NTP
National Toxicology Program

Draft NTP Brief on Bisphenol A (BPA)

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BSC Peer Review – June 11, 2008

Outline of Presentation

- CERHR process
- Overview of draft BPA Brief
  - CDC presentation on BPA biomonitoring
  - General comments from ad hoc reviewers and Board
  - Public comment
- Specific discussions
  - Mini-presentations and discussion by ad hoc reviewers and Board
    - Metabolism and route of administration
    - Brain and behavior
    - Puberty
    - Mammary gland
    - Prostate gland
  - General discussion and vote by the Board

CERHR Process

- Nomination and selection
- CERHR Expert Panel evaluation
- NTP Brief

Preparation of the NTP Brief on BPA

Public Comments Received on Final CERHR Expert Panel Report

Final CERHR Expert Panel Report

New Peer Reviewed Science (Feb 2007 – June 1, 2008)

Prepare & Release Draft NTP Brief on Bisphenol A

Solicit Public Comments on Draft NTP Brief on Bisphenol A (April 15 – May 23, 2008)

June 11, 2008 Peer Review by the NTP Board of Scientific Counselors (Supplemented with *Ad Hoc* Scientific Experts) public meeting

we are here

Finalize NTP Brief on Bisphenol A & Release Peer Review Report (Summer 2008)

Release NTP-CERHR Monograph

Summary of Draft NTP Brief on Bisphenol A

Rationale for CERHR Evaluation

- High production volume
  - Estimated U.S. production in 2004 was ~ 2.3 billion pounds
- Widespread human exposure
  - > 90% of people in the U.S.
- Sufficient database on developmental and reproductive toxicity in laboratory animals
- Public concern

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Format of the NTP Brief

- What is BPA?
- Are people exposed?
- Can BPA affect human development or reproduction?[1]
  - Hazard identification conclusion based on studies in humans and/or animals
  - Weight of evidence categories of adverse effects
- Are current exposures to BPA high enough to cause concern?[1]
- Conclusions on whether human development or reproduction might be adversely impacted by BPA
  - Conclusions range from “insufficient hazard and/or exposure data” to “negligible concern” to “serious concern”

[1]Yes, Probably, Possibly, Probably Not, No or Unknown

What is BPA?

- Used in the production of polycarbonate plastics and epoxy resins
  - Polycarbonate plastics have many uses including in certain food and drink containers, e.g., baby bottles, sippy cups, water bottles, tableware, etc.
  - Epoxy resins are used to coat metal products such as food cans
- Some polymers used in dental sealants or composites contain BPA-derived material

Are People Exposed?

- *Yes*
  - Most exposure is through the diet
  - Detected in the urine of 93% of people 6 years and older in the latest NHANES (>2500 people)
  - Detected in human blood and breast milk in numerous smaller studies
  - Estimated daily intakes are highest in infants and children
    - 1 - 13 μg/kg/day in formula-fed infants
    - 0.2 - 1 μg/kg/day in breastfed infants
    - < 0.300 μg/kg/day in adults (95^{th} percentile estimates)

Can BPA Affect Human Development or Reproduction?

- *Possibly*[1]
  - Conclusion can be based on adverse health effects identified in studies of humans and/or laboratory animals
  - Conclusion for BPA is based on studies in laboratory animals
  - Relationship between doses that cause these effects to human exposures is not considered in this conclusion, i.e., this is a hazard identification question

[1]Possible answers to this question are: *Yes, Probably, Possibly, Probably Not, No or Unknown*

Human Studies

- Only a small number of studies have been conducted in humans
  - Interpretation limited by small sample size, cross-sectional design, lack of large variations in exposure, or lack of adjustment for potential confounders.
  - The NTP concurs with the CERHR Expert Panel that there is a suggestion of effect on reproductive hormones, especially in men exposed occupationally
- Overall, the human studies provide insufficient information to make a conclusion on potential adverse health effects on development or reproduction

The weight of evidence that BPA causes adverse developmental or reproductive effects in humans*

Developmental and reproductive toxicity →

- Clear evidence of adverse effects
- Some evidence of adverse effects
- Limited evidence of adverse effects
- Insufficient evidence for a conclusion
- Limited evidence of no adverse effects
- Some evidence of no adverse effects
- Clear evidence of no adverse effects

* Based on epidemiological studies in humans

Laboratory Animal Studies

- For developmental effects the literature was separated into "high" dose (> 5 mg/kg/day) and "low" dose (≤ 5 mg/kg/day)
  - *Clear evidence* of adverse effects on development at high doses
    - Reduced survival and growth; delayed puberty
  - *Limited evidence* of adverse effects on development at low doses
    - Brain and behavior, lesions in the prostate and mammary glands, altered prostate gland and urinary tract development, and early onset of puberty in females
- *Some evidence* of adverse effects on reproduction in animals exposed only during adulthood
  - Decreased fertility, altered estrous cycling, testicular effects

The weight of evidence that BPA causes adverse developmental or reproductive effects in laboratory animals

"High" dose developmental toxicity →	Clear evidence of adverse effects
Reproductive toxicity →	Some evidence of adverse effects
"Low" dose developmental toxicity →	Limited evidence of adverse effects
	Insufficient evidence for a conclusion
	Limited evidence of no adverse effects
	Some evidence of no adverse effects
	Clear evidence of no adverse effects

How were these conclusions reached?

BPA Scientific Literature

	"Guideline" Studies	Academic Studies
Number	Several multigenerational studies in rats and mice	Many
Endpoint Assessment	Those included in EPA and OECD guidelines	Generally address specific experimental questions
Sample Size	Relatively large (> 20)	Smaller (often < 10)
Experimental Design	- Use standardized protocols - Records and reporting according to GLP	- Varies - Tend to have more reporting or technical shortcomings, e.g., control for litter effects
Route of Administration	Generally use most relevant for human exposure (oral for BPA)	Mostly oral and subcutaneous

Consideration of Effects

- Focused on effects highlighted by the CERHR Expert Panel and in other recent evaluations
- Are the *in vivo* effects biologically plausible?
- Do the *in vivo* effects represent adverse health findings in laboratory animals and/or humans?
- What are the potential impacts of any limitations in experimental design?
- Have the *in vivo* effects been reproduced?

Consideration of Limitations in Experimental Design

- NTP did not establish a single number for minimal acceptable sample size
  - Small sample size studies considered in the context of other studies assessing similar endpoints
- Inadequate control for litter effects was considered a significant design flaw
- Positive controls considered helpful when available but were not “required”

Are Current Exposures to BPA High Enough to Cause Concern?

- *Possibly*[1]
  - Estimated exposures in infants and children are similar to levels of BPA associated with several "low" dose laboratory animal findings that provide *limited evidence* that BPA has adverse effects on development

[1]Possible answers to this question are: *Yes, Probably, Possibly, Probably Not, No or Unknown*

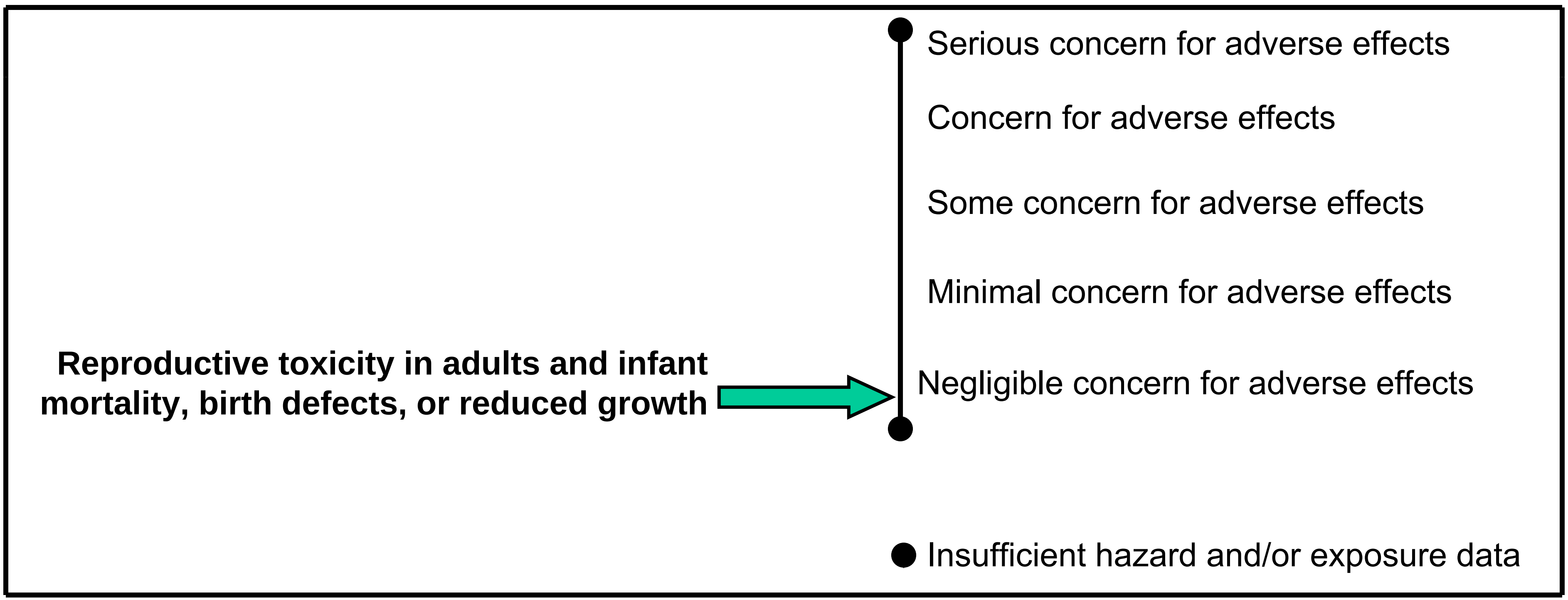
Draft NTP Conclusions

- **NTP concurs with the CERHR Expert Panel that there is *negligible* concern that BPA exposure causes reproductive effects in non-occupationally exposed adults**
  – Based on laboratory studies that provide “some” evidence of adverse effects on reproduction in animals exposed as adults at exposure levels far in excess of those experienced by humans

Draft NTP Conclusions

- **The NTP has *negligible* concern that BPA exposure to pregnant women will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring.**
  - Based on laboratory studies that provide “clear” evidence of adverse effects on development in animals exposed during perinatal life at exposure levels far in excess of those experienced by humans
  - No indication that BPA causes malformations

NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A



Draft NTP Conclusions

- **NTP concurs with the CERHR Expert Panel that there is *minimal* concern for workers exposed to higher levels in occupational settings.**
  - Data from studies in humans are not sufficient to determine if BPA *adversely* affects reproduction
    - A suggestion of a a possible effect on reproductive hormones, especially in men exposed to higher levels of BPA in the workplace

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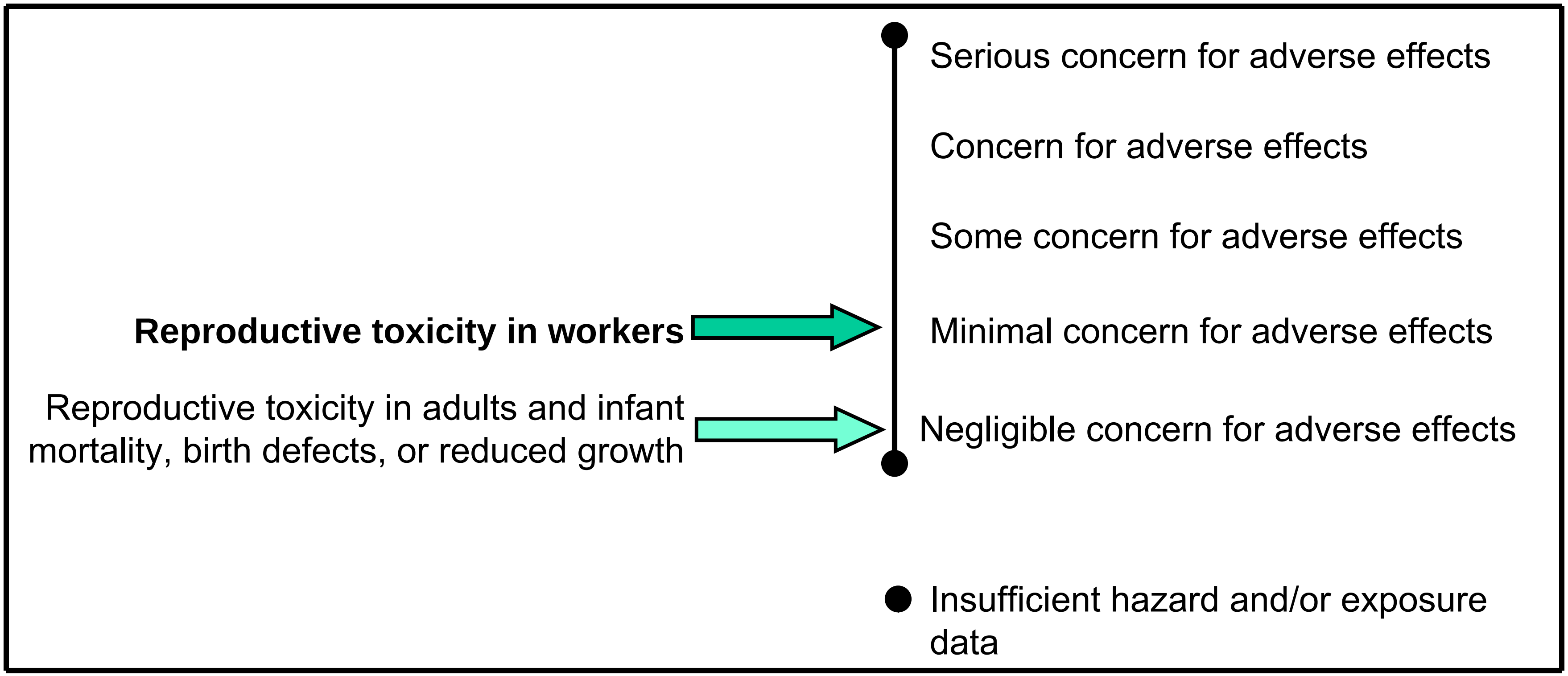
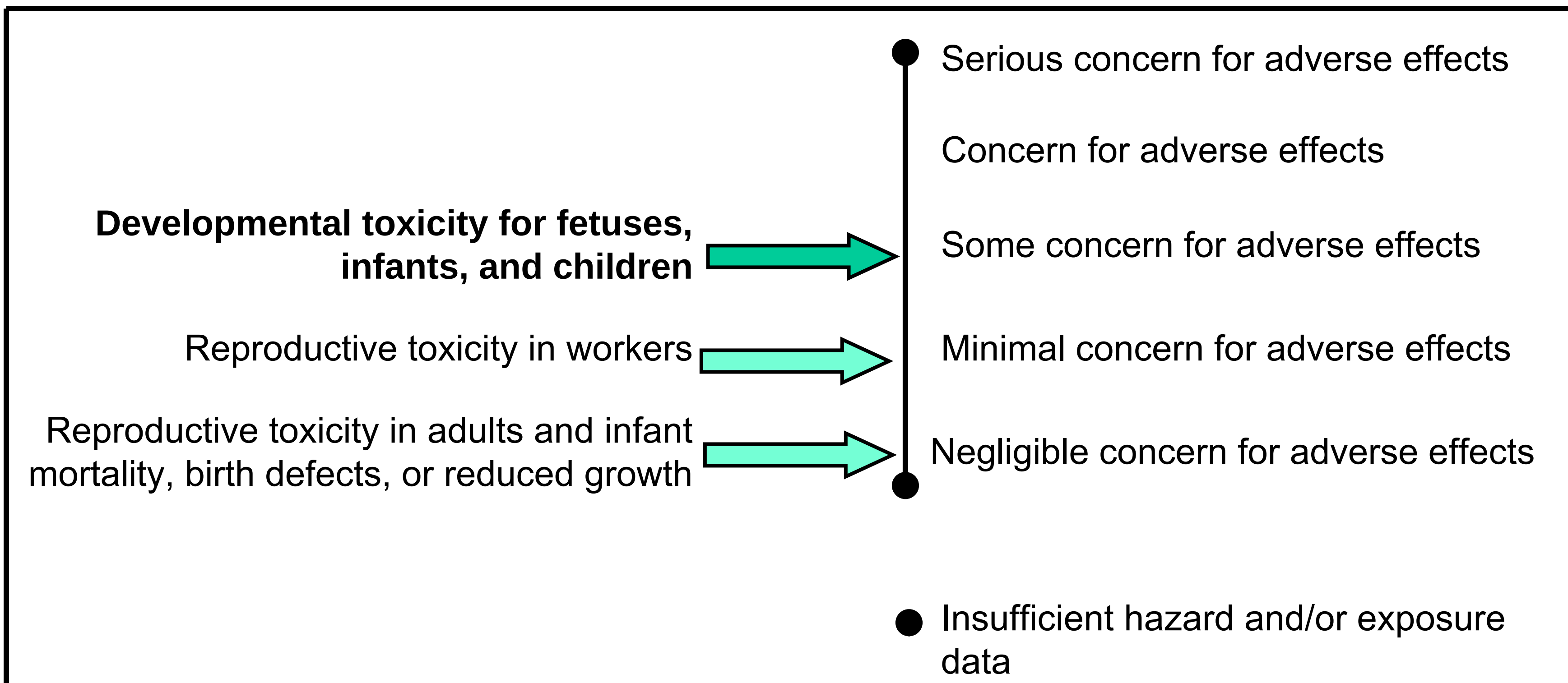
NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A



Draft NTP Conclusions

- **NTP concurs with the conclusion of the CERHR Expert Panel that there is *some* concern for neural and behavioral effects in fetuses, infants, and children**
- **NTP also has *some* concern for BPA exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females.**
  - Based on laboratory animal studies that provide “limited” evidence of adverse effects from “low” level exposure
  - Because these effects in animals occur at BPA exposure levels similar to those experienced by humans the possibility that BPA may alter human development cannot be dismissed.

NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A



Summary of Basis for "Some Concern"

- **"Limited evidence" for adverse effects at low doses similar to human exposures, e.g., infants**
- **Reported effects not assessed or expected to be detected in guideline studies**
- **New supportive data**

- **Interpretation of adversity or relevance to human health**
- **Additional replication with longer-term follow-up**
- **Better ability to link laboratory animal exposures to human exposures**

Serious concern for adverse effects

Concern for adverse effects

Some concern for adverse effects

Minimal concern for adverse effects

Negligible concern for adverse effects

Insufficient hazard and/or exposure data

Peer Review Charge

To determine whether the scientific information cited in the draft NTP Brief on Bisphenol A is technically correct, clearly stated, and supports the NTP's conclusions regarding the potential for bisphenol A to cause adverse reproductive and developmental effects in exposed humans.

Questions?

- **Upcoming**
  - Biomonitoring
  - Public comment
  - Age-dependent metabolism and route of administration
  - Low dose effects on brain, puberty, mammary gland, and prostate