BPA - Workshop
Berlin
March 31, 2009

Health Discussion Group

Criteria for discussion outcome

- Consent
- Disagreed
- Unable to conclude
- Need for clarification

- Evidence criteria
- Clear
- Some
- Equivocal
- No evidence
- Inadequate data

Consensus - Disagreement

1. Risk to infants from exposure to BPA and that the levels of exposure are very low and do not pose a significant health risk (FDA, EFSA)
2. Some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA (NTP)
3. That **adverse effects** occur at levels below NOELs of 5 mg/kg/day and are **relevant** for risk assessment

Terms of reference: Resolve uncertainties:

1. Disposition in rodents and humans
   Internal dose of free BPA
   Internal dose-extrapolation from rodents to human
   Biochemical effect marker
2. Validated reliable analytical method
3. GLP studies
4. non-GLP rodent studies indicating relevant effects at low-level exposures, which might have been overlooked in GLP-studies.
   relevant endpoints & effect-markers ?
   Brain, behavior, prostate
   More low-dose studies (oral) necessary?
   species, endpoints, design

Terms of reference: Resolve uncertainties:

Disposition

- Are there relevant differences in disposition between rodents and humans
- What is the bio-availability of free (unconjugated) BPA in humans? especially the fetus
- Do relevant differences exist with respect to

  Age, Gender, Pregnancy, Polymorphisms
- Extrapolation metrics by internal dose

Precaution ?

- There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already EU-RAP
- or
- Should the obvious *large* differences in exposure be addressed and measures taken to minimize exposure
- i.e. the use of alternatives to BPA in baby bottles (provided they are safe)

Consensus-Disagreement-Recommendation

- Human Effect-Exposure study (Lang 08)
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Critical design components for all future research on BPA:

- Appropriate experimental design and statistical analysis, especially accounting for litter effects;

1. Appropriate route (oral) of exposure. Studies with non-oral route of administration should include internal dose measurements of free BPA;
2. Multiple dose groups ranging from low to high;
3. Linkage of effects to adverse effects;
4. Relevant endpoints, with biologically plausible outcomes especially for estrogen-mediated effects on reproduction and behavior.

Recommendations (3 out of 9)

1. **Neural and behavioral endpoints**
   Gestational and lactational exposure to bisphenol A on maternal behavior and offspring brain structure and behavior
2. **Human exposure assessment**
   Additional data are needed to clarify bisphenol A exposures and internal dosimetry in the general population, newborns, and occupationally-exposed individuals
3. Human studies relating adult exposure to reproduction and development, including effects on hormone levels

Recommendations (6 out of 9)

1. Neural and behavioral endpoints
2. Human exposure assessment
3. Human srudies
4. Physiologically-based pharmacokinetic (PBPK) models
5. Effects on prostate and mammary gland development
6. Altered puberty
7. Biological mechanism for low-dose-only effects
8. More work directed toward urinary tract morphological and histologic changes
9. Inter-laboratory replication of studies

Recommendations (2 out of 6)

1. **additional low-dose studies**, including the development and use of sensitive and easily measured molecular endpoints, following in utero or early neonatal exposure to conclusively establish low-dose effects of BPA as a general, reproducible phenomenon
2. **pharmacokinetic data** in multiple species and strains of animals to characterize fetal uptake, metabolism, and elimination of BPA and its metabolites
3. mechanistic data on estrogen receptor occupancy during critical periods of development, effects of specific receptor antagonists, and responses in estrogen-receptor knock-out mice;
4. additional studies on intrauterine position effects;
5. characterization of genetic and epigenetic factors that affect responses to bisphenol A and hormones in general, e.g., factors that lead to strain and species differences in sensitivity;
6. mechanistic studies on the effects of bisphenol A on regulation of transcriptional activity, from gestation through adulthood.