is present, but low, and develops with age.
  - Other detoxification pathways: sulfotransferase activity is present at this stage of development.

Species Differences

Detoxification and elimination:

- BPA is metabolized to inactive forms, predominately BPAG
- Primate BPAG elimination is relatively rapid ($t_{1/2}$ = 3-4 hr) and primarily via urine (80-90%)
- Rodent BPAG elimination is complicated by the fact that it is routed primarily into bile.



Route of Exposure

- Oral exposure studies most relevant to safety assessment for food contact substance.
  - Recommended route for food additives is diet.
  - Subcutaneous or intraperitoneal exposures lack first pass metabolism.
  - Neonatal metabolic activity is present, though not at adult levels.

BPA Literature Dataset

- Limited usefulness in regulatory decisions:
  - Low number of replicates
  - Limited or no dose range
  - Selective endpoint analysis
  - Non-validated techniques or endpoints
  - Multiple routes of administration
  - Confounding dietary estrogens
  - Limited reported details or flawed study design
- Usefulness in guideline regulatory recommendations:
  - Alternative endpoints of examination
  - Recommendations of additional guideline style tests

Reproductive and Developmental Toxicity

- Two pivotal studies:
  - 3-Gen CD®SD Rat feed study (Tyl *et al.*, 2002)
  - 2-Gen CD-1® Swiss Mouse feed study (Tyl *et al.*, 2008)
    - Use of expanded range of doses, including low and high doses
    - Use of multiple generations (lifetime), including *in utero* subchronic exposure
    - Use of large number of replicates
    - Examination of an expanded range of endpoints
    - Conducted per EPA or OECD guidelines (acceptable alternatives to Redbook 2000)

Reproductive & Developmental Toxicity Conclusions

- 3-Gen CD[R] SD Rat feed study (Tyl *et al.*, 2002)
  - 0, 0.001, 0.02, 0.3, 5, 50, or 500 mg BPA/kg bw/day
  - Systemic NOAEL: 5 mg/kg bw/day
  - Reproductive NOAEL: 50 mg/kg bw/day
  - Offspring NOAEL: 50 mg/kg bw/day
- 2-Gen CD-1[R] Swiss Mouse feed study (Tyl *et al.*, 2008)
  - 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg BPA/kg bw/day
  - Systemic NOAEL: 5 mg/kg bw/day
  - Reproductive NOAEL: 50 mg/kg bw/day
  - Offspring NOAEL: 50 mg/kg bw/day

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Carcinogenesis

- CFSAN Cancer Assessment Committee
  - Evaluation of BPA 2008
  - Review of NTP bioassay, literature regarding prostate gland and mammary gland

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Carcinogenesis

- NTP bioassay: No evidence that BPA is carcinogenic under conditions tested.
  - Limitations: lack of *in utero* exposure, dated experimental design
- Other studies are insufficient to demonstrate clear findings with regard to progression or human health.
- NTP bioassays lacked adverse findings for mammary or prostate glands.

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Developmental Toxicity

- Acceleration of puberty in females:
  - Collective findings do not support a concern at a lower dose than the offspring NOAEL of 50 mg/kg bw/day for this endpoint.
- Alteration of prostate and urinary tract in males:
  - Collective findings do not support a concern at a lower dose than the offspring NOAEL of 50 mg/kg bw/day for this endpoint.

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Neurotoxicity

- Limitations of many of the studies reviewed:
  - Lack of concurrent examination of endpoints used for validating findings
  - Lack of consistent effects
  - Lack of effects interpretable as adverse to humans
  - Examination of only one sex or one dose
- Data collectively suggest that more research, using validated studies with feeding protocols modeling human exposure are necessary prior to establishing a NOAEL for this endpoint for use in regulatory safety assessments.

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Assumptions Underlying Conclusions

- The rodent animal model is appropriate.
- Studies using oral exposure are the most relevant.
- Regulatory guidance studies adequately model human infant BPA exposure.
- The development of the nervous system and its responses to hormonally active compounds is comparable across species.
- BPA acts mainly as an estrogenic compound.
- BPA exposure is continuous throughout life.
- Exposure occurs from multiple routes.

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Margins of Safety

NOAELs from Tyl *et al.* (2002, 2008) studies:

Endpoint	NOAEL	Maximum infant exposure	Infant MOS	Adult exposure	Adult MOS
Systemic	5 mg/kg bw/d	2.42 µg/kg bw/day	2,066	0.185 µg/kg bw/day	27,027
Reproductive	50 mg/kg bw/d	2.42 µg/kg bw/day	20,661	0.185 µg/kg bw/day	270,270
Offspring	50 mg/kg bw/d	2.42 µg/kg bw/day	20,661	0.185 µg/kg bw/day	270,270

Conclusions

- Margin of safety of ~ 2000 is adequate.
  - NOAELs in Tyl *et al.* (2002, 2008) studies.
  - Inadequate justification to alter conclusion based on:
    - Carcinogenesis;
    - Early onset of puberty in females and alterations of the male reproductive tract; and
    - Neurotoxicity.

Recommendations

- FDA proposes a multiple tiered testing strategy for improving uncertainties in evaluating the safety of all BPA regulated products:
  - Strategy strengthens oral (food contact) exposure assessment by decreasing uncertainties surrounding assumptions;
  - Strategy develops useful data for non-oral routes of exposure (medical devices, etc.); and
  - Strategy ensures the development of data meeting the standards acceptable to FDA for identified critical endpoints for use in safety assessments.

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Recommendations

- Rodent PK and toxicity data
- Biomonitoring data
- Estimated daily intake data
- BPA toxicity study in non-human primates

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QUESTIONS?

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